Bridging the gap between payer and provider perspectives

May 2014
Volume 20
Special Issue 8

THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based Diabetes Management™

Drug Pipeline

Inhaled Insulin's Long Journey to Commercialization

Stanton R. Mehr

What if patients with type 1 diabetes mellitus (T1DM) could be freed from needles, vials, and syringes? What if insulin didn't have to be injected, but instead could be inhaled, like an asthma medication?

What if a new technology considerably lowered their risk of hypoglycemia?

With the exception of a true artificial pancreas, this technology may top the wish list of persons with T1DM. Previous attempts at inhaled insulin won over the FDA but not the target audience, causing some pharmaceutical companies to reevaluate their commitment to this product. "The prospect of a viable inhaled insulin is exciting, but the patient community feels a bit jaded because of the experience with Exubera," said Amy Tenderich, founder and editor of the website Diabetes Mine (www.diabetesmine.com).

Indeed, a commercially viable inhaled insulin has turned out to be difficult to develop. Yet, one company may be getting close.

Pfizer's 2006 Approval and 2007 Withdrawal

Earlier attempts to market an inhaled insulin and its delivery system revealed the difficulty in reaching the goal: not only must the product deliver insulin to the

(continued on page SP253)

Technology

The Role of Bioinformatics in Diabetes Drug Development—and Precision Medicine

Surabhi Dangi-Garimella, PhD

According to the 2011 National Diabetes Fact Sheet, diabetes affects nearly 26 million Americans, 95% of whom suffer from type 2 diabetes mellitus (T2DM).[1] A 2014 report published by the Pharmaceutical Research and Manufacturers of America (PhRMA) documented the development of 180 medications to treat diabetes or diabetes-related conditions, a majority of which are to treat T2DM.[2] The drugs being developed are intended to improve on the current therapies to combat the health toll and the healthcare costs associated with the disease. Among the drugs under development is a human peptide, a bioactive part of a gene that regenerates pancreatic islets; additionally, there are novel inhibitors of the protein dipeptidyl peptidase-4 (DPP-4) being developed, as well as a drug that targets sorbitol, a sugar alcohol determined to be responsible for diabetic neuropathy.[2] These breakthrough advances are based on the research conducted by scientists to understand disease mechanisms, which include gene sequencing and protein structure elucidation.

Arathi Krishnakumar, PhD

GenBank, an all-inclusive, open-source database initiated by the National Center for Biotechnology Information (NCBI), has a very important role to play in this process. GenBank includes nucleotide sequences for more than 280,000 species and the supporting bibliographies, with submissions from individual laboratories as well as large-scale sequencing projects. Addi-

(continued on page SP255)

Stress, Diabetes, & Treatment

The How and Why of Stress, Diabetes, and the Brain

A Visit With Mark Feinglos, MD, and Richard Surwit, PhD

Stanton R. Mehr

The interaction between stress and diabetes mellitus, though long established, has flown under the radar in a flurry of new pharmacologic therapies in recent years. *Evidence-Based Diabetes Management* revisited this important finding and its implications for patient care with 2 pioneers of the field from Duke University who have worked together to elucidate much of what we know today: Mark Feinglos, MD, professor of medicine, endocrinology, metabolism, and nutrition; and Richard Surwit, PhD, vice chairman and head professor, department of psychiatry and behavioral sciences.

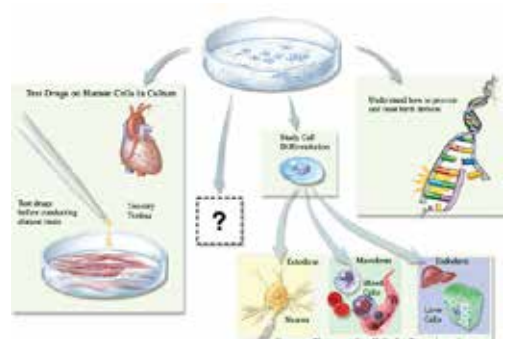
A Relationship Between Levels of Stress and Blood Glucose

Evidence-Based Diabetes Management: **You've been working on the effects of stress and blood sugar levels for 3 decades, but it has not received the kind of spotlight that pharmacologic treatments routinely receive. Why do you think that is?**

Richard Surwit, PhD: Speaking as the psychologist on the team, interest in many psychological issues, including stress, come and go in the popular press. People attend to them and then forget about them. We were on the cover of *Newsweek* magazine in 2004 regarding the role of stress and disease and there was a big to-do about it, but that faded.

Mark Feinglos, MD: As an endocrinologist, I believe physicians sometimes have a different approach to cognitive function. Some ignore it. Some tend to view their patients from the neck down, so to speak. They worry about the physiology

(continued on page SP258)

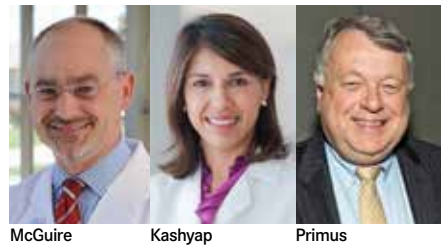


Progress in Regenerative Medicine to Treat Diabetes
Stem cells are increasingly being evaluated as an option to treat diseases, including diabetes. See page SP243.

Also in this issue...

The Rising Influence of Data Integration Platforms
From drug development to treatment options to healthcare services, big data analysis and integration tools are influencing every aspect of the healthcare industry. Read about it on page SP236.

Coverage Choices Affect Diabetics
States that are declining Medicaid expansion tend to have higher incidence of diabetes, with implications for care and prevention. Turn to page SP239.



McGuire Kashyap Primus

American College of Cardiology
Research presented at the recent annual meeting included the effects of bariatric surgery on diabetes. Sessions covered controversies in prevention and healthcare reform. Turn to pages SP245-SP250.

AJMC.com

Partner of Center For Value Based Medicine®

It’s not a pump. It’s not a pen.

It’s a V-Go®.

The V-Go may help improve glycemic control

For adults with Type 2 diabetes, the V-Go delivers a continuous preset basal rate of insulin plus on-demand bolus dosing at mealtimes.

Simplifies basal-bolus therapy

With basal-bolus therapy that’s all-in-1 (1 device, 1 insulin*), the V-Go helps simplify therapy and may support patient adherence.

1 injection, once a day

The V-Go helps reduce the burden of multiple daily injections from 4 to just 1 a day. It works with no electronics, batteries, or programming.

On call to help 24/7

Valeritas Customer Care is available 24/7 at 1-866-881-1209 to answer questions, provide expert reimbursement assistance, training, and more.

Learn more at www.go-vgo.com/simple

Important Risk Information: If regular adjustments or modifications to the basal rate of insulin are required in a 24-hour period, or if the amount of insulin used at meals requires adjustments of less than 2-Unit increments, use of the V-Go Disposable Insulin Delivery Device may result in hypoglycemia. The following conditions may occur during insulin therapy with the V-Go: hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose). Other adverse reactions associated with V-Go use include skin irritation from the adhesive pad or infections at the infusion site. The V-Go should be removed before any magnetic resonance imaging (MRI) testing.

*A U-100 fast-acting insulin should be used with the V-Go. Humalog® (insulin lispro, rDNA origin) and NovoLog® (insulin aspart, rDNA origin) have been tested by Valeritas, Inc. and found to be safe for use in the V-Go Disposable Insulin Delivery Device.

VGO® DISPOSABLE INSULIN DELIVERY

FREEDOM TO GO

valeritas

ART-516 Rev: A 05/2013

The American Journal of Managed Care ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 666 Plainsboro Rd, Bldg. 300, Plainsboro, NJ 08536.

SP234 PUBLISHER'S NOTE

SP236 TECHNOLOGY DEVELOPMENT
The Big Data Revolution: From Drug Development to Better Health Outcomes?
Andrew Smith

"When you can't afford the care to manage your disease, you scale back the care. Without adequate care, you increase risk of complications. The states that don't expand Medicaid are, essentially, waiting for the person to become so sick they are disabled to be eligible. If they expanded eligibility these people could receive care before they are disabled."
Krista Maier,
associate director of public policy, American Diabetes Association

SP239 IMBALANCE OF COVERAGE
Medicaid Expansion Choices Mean Different Care for Poor Patients, Depending on Where They Live
Peter Page

SP241 DIABETES AND RISK FACTORS
The Yin and Yang of CV Risks in Patients With Diabetes
Surabhi Dangi-Garimella, PhD

SP243 RESEARCH REPORT
Stem Cells Create a Therapeutic Niche
Surabhi Dangi-Garimella, PhD

SP245 CONFERENCE COVERAGE: AMERICAN COLLEGE OF CARDIOLOGY 2014
Mary K. Caffrey
- Cleveland Clinic Study: Use of Bariatric Surgery Beats Medical Therapy in Diabetes Management
- Diet Drinks Linked to Heart Trouble for Older Women
- Aims of ACA Get Better Reviews Than Implementation at Cardiologists' Meeting
- To Treat or Not to Treat? Questions, Controversies in Prevention
- Use of Rivaroxaban Could Trim Hospital Spending in Treating Pulmonary Embolism
- Relationship Between Cardiac Issues, Diabetes Gets Plenty of Attention
- Study Answers Long-Standing Question About Meformin After Heart Attack

SP251 NEURAL CONNECTIONS
The Persistent Complication of Hypoglycemia in Diabetics
Surabhi Dangi-Garimella, PhD

SP253 DRUG PIPELINE
Inhaled Insulin's Long Journey to Commercialization
Stanton R. Mehr

SP254 A Patient's Opinion of Unmet Need
Stanton R. Mehr

SP255 TECHNOLOGY
The Role of Bioinformatics in Diabetes Drug Development and Precision Medicine
Surabhi Dangi-Garimella, PhD

Beyond attempting behavioral approaches to modifying stress, making people aware of what's happening is important. If they can't avoid the stress, they can modify their diabetes treatment to better cope with it.
Mark Feinglos, MD

SP258 STRESS, DIABETES, AND TREATMENT
The How and Why of Stress, Diabetes, and the Brain
A Visit With Mark Feinglos, MD, and Richard Surwit, PhD
Stanton R. Mehr

SP260 PAYERS AND YOGA
Evidence Builds on Yoga, but No Reimbursement Yet
Mary K. Caffrey

Scan here to visit ajmc.com

From the Publisher

This issue of *Evidence-Based Diabetes Management* examines the chain reaction that occurs when stress hits our brains, sending off interactions through our bodies down to the cellular level. How we process stress, including the foods we eat, has a role in how our bodies respond. Decades of work by researchers such as Duke University's Mark Feinglos, MD, and Richard Surwit, PhD, have explored mind/body connections, how they play out in diabetes, and their role in developing therapies to treat the disease. This issue also has plenty about the role of technology in treating diabetes, from the importance of a publicly accessible research collaborative, GenBank, in developing new therapies, to the role of Big Data through efforts such as the partnership between Pfizer and UnitedHealth. Better technology may literally breathe new life into a treatment that had been abandoned, as an FDA advisory panel voted favorably on Afrezza, an inhaled insulin. This treatment for both type 1 and type 2 diabetes mellitus shows promise 7 years after an earlier inhaled insulin was pulled from the market, after consumers and physicians rejected its unwieldy, hard-to-use delivery system. This issue also contains coverage from the recent meeting of the American College of Cardiology, including sessions on the relationship between heart disease and diabetes and debates on the best approaches to disease prevention. Despite evidence we reported in our last issue that a form of bariatric surgery may be linked to alcohol abuse, the meeting highlighted a study on using surgery to reduce glycated hemoglobin levels in patients who are not technically obese. Finally, our story on the rollout of the Affordable Care Act discusses the impact of state-level decisions on whether to expand Medicaid to those just above the poverty line. We explore what this means for diabetes prevention in different states by speaking with front-line providers in Kentucky and Louisiana, 2 states where governors have staked out very different positions on Medicaid expansion. This issue of *Evidence-Based Diabetes Management* covers a lot of ground, and we welcome your feedback.

Better technology may literally breathe new life into a treatment that had been abandoned, as an FDA advisory panel voted favorably on Afrezza, an inhaled insulin. This treatment was rejected by consumers 7 years ago when a prior delivery system proved unwieldy.

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.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

10282400 K02CAN13080B

janssen

The Big Data Revolution: From Drug Development to Better Health Outcomes?

Andrew Smith

Normal analysis of discrete health data, like blood pressure and cholesterol, identified 5000 patients at risk of developing congestive heart failure.

Automated analysis of doctors' notes and other unstructured information from Carilion Clinic's 8 hospitals turned up 3500 more.[1]

Early treatment should prevent many of those extra cases from ever developing and save the communities of western Virginia hundreds of lives and millions of dollars.

Such efforts to avert the chronic diseases that kill the majority of Americans and consume the majority of their healthcare dollars rank among the most promising medical applications for "Big Data" analysis.

But there are countless others.

An unbelievably large amount of medically useful information is available for study—a century of published studies, decades of insurance claims—and that stock expands every time a doctor completes an electronic medical record or a runner dons a heart-rate monitor.

Software that can find, interpret, and analyze it all may eventually revolutionize healthcare.

A McKinsey & Company analysis, for example, predicts such programs will soon save at least $300 billion a year in American healthcare spending—and possibly much more.[2]

"Why is Big Data emerging in healthcare now? There are really 3 reasons," said McKinsey director Nicolaus Henke. "The first is availability. We have so much more captured, machine-readable data available to us than we did just a few years ago. The second reason is that it's much cheaper and easier to link these data. The third reason is a big imperative to understand population health better…it's important both for outcomes and costs."

Indeed, even with all the limitations in both data and software, would-be innovators are already finding significant ways to use the existing data to improve patient health.

The most famous applications to date lie in taking some of the data that modern life automatically generates about individual activity and reusing it to benefit that individual.

Smartphone applications that tap GPS and clock functionality to track runs have millions of users. Diet applications that use phone cameras and Internet connectivity to help users track what they eat have even more.

Medical practices are using similar tools to help patients.

Billing records have always recorded when patients come in for Papanicolaou tests (Pap smears), but now software sold to gynecologists can automatically look through those records, infer which patients are overdue for another Pap smear, and send reminders to those patients.[3]

Such programs can also look through medical records to see which women began receiving the sequence of shots needed for human papilloma virus vaccination and call to remind them about the next shot.[3]

Applications like that, which use relevant data from each individual to help that same individual, may provide substantial health benefits, but experts see even more promise in tools that use both individual data and collective data, such as the tools that IBM used to predict congestive heart failure (CHF) at Carilion.

Ed Macko

"Traditional models use a handful of medical measurements to predict CHF," said Ed Macko, IBM's chief technology officer for healthcare & life sciences.

"Our systems—after scanning not only structured data but also free-written material from doctors' notes, journals, and other sources—found dozens of relevant factors, including stuff that has rarely been considered before, like whether the patient has a job or someone at home that can provide care during illness."

Such deep analysis allowed IBM's technology to identify 70% more at-risk patients than traditional tools, all while maintaining an estimated 85% accuracy rate that matches prior standards.

And each passing month increases both the number of patients identified and the accuracy of the prediction.

IBM has plenty of competitors, big and small, that want to use Big Data to improve healthcare. The McKinsey report estimates that 200 new companies have already entered the space. Older companies, universities, government agencies, and various nonprofits are also getting into the act.

Erica Mobley

Much of their work resembles the project at Carilion. Its purpose is to predict which people will become chronically ill—be it from CHF, diabetes, chronic obstructive pulmonary disease, drug addiction, or a handful of other problems—and prevent the downward spiral.

"It makes sense to focus here because a relatively small number of very ill people account for a huge percentage of both the suffering and the cost," said Erica Mobley, senior manager at a hospital-monitoring nonprofit called The Leapfrog Group.

"Hospital systems have also focused on using Big Data to expand and improve upon data-driven decision making," said Mobley, who noted that the real analytical pioneers among hospitals tend to be self-insuring university systems that can get a full picture of patients by using complete medical records, drug records, and insurance records.

The University of Pittsburgh Medical Center, for example, announced in 2012 that it was working with outside companies to create an enterprise data warehouse that would draw on more than 200 data sources to provide doctors with individualized care recommendations for particular patients.[4]

"Ever more data, sometimes right down to the genetic level, give hospitals the ability to help staff determine the correct decision in ever more specific situations. These data-driven decisions replace instinct or gut feeling, which studies have generally shown to be little better than raw guesswork."

Big Data is also helping groups like Leapfrog improve their hospital rankings.

When Leapfrog was founded in 2000, hospitals reported so little data on safety that sophisticated analysis was unnecessary. Now, thanks to efforts by Leapfrog and other groups to increase transparency, patients can compare hospitals on issues as specific as the likelihood that the doctors will leave something inside them after surgery or that the staff will give them the wrong type of blood.

To help patients understand how to value all those extra data, Leapfrog (which still wants way more data) now uses sophisticated analytics to weigh the different factors and compile a single letter grade for each facility.

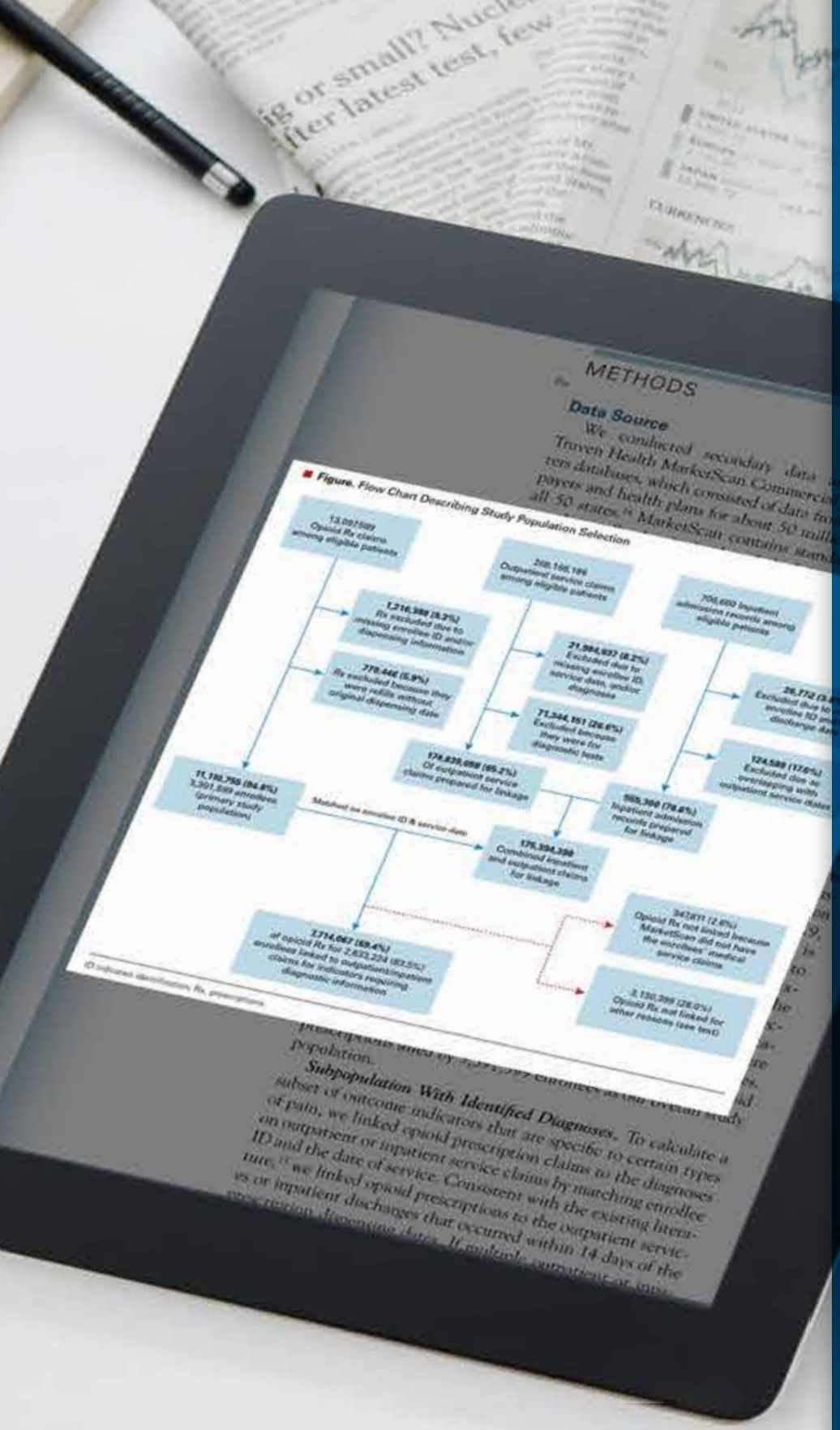
Government agencies have also begun using Big Data to improve healthcare.

The FDA has launched a number of projects that mine and analyze data, including a program called Mini-Sentinel that automatically combs medical databases for signs of drug safety issues that were not detected before approval.

The numbers involved are vast. An FDA report from January revealed that as of July 2012, the Mini-Sentinel system had already collected records of some 3.8 billion medical visits and 3.5 billion dispensations of medication for 160 million Americans.[5]

For all those records, however, questions remain about the reliability of the analysis performed by the current system. A research letter published in January's edition of the *Journal of the American Medical Association*, for example, noted that traditional studies comparing the bleeding risk of warfarin (Coumadin) and dabigatran (Pradaxa) have all found substantially more risk with dabigatran, while Mini-Sentinel found more with warfarin.[6]

Looking forward, the FDA reportedly plans to expand its automatic



A One-Stop App for *Managed Care Professionals*

All our print and digital content in one place!

Access exclusive, original content from the industry's most trusted and most referenced managed care publication, *The American Journal of Managed Care* (*AJMC*). Whether on the road or in the home, managed care news and media are now at your fingertips—whenever you want it!

By downloading the *AJMC* app, you will gain access to exclusive content not seen anywhere else on the Web or in print. In addition to our peer-reviewed research, the app includes:

- In-depth author commentaries
- AJMCTV Peer Exchange videos
- CME resources
- Monthly "Payer Perspectives" Column
- And so much more

AJMC

Tablet Edition

Download to your tablet today!

Available on the App Store

ANDROID APP ON Google play

THE AMERICAN JOURNAL OF MANAGED CARE®

AJMC.com

monitoring system to read sources like Facebook and Twitter for signs of drug safety issues.[7]

Similar techniques have already shown some usefulness. Google, for example, has demonstrated that it can often spot a regional outbreak of flu earlier than health authorities simply by noting the prevalence of flu-related Web searches.

Researchers at Stanford and Columbia, moreover, were able to find a drug interaction the FDA had missed—the tendency of paroxetine (Paxil) and pravastatin (Pravachol) to raise blood sugar when used together—by analyzing tens of millions of search queries.[8]

Amid its efforts to use Big Data to monitor the safety of marketed drugs, the FDA also hopes its collection of drug trial information can help it develop software to better predict the behavior of experimental drugs in the human body.

Agency officials are using their vast archives of data to help build physiologically based pharmacokinetic models to predict drug absorption. Such models may spot potential problems with new drugs and improve the FDA's ability to evaluate them.[9]

Data-driven decisions have replaced instinct or gut feeling, which studies have generally shown to be little better than raw guesswork.

Of course, the FDA's mountain of trial data could prove useful to many health-related analyses, so the agency plans to throw much of it open to outside researchers. FDA officials have launched a resource called the Janus Clinical Trials Repository, designed not only to release terabytes of information but also to make it user friendly.[10]

The FDA is also tapping outside organizations for help.

It funded a Center for Excellence in Regulatory Science and Innovation (CERSI) at the University of Maryland to help it use Big Data (and many other tools) to modernize and improve the review and evaluation of drugs and medical devices.[11]

The CERSI's work on Big Data and healthcare, which includes a recent conference on the subject, nicely complements other efforts by Maryland to collect and harness records, efforts like its Research HARBOR (Helping Advance Research By Organizing Resources) project.[12]

"Assembling databases in useful ways has been very hard work. Claims databases lack the detail that researchers want. Medical records are only just going electronic—and even the electronic records we have are often incomplete and sometimes inaccurate," said Eleanor M. Perfetto, PhD, MS, professor of pharmaceutical health services research at the University of Maryland's School of Pharmacy.

"Still, while there is much work to be done, not only with traditional data sources but also completely new ones such as social media, we are making progress."

Indeed, researchers can access data from insurers such as UnitedHealthcare, government entities such as the United Kingdom's National Health Service, or the companies that make electronic medical record software. There are also data sellers like Humedica that try to link data from several sources to give researchers more holistic views of patient health.

Such data have many uses, but the most valuable, commercially speaking, may be the development of new treatments.

Many device and drug makers think Big Data can significantly improve the success rates of their laboratories and help them bring drugs to market faster, and more of them. Their projects vary widely. Some are monitoring social media, analyzing what people say about their products, and considering that feedback in new designs. Others are using archived medical records to determine the characteristics of target populations and thus improve enrollment criteria for drug trials.

Most of these projects have yet to advance beyond pilot programs and other early-stage initiatives.

The same could be said about virtually all efforts to better healthcare with Big Data. The successes of these efforts, while sometimes impressive, have generally been limited in scope, and many obstacles will hinder attempts to expand them to the system as a whole.

Patient data, as Perfetto said, is sometimes wrong, often sketchy, and almost always stored in dozens of different databases that must be accessed separately, if they can be accessed at all. Territorialism, privacy concerns, and other issues will hinder adequate data assembly. What's more, computer software suffers real limitations in its ability to interpret and analyze the available material.

Big Data failures still outnumber successes, and some very easy sounding analyses still lie outside the realm of possibility.

That said, each week brings news of another promising application for data-parsing software, applications such as ones that help drug development by "reading up" on the nearly endless supply of peer-reviewed articles that have been published over decades of time.

No 1 person—no team of people—could ever read all the relevant studies before choosing a drug target or a promising design, but programmers are "teaching" their computers to understand subject areas such as biology and chemistry and to "read" far more research than humans ever could.

One research hospital, in collaboration with IBM, used software IBM to analyze decades' worth of literature about p53, a protein involved in both normal cell growth and many types of cancer. Using information in those papers about kinases that are known to act on p53, the software created a general understanding of p53-kinase interaction. It then made a list of other proteins mentioned in the literature that were probably kinases that would interact with p53.

Most of the computer's predictions proved accurate.

"This software isn't going to cure cancer yet, but it did make significant new discoveries about a very heavily studied protein, and there is a significant possibility that some of these proteins could be medically useful," said Ying Chen, a research staff member from IBM's Watson Group.

"This technology is ready to make real contributions." **EBDM**

References

1. IBM predictive analytics to detect patients at risk for heart failure [press release]. Armonk, NY: IBM Newsroom; February 19, 2014. http://www-03.ibm.com/press/us/en/pressrelease/43231.wss. Accessed April 30, 2014.

2. Kayyali B, Knott D, Van Kuiken S. The big data revolution in US healthcare: accelerating value and innovation. McKinsey & Company website. http://www.mckinsey.com/insights/health_systems_and_services/the_big-data_revolution_in_us_health_care. Published April 2013. Accessed April 30, 2014.

3. Tracey JK. Big Data and the research HARBOR. Presented at: Leveraging Big Data II: What Does It Mean for Improving Product Development and Health Care? February 11, 2014; University of Maryland School of Pharmacy, Baltimore, MD. http://www.pharmacy.umaryland.edu/centers/cersievents/pdf/presentations/TracyNotes.pdf. Accessed April 30, 2014.

4. UPMC fosters 'personalized medicine' with $100 million investment in sophisticated data warehouse and analytics [press release]. Pittsburgh, PA: University of Pittsburgh Medical Center; October 1, 2012. http://www.upmc.com/media/newsreleases/2012/Pages/upmc-personalized-medicine-investment.aspx. Accessed April 30, 2014.

5. Mini-Sentinel Data Score: Mini-Sentinel Distributed Database Year 3 Summary Report. Mini-Sentinel website. http://www.mini-sentinel.org/work_products/Data_Activities/Mini-Sentinel_Year-3-Distributed-Database-Summary-Report.pdf. Published July 2012. Accessed April 30, 2014.

6. Sipahi I, Celik S, Tozun N. A comparison of results of the US Food and Drug Administration's Mini-Sentinel program with randomized clinical trials: the case of gastrointestinal tract bleeding with dabigatran. *JAMA Intern Med.* 2014;174(1):150-151.

7. Karlin S. Adverse events in social media: FDA expects Signal Detection Revolution. The Pink Sheet. http://www.pharmamedtechbi.com/publications/the-pink-sheet/76/4/adverse-events-in-social-media-fda-expects-signal-detection-revolution. Published January 27, 2014. Accessed April 30, 2014.

8. Markhoff J. Unreported side effects of drugs found using data, study finds. *The New York Times.* March 7, 2013. http://www.nytimes.com/2013/03/07/science/unreported-side-effects-of-drugs-found-using-internet-data-study-finds.html. Accessed April 30, 2014.

9. Florian J. FDA use of Big Data in modeling and simulations. Presented at: Leveraging Big Data II: What Does It Mean for Improving Product Development and Health Care? February 11, 2014; University of Maryland School of Pharmacy, Baltimore, MD. http://www.pharmacy.umaryland.edu/centers/cersievents/pdf/presentations/FlorianNotes.pdf. Accessed April 30, 2014.

10. Rosario L. Janus Clinical Trials repository: an update and insights into future directions. Presented at: Leveraging Big Data II: What Does It Mean for Improving Product Development and Health Care? February 11, 2014; University of Maryland School of Pharmacy, Baltimore, MD. http://www.pharmacy.umaryland.edu/centers/cersievents/pdf/presentations/RosarioNotes.pdf/. Accessed April 30, 2014.

11. Center of Excellence in Regulatory Science and Innovation website. University of Maryland. http://cersi.umd.edu/. Accessed April 30, 2014.

12. Clinical and Translational Sciences Institute website. University of Maryland. http://medschool.umaryland.edu/ctsi/harbor.asp. Accessed April 30, 2014.

Medicaid Expansion Choices Mean Different Care for Poor Diabetics, Depending on Where They Live

Peter Page

Patients with diabetes, and public health efforts to combat the rising incidence of the disease, have starkly different prospects in states that have expanded Medicaid eligibility under the Affordable Care Act (ACA) compared with patients and programs in states that do not.

The 2012 US Supreme Court ruling that generally upheld the constitutionality of the ACA struck down a provision penalizing states that do not expand Medicaid to all adults earning no more than 133% of the federal poverty level, plus 5% set aside for cost sharing, which came to $15,415 for an individual or $26,344 for a family of 3 in 2012. If expanded to all 50 states, Medicaid would be covering an additional 21.3 million people by 2022, a 41% increase compared with Medicaid before passage of the ACA. Almost all the newly eligible are adults.[1]

Nearly half the states,[2] including 7 of the 10 reporting the highest diabetes prevalence to the CDC in 2012, have chosen to not expand Medicaid.[3] A Harvard study found that, among many health consequences, these state-level decisions mean that more than 400,000 diabetics will not get care they could otherwise receive.[4]

The ACA allocates to states 100% federal funding to expand Medicaid, a change that took effect January 1, 2014. Federal funds will continue paying the entire cost of the expansion through 2017, and 90% of the cost thereafter. Arguments against expanding Medicaid have been a mix of concern about long-term costs and an expressed philosophy that government programs should not grow. Most states where Medicaid did not immediately expand have Republican governors—1, Arkansas, has a Democratic governor and a Republican legislature, and had a protracted debate toward a "private option" that has allowed new Medicaid recipients to use federal funds to purchase private insurance.[5]

Representative of the Republican governors opposing Medicaid expansion is Bobby Jindal of Louisiana, who claims to be the first governor to do so. His op-ed in *The Times Picayune* of New Orleans stated that Medicaid expansion would have cost Louisiana taxpayers $1.7 billion over 10 years. "Expansion would result in 41% of Louisiana's population being enrolled in Medicaid. We should measure success by reducing the number of people on public assistance. But the Left has been very clear: their goal is to transform all healthcare in America into government-run healthcare," he wrote.[6]

Louisiana Governor Bobby Jindal

Across the nation, the Medicaid provision would have expanded coverage to 16 million adults previously excluded. The decision by some states not to expand means that 3.6 million people will remain uninsured, and the affected states will not receive $8.4 billion in federal payments.[7]

The Harvard study, "Opting Out of Medicaid Expansion: The Health and Financial Impacts," determined that state-level decisions to not expand Medicaid will result in 422,553 diabetics not receiving medication. Also, 712,037 persons with undiagnosed depression will not receive mental health screening, an estimated 240,700 individuals will suffer catastrophic medical expenditures that otherwise would have been covered, 195,492 women aged 50 to 64 years will not receive mammograms, and 443,677 women aged 21 to 64 years will not receive the Papanicolaou test (Pap smear). Full expansion "would have resulted in an additional 658,888 women in need of mammograms gaining insurance, as well as 3.1 million women who should receive regular Pap smears," the study found.[4]

Most sobering of all, the study projected between 7115 and 17,104 deaths attributable to the lack of Medicaid expansion in opt-out states.[4] In Florida, where Republican governor Rick Scott called for a limited expansion of Medicaid[8] but faced resistance from the legislature, the media has reported on the death of a young uninsured woman from a diagnosed heart condition she could not afford to have treated.[9]

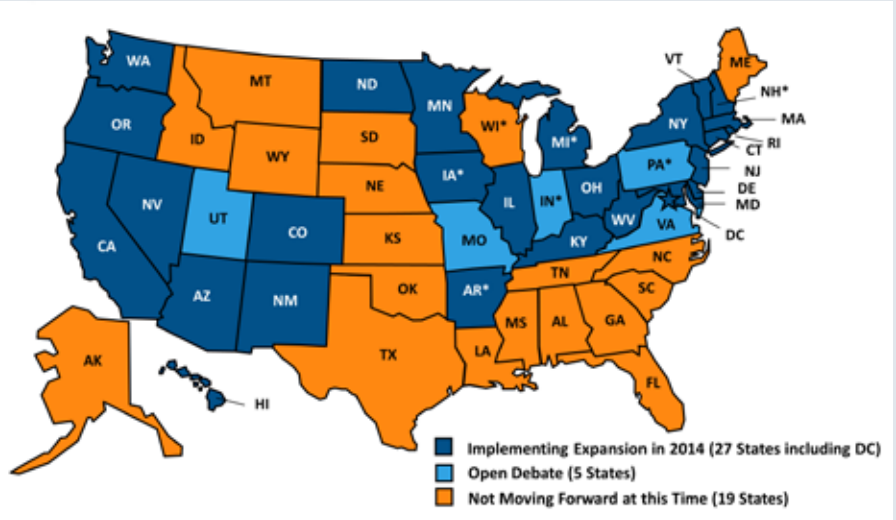
Krista Maier, associate director of public policy for the American Diabetes Association, noted that states declining to expand Medicaid are effectively closing off health insurance to some of their poorest residents. The ACA assumed everyone earning 133% or less of the federal poverty level would be enrolled in Medicaid, so the law does not provide tax credits to purchase insurance on exchanges to persons earning less than 100% of the federal poverty level.[4]

"We fully support states accepting the federal funding; otherwise the poorest people have no viable option for acquiring," she said.

The states with the most restrictive income eligibility for Medicaid still must enroll the poor who become disabled, Maier noted.

"When you can't afford the care to manage your disease, you scale back the care. Without adequate care, you increase risk of complications," she said. "The states that don't expand Medicaid are, essentially, waiting for the person to become so sick they are disabled to be eligible. If they expanded eligibility these people could receive care before they are disabled."

Figure 1. Current Status of State Medicaid Expansion Decisions, 2014



Source: Kaiser Family Foundation. Data current as of March 26, 2014.

A Movement Toward Prevention

According to the Trust for America's Health and the Robert Wood Johnson Foundation,[10] the 10 states with prevalence of type 2 diabetes mellitus (T2DM) above 11% are West Virginia, Mississippi, Alabama, Louisiana, Tennessee, Ohio, South Carolina, Oklahoma, Florida, and Arkansas. Louisiana, Alabama, and Mississippi each top 12%, while West Virginia has the unwanted first place spot with 13%. Of the 10 states, only West Virginia, Ohio, and Arkansas are expanding Medicaid.[2]

Under current cost-sharing formulas, Medicaid expansion is a bargain for the states. A study by the Kaiser Family Foundation calculated that if every state expanded Medicaid, cumulative state Medicaid spending would increase by $76 billion from 2013 to 2022, while federal Medicaid spending would increase by $952 billion. Some states would enjoy decreases in Medicaid spending while states with the largest populations of poor, uninsured people would shoulder "relatively small increases in spending."[1]

While expanding Medicaid appears inexpensive for states, studies show that refusing the influx of federal funds is costly. Texas, the largest opt-out state, would have to spend $15 billion over 10 years as its portion of increased Medicaid spending, but the state, local governments, and hospitals will spend about that much anyway on adult healthcare that would be covered by Medicaid, if expanded. Local taxpayers across the Lone Star State already spend $2.5 billion for indigent care, inpatient hospital care for jailed individuals, and charity care, most of which

the expansion would cover. Texas hospitals write off $1.8 billion in unreimbursed charity care, some of which funds individuals that Medicaid would cover under an expansion.[11]

Kentucky, with a 10.7% diabetes prevalence, is expanding Medicaid. An analysis commissioned by the Cabinet for Health and Family Services found, aside from "tremendous benefits for the health of hundreds of thousands of Kentuckians," that "It would cost Kentucky more" to not expand Medicaid eligibility than to accept the fede ral money. The analysis, done by PriceWaterhouseCooper and the University of Kentucky, concluded that expanding Medicaid would pump $15.6 billion into the state economy between this year and 2021, create 17,000 new jobs, and have a net positive impact on state and local government budgets of $802 million over the same period. The report estimated the cost of care for Kentucky's uninsured population at $1.1 billion annually, with costs spread to government, hospitals, public clinics, and patients or their unpaid doctors.[12]

Governor Steve Beshear has decried Kentucky's poor health statistics as not only morally unacceptable but also as a barrier to lifting large portions of the commonwealth out of poverty.[13] The state ranks first among the 50 states in mortality and at or near the top for mortality from cancer, where it ranks first; cardiovascular disease, where it ranks fourth; heart disease, where it ranks fifth; and stroke, where it ranks twelfth. Kentucky is 50th among the states in per capita income and 5th in percent of the population earning under the federal poverty level. Prior to Medicaid expansion, 600,000 residents lacked health insurance.[9,10] Diabetes prevalence among adults in Kentucky has tripled from 3.5% in 1995 to 10.7% of the population in 2012, said Theresa Renn, coordinator of the state's Diabetes Prevention and Control program.

Kentucky Governor Steve Beshear

Diabetes is a costly disease to treat. Medicaid spending on persons with diabetes averages $14,229, versus $4568 on those without diabetes.[14]

"We know many people have diabetes many years before diagnosis and diabetes prevalence tends to be higher in the Medicaid population, so Medicaid expansion will probably increase the number of people we see, but the number of hospitalizations and complications will go down," Renn said.

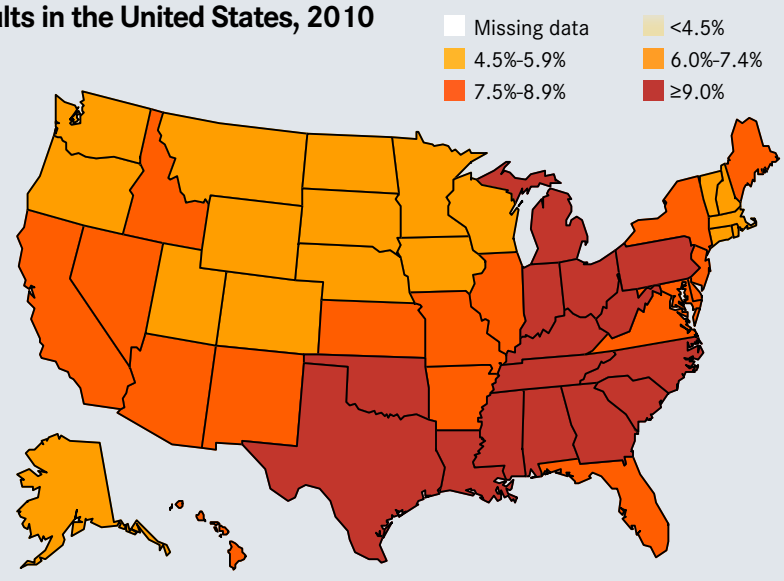
The ACA contains several provisions to encourage state Medicaid programs to reimburse for diabetes screening, prevention, care, and treatment.[3] John Langefeld, MD, medical director of the Kentucky Department of Medicaid Services, said in an e-mail that the state is exploring how to utilize incentives within the ACA to expand prevention services for diabetes and other chronic diseases.

"Medically necessary services related to diabetes along with other chronic conditions are covered by Medicaid. The Kentucky Department for Medicaid Services has had discussions with the MCOs (managed care organizations) regarding DPPs (diabetes prevention programs). There is interest in supporting this initiative; however, currently there are limited examples of DPP deployment in Medicaid populations. The active discussion is around potentially starting a pilot program. The MCOs are actively monitoring chronic conditions—including diabetes—from a quality-of-care and outcomes standpoint, and we also are actively discussing how to establish a diabetes registry."

Renn, whose entire career has been focused on caring for people with diabetes, said there is great interest in Kentucky in bringing much greater public health resources to bear on prediabetes.

"Diabetes education is a huge help, but often not well reimbursed," she said. "Medical nutrition training is another, helping people learn what they can eat to keep their blood sugar under control. We have great interventions coming along for people who are at high risk, but you need screening to find them. There are evidence-based approaches we can employ. Tackling prediabetes is a whole new world."

Figure 2. Age-Adjusted Prevalence of Diagnosed Diabetes Among Adults in the United States, 2010



Source: CDC's Division of Diabetes Translation. National Diabetes Surveillance System http://www.cdc.gov/diabetes/statistics.

Where Is Public Opinion?

Governors in Southern states with high rates of diabetes who decline to expand Medicaid may run into evolving public opinion on this portion of the ACA. In late April, the Kaiser Family Foundation and *The New York Times* released a poll that showed despite continued distrust among Southerners for the term "Obamacare," there appears to be support for Medicaid expansion, even in states where it has faced resistance from elected officials.[15]

The poll was conducted April 8 to 15, 2014, in Kentucky, North Carolina, Louisiana, and Arkansas. (North Carolina has not expanded Medicaid.) All 4 states have competitive United States Senate races where residents have seen advertising about the ACA.

In Kentucky, Louisiana, and North Carolina, sizable segments of the population did not know whether their states had expanded Medicaid, which is consistent with earlier Kaiser polling that revealed much of the population is confused about the new law.[16] In Kentucky, 45% were unsure about expansion or did not answer; in Louisiana the share was 36%, and in North Carolina it was 39%. When asked whether their states *should* expand Medicaid, 52% in Louisiana and 54% in North Carolina said yes, compared with the 40% in Louisiana and 36% in North Carolina who preferred to "keep Medicaid as it is today."[15]

Arkansas respondents received different questions; 52% favored expanding "government programs like Medicaid to cover more low-income people," while 23% favored the use of government funds "to purchase private health insurance for low-income people through the new healthcare marketplace." Only 7% said "the state shouldn't do anything to help low-income people get health insurance."[15]

Jindal faces term limits in 2015. Should Louisiana's next governor expand Medicaid, it has a model community healthcare program to deliver diabetes care. The Greater New Orleans Community Health Connection, known by its acronym GNOCHC (pronounced like the round pasta), was created with a Medicaid waiver to deliver care after Hurricane Katrina. The program grants Medicaid to otherwise uninsured people making no more than the federal poverty level, which is $1963 per month for a family of 4. The program pays for primary and mental healthcare visits with no out-of-pocket costs at 40 community health centers.

"It really is community-based healthcare," said Susan Todd, executive director of 504HealthNet, which takes its name from the region's area code, and is among 18 healthcare nonprofits that make up GNOCHC. The well-functioning network already features an electronic health record system called for by the ACA, and is ready to expand if Medicaid does.

"Three years ago, after passage of the ACA but before the Supreme Court ruling, we were preparing for Medicaid expansion," Todd said. "I think it will come, eventually, and we have a program we can scale up when it does." **EBDM**

References

1. Holahan J, Buettgens M, Carroll C, Dorn S; the Urban Institute. The cost and coverage implications of the ACA Medicaid expansion: national and state-by-state analysis. Kaiser Family Foundation website. http://kaiserfamilyfoundation.files.wordpress.com/2013/01/8384.pdf. Published November 1, 2012. Accessed April 9, 2014.

2. How will the uninsured fare under the Affordable Care Act? Kaiser Family Foundation website. http://kff.org/health-reform/fact-

sheet/how-will-the-uninsured-fare-under-the-affordable-care-act/. Published April 7, 2014. Accessed April 15, 2014.
3. Diabetes Report Card 2012. CDC website. http://www.cdc.gov/diabetes/pubs/pdf/diabetesreportcard.pdf. Published 2012. Accessed April 19, 2014.
4. Dickman S, Himmelstein D, McCormick D, Woolhandler S. Opting out of Medicaid expansion. *Health Affairs Blog*. http://healthaffairs.org/blog/2014/01/30/optingoutofmedicaidexpansionthehealthandfinancialimpacts/. Published January 30, 2014. Accessed April 19, 2014.
5. DeMillo A. Arkansas house approves private option funding. Associated Press. http://www.arkansasbusiness.com/article/97474/house-approves-private-option-funding?page=all. Published March 4, 2014. Accessed April 24, 2014.
6. Jindal B. Why I opposed Medicaid expansion. *The Times Picayune*. http://www.nola.com/opinions/index.ssf/2013/07/gov_bobby_jindal_why_i_opposed.html. Published July 23, 2013. Accessed April 21, 2014.
7. Price CC, Eibner C. For states that opt out of Medicaid expansion: 3.6 million fewer insured and $8.4 billion less in federal payments. *Health Aff*. 2013;32(6):1030-1036.
8. Governor Rick Scott: We must protect the uninsured and Florida taxpayers with limited Medicaid expansion [press release]. Tallahassee, FL: Office of the Governor; February 2, 2013. http://www.flgov.com/2013/02/20/governor-rick-scott-we-must-protect-the-uninsured-and-florida-taxpayers-with-limited-medicaid-expansion/. Accessed April 21, 2014.
9. Manes B. The perils of Florida's refusal to expand Medicaid. *Orlando Weekly*. http://orlandoweekly.com/news/theperilsoffloridas-refusaltoexpandmedicaid1.1665144. Published April 9, 2014. Accessed April 14, 2014.
10. Trust for America's Health. A healthier American 2013: strategies to move from sick care to healthcare in the next 4 years. Robert Wood Johnson Foundation website. http://www.rwjf.org/content/dam/farm/reports/reports/2013/rwjf403989. Published January 2013. Accessed April 21, 2013.
11. Caffrey MK. Leveraging healthcare reform to combat a history of cancer: Kentucky to expand Medicaid, increase clinical trials as U of K Markey Center gains NCI status. *Am J Manag Care*. 2013:19(SP6)SP212-SP218.
12. Hamilton B. Expanding Medicaid in Texas: smart, affordable and fair. Texas Impact and Methodist Healthcare Ministries of South Texas Inc. http://www.mhm.org/images/stories/advocacy_and_public_policy/Smart%20Affordable%20and%20Fair_FNL_FULL.pdf. Published January 2013. Accessed April 14, 2014.
13. Kentucky Cabinet for Health and Family Services. Analysis of the Affordable Care Act (ACA): Medicaid expansion in Kentucky. http://governor.ky.gov/healthierky/Documents/MedicaidExpansionWhitePaper.pdf Published October 2012. Accessed April 14, 2014.
14. Garfield RL, Damico A. Medicaid expansion under health reform may increase service use and improve access for low-income adults with diabetes. *Health Aff*. 2012;(1):159-167.
15. Hamel L, DiJulio B, Firth J, Brodie M. New York Times Upshot/Kaiser Family Foundation polls in four Southern states. Kaiser Family Foundation website. http://kff.org/other/poll-finding/new-york-times-upshotkaiser-family-foundation-polls-in-four-southern-states/. Published April 24, 2014. Accessed April 25, 2014.
16. Caffrey MK. Kathleen Sebelius' name isn't on any ballot, but make no mistake, this is her campaign. *Am J Account Care*. 2014;2(1):28-32.

The Yin and the Yang of CV Risks in Patients With Diabetes

Surabhi Dangi-Garimella, PhD

Back in 2007, a paper published in the *New England Journal of Medicine* based on the observations of Steven Nissen, MD, Cleveland Clinic, identified a significant increase in the risk of myocardial infarction (MI) in patients administered rosiglitazone (Avandia), a thiazolidinedione made by GlaxoSmithKline (GSK) that was then widely used to treat patients with type 2 diabetes mellitus (T2DM).[1] The study also observed a slightly increased risk of death from cardiovascular events.


Steven Nissen, MD

Avandia, originally approved by the FDA in 1999,[2] was a top-selling drug in 2006 with net sales of nearly $3 billion, before the risks were identified.[3] In 2010, regulatory agencies in the United States as well as Europe announced the limited availability of Avandia for use in treating diabetes. While the European Medicines Agency (EMA) completely banned the sales of the drug,[4] the FDA limited its use by requiring GSK to develop a restricted access program under a Risk Evaluation and Mitigation Strategy, whereby Avandia would only be available to T2DM patients as a last resort when all other drugs have failed to regulate their glycemic levels.[5]

Following the FDA decision, Nissen expressed relief that the decision brought an end to "one of the worst drug safety tragedies in our lifetime."[6] He believes the drug is far too dangerous to use in diabetes treatment based on more than 50 studies that have linked Avandia to an elevated risk of heart attack.[3] However, in a surprising move last year, the FDA convened a 26-member panel to loosen restrictions on prescription of Avandia. The result: half of the advisory committee voted in favor of softening the restrictions, and GSK vowed to work with the FDA to implement potential changes.[7]

In an article that was published in the September 2013 issue of *Evidence-Based Diabetes Management* on the roller coaster treatment of Avandia by the FDA, G. Alexander Fleming, MD, president and CEO of the healthcare consulting firm Kinexum and a former FDA regulator, recalled Nissen's evaluation, stating: "While the medical community was given the impression with his meta-analysis that the drug was dangerous, to be fair, the meta-analysis was incomplete and heavily criticized by statisticians, but that didn't matter in the ensuing public controversy. Things became politicized and the debate was no longer based on science."[8]

In a press release late in 2013, the FDA announced that it had removed certain restrictions on prescribing the drug based on newer meta-analysis that showed a lower risk of heart attack or death in patients taking Avandia versus patients taking standard diabetes medications. Although the FDA requires GSK to work with physicians and train them on the current knowledge on the associated CV risks, GSK is no longer required to conduct a postmarketing clinical trial comparing Avandia with Actos (the only other approved thiazolidinedione, manufactured by Takeda) and other standard diabetes drugs.[9]

Avandia though, seems to have lost the battle. In an e-mail response, Heidi Siegel, director of external communications at GSK, said about the company's plans to "relaunch" the drug, "We are not planning to promote Avandia in the United States. We believe it is important for patients and their healthcare providers to have a range of options to treat diabetes, and Avandia (rosiglitazone) will continue to be an option for physicians."

Heart Failure in Patients With Diabetes

Hospital admission for heart failure is a very common complication of diabetes, since glycemic exposure has been found to be strongly associated with the risk of developing microvascular and macrovascular complications.[10] Arterial damage, which can lead to a heart attack or stroke, is a major threat among individuals with diabetes. High blood sugar levels can increase blood pressure, body weight, and cholesterol levels. Together, these factors promote arterial disease.[11]

According to the American Heart Association, heart disease and stroke are the primary causes of death and disability among patients with T2DM, and 60% of patients with diabetes die from some form of heart disease or stroke. Patients with T2DM are also 2 to 4 times more likely to suffer from heart disease or stroke than those without diabetes (**Figure**).[12] Improved glycemic control could substantially reduce the risk of CV events, assuming that lowering of glucose levels would, in the long term, result in fewer microvascular and macrovascular events.

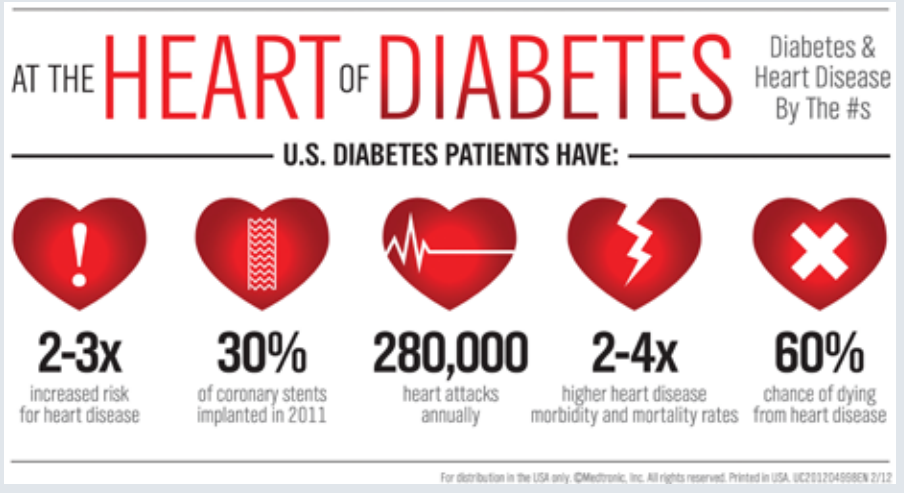
Considering these preexisting complications in patients with diabetes, the added risk of a blood glucose–lowering drug causing CV events would be a big no-no. Following the initial rosiglitazone debacle, both the FDA and EMA issued new guidance to ensure CV safety of newer therapeutic options for diabetes under development. A consequence of these guidelines was the inclusion of the major adverse cardiovascular events (MACEs) as the primary outcome of a number of safety trials. MACE has been defined as a composite of cardiovascular death, myocardial infarction, or stroke, along with other end points, such as hospital admission for acute coronary syndrome. Additionally, experts in the field recommend including hospital admission for heart failure as a prespecified component of MACE.[10]

Markers for Increased CV Risk

A recently published study identified serum markers as strong predictors of an increased risk of CV events. This trial, which enrolled 352 South Asian patients with T2DM, found that the levels of a serum immunoglobulin (cFLC) were significantly elevated in 8% of patients with CV disease events over a 2-year follow-up period. Results indicate that cFLC could be used as a marker for adverse CV events.[13]

A recent study of 12,000 patients with T2DM from the SAVOR-TIMI 53 trial was presented at the 63rd annual meeting of the American College of Cardiology held in Washington, DC (**complete coverage on pages SP245-SP250**). The trial found that, regardless of baseline risk, a substantial share of stable patients with this disease have signs of ongoing myocardial damage or hemodynamic stress. These conditions were strongly associated with later risk of death from MI. For enrolled patients, biomarkers measured in the study were high-sensitivity troponin, NT-proBNP, and hsCRP. Researchers found a stepwise increase in rates of CV death and MI with higher quartiles of each biomarker.[14]

Figure. Research Shows a Strong Relationship Between Diabetes and Heart Disease



Source: Medtronic Inc; http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-imagelibrarybu.

Recent Trends With the Newer Therapies

According to the *Lancet* paper, heart failure, stroke, and MI were quite common among patients participating in the recent large-scale clinical trials that evaluated Actos and Onglyza (a DPP-4 inhibitor by BMS/AstraZeneca). Another trial that evaluated Nesina (Takeda Pharmaceuticals) also found a trend toward increased CV risk.[10] With this knowledge, physicians should monitor their diabetic patients for CV events, especially those with a preexisting risk, who are administered these drugs.

Hypoglycemia and Heart Rhythm

Contradicting the preexisting knowledge about the relation between diabetes and heart health, scientists found that hypoglycemia in patients with diabetes could result in irregular heart rhythms. The study conducted among patients in the United Kingdom continuously monitored glucose levels and electrocardiograms for a week in older T2DM patients with a history of CV disease. This was more commonly observed as patients slept at night, when glucose levels dropped to low levels for several hours, during which period a markedly slower heart rate and abnormal heartbeats were observed.[15]

Complementing this observation about CV risks is a recent editorial published in the *American Family Physician*, highlighting the hierarchical importance of various interventions for improved control of CV risks. The editorial points out that smoking cessation, blood pressure control, metformin treatment, and lipid level reduction (in that order) would be more beneficial than glycemic control in patients with CV risk, specifically noting recent evidence that tight glucose control can be harmful. "It's not to say that blood sugar is not important at all, but there are other much more important interventions," according to the lead author on the editorial, Deborah R. Erlich, MD, of the Tufts University School of Medicine.[16]

Meanwhile, *preventive* wellness programs abound. Aetna, in collaboration with a Toronto-based company called Newtopia, has launched a metabolic syndrome (a condition that increases the chances of developing diabetes, stroke, or coronary artery disease) reduction program as part of its overall wellness program to help its employees develop personalized lifestyle plans (**see page SP260**). Newtopia is a personalized health company that employs next-generation approaches such as developing individualized lifestyle plans based on genetic testing and behavioral science, as well as assigning personal coaches. The pilot program will initially be delivered to 500 Aetna employees who will be monitored for 1 year.[17] **EBDM**

References

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:2457-2471.

2. Drugs@FDA: FDA approved drug products. FDA website. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed April 29, 2014.

3. Thomas K, Tavernise S. F.D.A. to reconsider restrictions on diabetes drug. *The New York Times*. June 2, 2013. http://www.nytimes.com/2013/06/03/business/second-thoughts-on-safety-of-avandia-stir-a-dispute.html?pagewanted=all&_r=0.

4. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim [press release]. London, UK: European Medicines Agency; September 23, 2010. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp&mid=WC0b01ac058004d5c1.

5. FDA significantly restricts access to the diabetes drug Avandia [press release]. Silver Spring, MD: FDA; September 23, 2010. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm226975.htm.

6. Harris G. F.D.A. to restrict Avandia, citing heart risk. *The New York Times*. September 30, 2010. http://www.nytimes.com/2010/09/24/health/policy/24avandia.html.

7. Tavernise S, Thomas K. F.D.A. vote is minor victory for troubled diabetes drug. *The New York Times*. June 6, 2013. http://www.nytimes.com/2013/06/07/business/fda-advisers-vote-to-lift-restrictions-on-avandia.html?_r=0.

8. Regan TL. FDA "Mea Culpa" part of a cautionary tale. *Am J Manag Care*. 2013;19(SP7):SP242-SP243.

9. FDA requires removal of certain restrictions on the diabetes drug Avandia [press release]. Silver Spring, MD: FDA; November 25, 2013. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm376516.htm.

10. McMurray JJV, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored [published online March 13, 2014]. *Lancet Diabetes Endocrinol*. doi:10.1016/S2213-8587(14)70031-2.

11. Diabetes and your risk of heart disease. InteliHealth website. http://www.intelihealth.com/article/diabetes-and-your-risk-of-heart-disease. Accessed April 30, 2014.

12. Cardiovascular disease & diabetes. American Heart Association website. http://www.heart.org/HEARTORG/Conditions/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313865_Article.jsp. Accessed April 30, 2014.

13. Bellary S, Faint JM, Assi LK, et al. Elevated serum free light chains predict cardiovascular events in type 2 diabetes [published online April 17, 2014]. *Diabetes Care*. doi:10.2337/dc13-2227.

14. Scirica B, Bhatt D, Braunwald E. Prognostic implications of simultaneous biomarker assessments in patients with type 2 diabetes mellitus: observations from the SAVOR-TIMI 53 trial. *JACC*. 2014;63(12, suppl A):Abstract 1121-1337.

15. Hypos at night linked to heart rhythm problems in type 2 diabetes patients. Diabetes.co.uk. website. http://www.diabetes.co.uk/news/2014/apr/hypos-at-night-linked-to-heart-rhythm-problems-in-type-2-diabetes-patients-93716304.html. Published April 23, 2014. Accessed April 28, 2014.

16. Busko M. Give us a hand! focus first on CVD risk in diabetes. Medscape website. http://www.medscape.com/viewarticle/822132. Published March 18, 2014. Accessed April 30, 2014.

17. Aetna announces new metabolic syndrome risk-reduction pilot program with Newtopia [press release]. Hartford, CT: Aetna; October 10, 2013. http://newshub.aetna.com/press-release/products-and-services/aetna-announces-new-metabolic-syndrome-risk-reduction-pilot-prog.

Stem Cells Create a Therapeutic Niche

Surabhi Dangi-Garimella, PhD

Stem cell therapy has gained increasing traction in various therapeutic areas, from diabetes to cancer to ocular regeneration. Although the use of embryonic stem cells is controversial, remarkable research in the field of adult induced pluripotent stem cells (iPSCs) has highlighted the tremendous potential of this unique treatment in development and regeneration. Additionally, understanding how stem cells function would improve our insight into various diseases—to fathom "what went wrong."

Distinct from other cell types, stem cells have the ability to undergo cell division and replicate, even after dormancy.

Globally, patients are actively being recruited to participate in clinical trials of these regenerative therapies. A biotechnology company, Advanced Cell Technology, is testing human embryonic stem cell (hESC)-derived retinal cells for 2 different eye diseases: Stargardt's macular dystrophy,[1] which is a form of juvenile macular degeneration, and age-related macular degeneration.[2] These are primarily phase 1 and 2 safety and efficacy trials, and a preliminary report published in early 2012 did not observe any safety issues with the therapy.[3] Hematopoietic stem cells (HSCs), isolated from the bone marrow or umbilical cord blood, have been widely used to treat blood cancers and other blood disorders for a while now. Osiris Therapeutics, based out of Columbia, Maryland, is currently conducting phase 2 trials using human mesenchymal stem cells (MSCs) to repair heart tissue following a heart attack, repair lung tissue in chronic obstructive pulmonary disease patients, and protect pancreatic beta cells in patients with newly diagnosed type 1 diabetes mellitus (T1DM).[4]

Researchers at the Joslin Diabetes Center, an affiliate of Harvard Medical School, believe that stem cells have tremendous potential for treating many diseases, including T1DM and type 2 diabetes mellitus (T2DM). The current research at the institute is geared toward generating insulin-producing stem cells for islet transplant and regenerative medicine to repair tissue damage associated with long-term diabetes.[5]

Table. Stem Cell Therapies Under Development for Diabetes Mellitus

Company	Product	Stem Cell Type	Clinical Stage
Athersys	MultiStem	Adult-derived	Preclinical (immune modulation)
Mesoblast	MPCs	Adult-derived	Phase 2a
Osiris	Grafix	Adult MSCs	Approved for wound healing
	Prochymal	Adult MSCs	Phase 3
ViaCyte	VC-01	hESCs	Pre-clinical

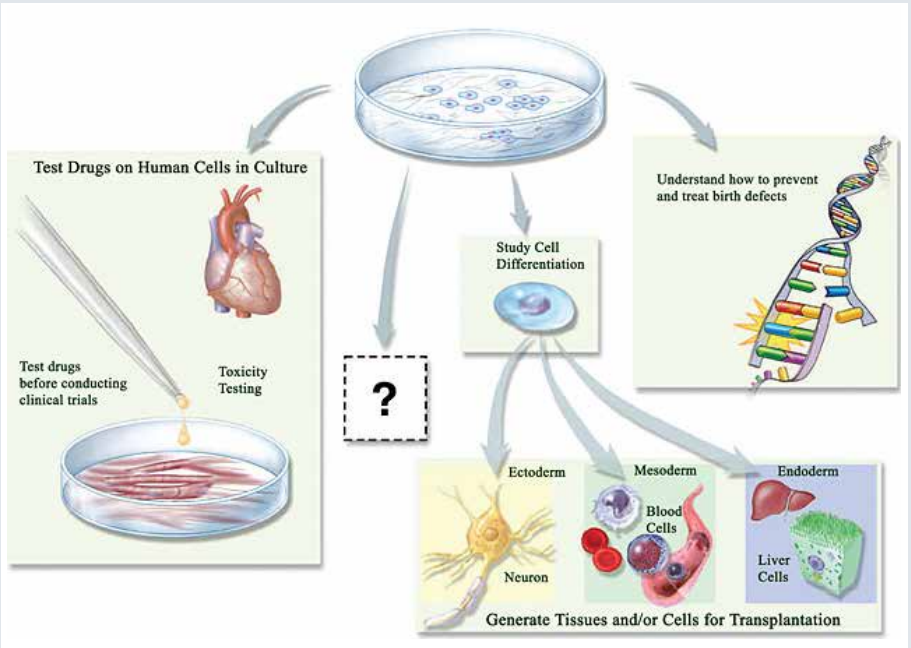
hESC indicates human embryonic stem cell; MPC, mesenchymal precursor cell; MSC, mesenchymal stem cell.
Sources: http://www.athersys.com/, http://www.mesoblast.com/, http://www.osiris.com/, www.viacyte.com.

The Basics

Stem cells, during early stages of development (in infants and children), have the unique potential to develop into any cell type, a property defined as "pluripotency." Additionally, stem cells, even in adults, have "regenerative" potential, which helps them replenish damaged tissues and organs. These cells present distinct behavior depending on their site or location in the body, and they respond to specific environmental cues. For example, stem cells in the gut and HSCs regularly divide to repair and replenish worn-out tissues, while stem cells in organs like the pancreas or the heart divide only under specific conditions.[6]

Distinct from other cell types, stem cells have the ability to undergo cell division and replicate, even after dormancy. Additionally, following specific cues, they can be prompted to differentiate into tissue- or organ-specific cells with special functions.[6] Although every human organ (except nerve cells) can undergo repair by stem cells, the process dwindles with age, or is quite inactive in some organs and tissues.[7] Most of the current research, independent of the therapeutic area, is geared toward understanding the stimuli that activate/reactivate stem cells to allow for age- or disease-related tissue damage.

Figure 1. The Tremendous Potential Offered by Stem Cell Research[10]



Types of Stem Cells

The human body is primarily the source of 2 types of stem cells: *embryonic stem cells* and *adult* or *somatic stem cells*. hESCs are derived from embryos that remain unused following in vitro fertilization, following the informed consent of the donor.[6] These cells need specific signals to differentiate to the required cell type, but they run the risk of developing into a tumor if injected directly.[8] Thus, in addition to the associated ethical issues, tumor formation and transplant rejection are some of the barriers faced with hESCs.[9]

The use of adult stem cells, such as HSCs, does not involve any ethical issues, and when obtained from the recipient, the cells are not susceptible to immune rejection. An adult stem cell—an undifferentiated cell that exists among differentiated cells in a tissue or organ—is capable of generating the cell types of the tissue in which it resides, and maybe unipotent or multipotent. The field is burgeoning, and there is tremendous excitement among researchers to use adult stem cells in therapy. While HSCs have long been used in stem cell transplants, MSCs (non-HSCs) can generate cartilage, bone, and fat cells to form blood and fibrous connective tissue (**Figure 1**).[6]

Exciting, albeit controversial, results of human cloning were recently published in the journal *Cell Stem Cell* following collaborative research conducted by scientists at the CHA Stem Cell Institute in Seoul, Korea, the Research Institute for Stem Cell Research (a part of the CHA Health Systems), and the company Advanced Cell Technology. The scientists "reprogrammed" an egg cell by removing its DNA and replacing it with nuclei from 2 adult donors aged 35 years and 75 years. The experimental procedures could successfully generate 2 karyotypically normal diploid ESC lines. This technique had previously been developed, but with infant/fetal donor cells, which, unlike adult cells, are not associated with age-related changes such as shortened telomerases and oxidative DNA damage.[10]

A company called ViaCyte, which partners with Johnson & Johnson Development Corporation among others and is funded by the California Institute of Regenerative Medicine, has developed an implantable device by fusing stem cell engineering with biotechnology. The company has developed a patented process to reproducibly differen-

tiate hESCs into pancreatic endoderm cells, using specific types and amounts of growth factors, growth media, and supplements.[11] Following subcutaneous implantation in individuals with diabetes, the cells are expected to mature into functional beta cells, a technique that proved promising in an animal model.[12] The company hopes to initiate phase 1/2a trials this year and also file for an investigational new drug application.


Rohit Kulkarni, MD, PhD

iPSCs

Extracting and then maintaining adult stem cells in the laboratory is extremely difficult, as they have a limited capacity to divide in culture.[6] The discovery of the "transdifferentiation" process of adult stem cells, wherein adult stem cells are subjected to certain differentiation techniques to generate cell types different from the predicted types, was therefore very exciting.[9] Taking the process a step further, researchers in Japan developed a technique to reprogram normal adult cells into stem cells, called iPSCs, by the forced introduction of a set of transcription factors into the cells.[13] These transcription factors (different combinations of Oct4, Sox2, Klf4, c-Myc, Nanog, Lin28) regulate important steps in early embryonic development and force the adult somatic cells into an embryonic stem cell–like state. This technique has essentially revolutionized the field of regenerative medicine; the patient himself could now be an unlimited source of immune-matched pluripotent cells.[14]

As promising as the therapy sounds, it is riddled with its own problems. It has always been known that the genes that regulate developmental pathways also regulate cancer, and are especially potent when expressed in combination. Therefore, researchers have trimmed the initial group of 4 transcription factors down to 2, with the aim of simultaneously treating the cells with various chemicals to boost reprograming efficiency. Additionally, the use of either lentiviruses or retroviruses (**Figure 2**) to introduce the genes into the host cell can result in uncontrolled effects of viral integration. Current efforts are directed toward reprograming cells without viruses or using more efficient integration techniques.[14]

Applications of iPSCs

iPSCs offer tremendous potential in understanding disease, developing drug candidates, and regenerative medicine. Disease-specific iPSCs are being developed to treat Alzheimer's disease, Parkinson's disease, cardiovascular disease, diabetes, and ALS/Lou Gehrig's disease.[14] Researchers at the RIKEN Center for Developmental Biology in Japan have piloted the first set of studies to evaluate iPSCs in humans. In August 2013, patient recruitment was initiated to evaluate the safety and efficacy of iPSC-derived retinal pigment epithelium (RPE) cells in patients with age-related macular degeneration.[15] The premise for using iPSCs is the fact that the current remedies for the disease prevent further damage without promoting any repair.

A new iPSC transplantation therapy will also be evaluated for safety in patients with Parkinson's disease. Jun Takahashi, MD, PhD, and his colleagues at the Kyoto University's Center for iPS Cell Research and Application have successfully developed a technique to generate dopamine-producing nerve cells from patient-derived iPSCs for transplantation into the patient's brain, an attempt at regenerating the damaged dopaminergic neurons.[16] When contacted by e-mail, Takahashi responded that they are currently conducting preclinical studies, the results from which will be submitted for approval prior to initiating clinical trials.

In an encouraging development on the diabetes front, Rohit Kulkarni, MD, PhD, and his team at Joslin reported the generation of human iPSCs (hiPSCs) from patients suffering from maturity onset diabetes of the young (MODY). MODY accounts for 1% to 5% of diabetics in the United States and is monogenic (mutation of a single gene), unlike T1DM and T2DM, which are polygenic and are influenced by genetic and environmental factors. By stimulating the MODY-hiPSCs to differentiate into beta cells, the research team plans to evaluate potential blocks in the process, as well as explore means to correct the genetic defect with the objective of developing personalized disease treatments.[17]

Healthcare Coverage

Is regenerative medicine covered? Payers such as Humana, Blue Cross and Blue Shield, Aetna, and UnitedHealthcare definitely have policies in place for HSC and bone marrow transplants, a procedure that has been in use for a long time now for patients with blood disorders. However, companies that have developed, or are in the process of developing, regenerative therapies, face hurdles with not just the FDA, but also reimbursement.

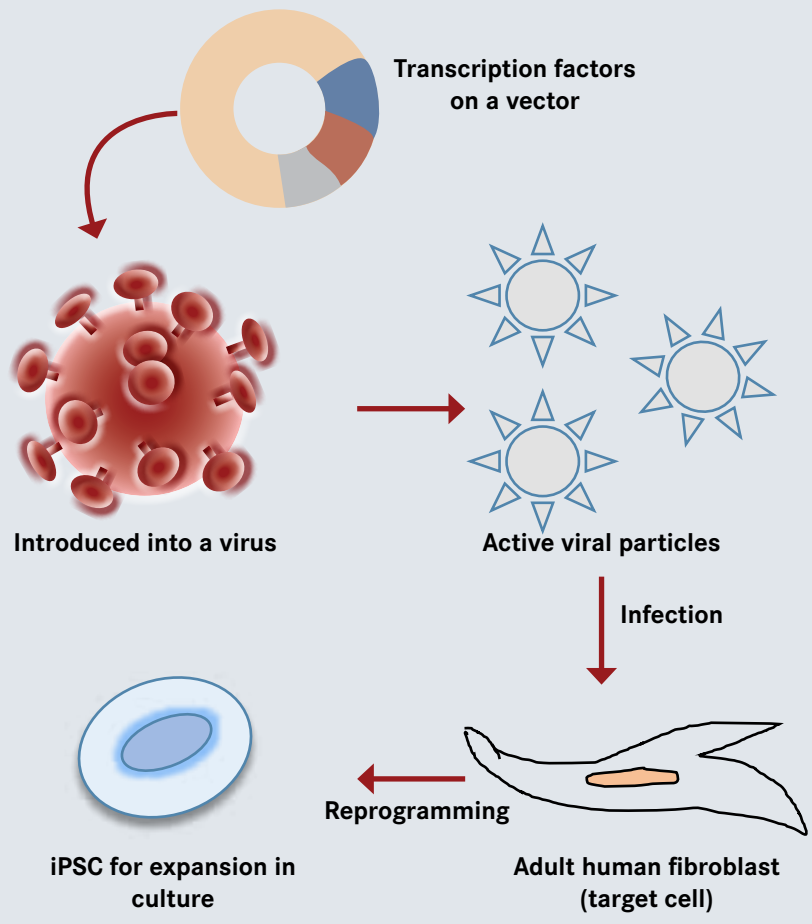
The company Advanced BioHealing developed *Dermagraft*, a product that consists of allogenic human fibroblasts, to aid with wound closures in diabetic foot ulcers. In 2011, the company was acquired by Shire Pharmaceuticals, which immediately initiated the task of improving the reimbursement profile for *Dermagraft* and put 2 new procedure codes in place for the product.[18]

Provenge, an autologous dendritic cell therapy manufactured by Dendreon for the treatment of advanced prostate cancer, also faced stumbling blocks, initially for FDA approval. Subsequently, CMS did not provide an automatic coverage for this expensive treatment ($93,000 for 3 doses) following the approval, but rather reviewed the payment process first before approving it after a year. Medicare coverage was absolutely essential for this drug, since 75% of the target population was Medicare eligible (65 years or older). Thus the combination of the price and the large number of patients that would be eligible for this treatment was the premise for Medicare's extended review.[19,20]

According to a brief released by the Alliance for Regenerative Medicine, an advocacy organization that creates a common platform for commercial, academic, and not-for-profit institutions, Medicare requires that the regenerative therapy should fall within a defined Medicare benefit and the parameters of one of these segments to qualify for payment. Medicaid relies more on managed care and strict formularies, while private health plans may primarily be concerned with whether the therapy falls under the medical benefit or prescription drug benefit. FDA approval is necessary but no longer sufficient for reimbursement.[21]

Defining the bottom line for the high-cost coverage of regenerative medicine requires answering the same question that must be asked in considering expensive treatments such as Sovaldi and Olysio (hepatitis C). Although the upfront cost of treatment is very high, if the therapy proves to have *breakthrough* effects, it could help avoid long-term treatment costs, especially for chronic conditions. In order for insurance companies to cover these therapies, stem cell therapy would need to prove a substantial advantage over preexisting and

Figure 2. Generation of iPSCs From Adult Somatic Cells



iPSC indicates induced pluripotent stem cell.
Adapted from: *Regenerative Medicine*. US Department of Health and Human Services. http://stemcells.nih.gov/info/scireport/Pages/2006report.aspx. Published August 2006. Accessed April 4, 2014.

relatively inexpensive treatment options. **EBDM**

References

1. Sub-retinal transplantation of hESC derived RPE (MA09-hRPE) cells in patients with Stargardts macular dystrophy. ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01345006?term=ACT+and+human+embryonic&rank=1. Accessed April 4, 2014.

2. Safety and tolerability of sub-retinal transplantation of hESC derived RPE (MA09-hRPE) cells in patients with advanced dry age related macular degeneration (Dry AMD). ClinicalTrials.gov website. http://www.clinicaltrials.gov/ct2/show/NCT01344993?term=ACT+and+human+embryonic&rank=2. Accessed April 4, 2014.

3. Schwartz SD, Hubschman JP, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012;379(9817):713-720.

4. Stem cells and diseases. National Institutes of Health website. http://stemcells.nih.gov/info/pages/health.aspx. Accessed April 4, 2014.

5. What is stem cell research? Joslin Diabetes Center website. https://www.joslin.org/diabetes-research/stem_cell_research.html. Accessed May 2, 2014.

6. Stem cell basics. National Institutes of Health website. http://stemcells.nih.gov/info/basics/Pages/Default.aspx. Accessed April 3, 2014.

7. Stem cells and cancer. Ludwig Center for Cancer Stem Cell Research and Medicine website. http://ludwigcenter.stanford.edu/overview/. Accessed April 14, 2014.

8. Types of stem cells. GE Healthcare Life Sciences website. http://www.gelifesciences.com/webapp/wcs/stores/servlet/catalog/en/GELifeSciences-us/applications/types-of-stem-cells/. Accessed April 14, 2014.

9. Cha HJ, Hwang ES. Current status of biology, bioengineering, and therapeutic potential of stem cells. *Arch Pharm Res*. 2012;35(2):193-196.

10. Chung YG, Eum JH, Lee JE, et al. Human somatic cell nuclear transfer using adult cells [published online April 17, 2014]. *Cell Stem Cell*. doi:http://dx.doi.org/10.1016/j.stem.2014.03.015.

11. Engineering therapeutic cells. ViaCyte website. http://viacyte.com/technology/stem-cell-engineering/. Accessed May 2, 2014.

12. Kroon E, Martinson LA, Kadoya K, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. *Nat Biotech*. 2008; 26:443-452 .

13. Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. *Nature*. 2007;448(7151):313-317.

14. Regenerative medicine. Department of Health and Human Services. http://stemcells.nih.gov/info/scireport/Pages/2006report.aspx. Published August 2006. Accessed April 4 2014.

15. Pilot clinical study into iPS cell therapy for eye disease starts in Japan [press release]. RIKEN; July 30, 2013. http://www.riken.jp/en/pr/press/2013/20130730_1/. Accessed April 4, 2013.

16. Geji K. Scientists to test iPS cells for Parkinson's disease therapy. *The Asahi Shimbun*. http://ajw.asahi.com/article/behind_news/social_affairs/AJ201306070062. Published June 7, 2013. Accessed April 15, 2013.

17. Joslin scientists generate first human induced pluripotent stem cells from patients with maturity onset diabetes of the young [press release]. Boston, MA: Joslin Diabetes Center; January 31, 2013. http://www.joslin.org/news/Joslin-Scientists-First-Human-iPSC-from-Patients-with-MODY-Diabetes.html.

18. Schaffer C, Littman N. Why planning your payment strategy is critical in early product development. California Institute for Regenerative Medicine website. http://cirmresearch.blogspot.com/2013/06/cirm-webinar-why-planning-your-payment.html. Published June 17, 2013. Accessed April 17, 2014.

19. Larkin C. Dendreon wins final Medicare coverage decision on prostate cancer drug. Bloomberg website. http://www.bloomberg.com/news/2011-06-30/dendreon-wins-final-medicare-coverage-decision-on-prostate-cancer-drug.html. Published June 30, 2011. Accessed April 17, 2014.

20. Maziarz R, Driscoll D. Hematopoietic stem cell transplantation and implications for cell therapy reimbursement. *Cell Stem Cell*. 2011; 8:609-612.

21. Alliance for Regenerative Medicine. Alliance for Regenerative Medicine reimbursement portfolio. http://www.cirm.ca.gov/sites/default/files/files/agenda/ARM_Reimbursement_Portfolio_Oct_2013_0.pdf. Accessed April 17, 2014.

Cleveland Clinic Study: Use of Bariatric Surgery Beats Medical Therapy in Diabetes Management

Mary K. Caffrey

Bariatric surgery has more powerful long-term effects on controlling type 2 diabetes mellitus (T2DM) than medical therapy alone, according to the largest long-term study comparing methods.[1]

Results of the Cleveland Clinic's STAMPEDE study were shared March 31, 2014, at the final late-breaking session of the 63rd Scientific Sessions of the American College of Cardiology, held in Washington, DC. The results were simultaneously published in *The New England Journal of Medicine*,[1] and the study's presenter, Sangeeta Kashyap, MD, answered questions immediately afterward at a press briefing.

Kashyap captured headlines in February 2013[2] when she published a substudy of STAMPEDE in *Diabetes Care*,[3] the journal of the American Diabetes Association (ADA). In that article, Kashyap outlined the mechanism by which bariatric surgery, which has been used primarily to help obese patients lose large amounts of weight, has helped patients overcome their T2DM status within days, long before they shed the pounds.

As she explained at the time, "A gastric bypass changes hormones in the gut, which triggers the pancreas to start making insulin again."[2]

Sangeeta Kashyap, MD

Researchers at the Cleveland Clinic designed STAMPEDE, which stands for Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently, to assemble evidence that might make surgery an acceptable alternative to medication in combating T2DM, which affects 25 million Americans. According to the ADA, an estimated 79 million also have prediabetes.[4]

The results involved 150 patients aged 41 to 57 years who received 1 of 3 treatment options: intensive medical therapy that included lifestyle changes and counseling along with medication; medical therapy plus Roux-en-Y gastric bypass; or medical therapy plus sleeve gastrectomy. Almost all of the patients, 91.3%, remained in the study at the 3-year mark.

At the start of the study, the average glycated hemoglobin (A1C) level for all patients was 9.2%. Most patients had been living with the disease at least 8 years and were taking at least 3 antidiabetic medications. All were overweight, although some patients had a body mass index as low as 27 kg/m^2, which might not make them a candidate for bariatric surgery without T2DM. Women made up 66% of the study group.

All 3 groups saw a drop in A1C levels at the 6-month mark; however, the groups receiving surgery were largely able to sustain the declines over 3 years, while the group receiving only medical therapy experienced a gradual rise to levels approaching preintervention rates. Results were:

- The medical-only group began with an average A1C of 9.0%, followed by an average of 7.1% at 6 months; 7.5% at 12 months; 7.7% at 24 months; and 8.4% at 36 months.
- The gastric bypass (Roux-en-Y) group began with an average A1C of 9.3%, followed by averages of 6.3% at 6 months; 6.5% at 12 months; 6.5% at 24 months; and 6.7% at 36 months.
- The sleeve gastrectomy group began with an average A1C of 9.5%, followed by averages of 6.7% at 6 months; 6.6% at 12 months; 6.8% at 24 months; and 7.0% at 36 months.

At the 3-year mark, weight loss was 5 to 6 times greater for patients who received gastric bypass or sleeve surgery

compared with those receiving medical therapy only. Average loss for the gastric bypass group was 24%; average loss for the sleeve group was 21%; and average loss for the medical-therapy only group was just 4%.[5]

Researchers acknowledge that these surgical procedures are not without risks, which they listed as bleeding, infection, or blood clots. The study team reported that the most common issues at 12 months were short-term dehydration, bleeding, and 1 leak. Four of the 100 surgical patients needed an additional surgery for complications within the first year.

One issue that was not reported came up in response to a question from *Evidence-Based Diabetes Management (EBDM)*. Kashyap was asked if investigators observed the phenomenon, reported in the literature since 2012, that some gastric bypass patients experience alcohol abuse in year 2 after surgery. This topic was explored in a recent issue of *EBDM*.[5]

Kashyap said that "2 or 3" patients experienced alcohol abuse, but that it turned out that those patients had had some history of substance abuse issues. When asked why these incidents were not reported as adverse events, Kashyap said it was due to the patients' histories.

In her presentation, Kashyap emphasized that surgical patients outscored the medical therapy group on quality-of-life tests; when asked about this at the late-breaking session, she said that the weight loss gave patients confidence, and that for patients who no longer had needed insulin injections, quality of life improved enormously.

The lead author on the study, Philip Schauer, MD, said endocrinologists were interested in the phenomenon, but without long-term results, most were unwilling to consider surgery as a therapy alongside traditional pharmacologic therapies and lifestyle modifications. "Now the evidence is mounting, and we see the benefits of surgery over medical therapy for these patients," he said in a statement.[6] **EBDM**

References

1. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery vs. intensive medical therapy for diabetes [published online March 31, 2014]. *N Engl J Med*.

2. Theiss E. Cleveland Clinic shows why gastric bypass can trounce diabetes. *The Plain Dealer.* www.cleveland.com/healthfit/index.ssf/2013/02/cleveland_clinic_study_shows_w.html. Published February 26, 2013. Accessed March 31, 2014.

3. Kashyap SR, Bhatt DL, Wolski K, et al. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: analysis of a randomized control trial comparing surgery with intensive medical treatment. *Diabetes Care.* 2013;36(8):2175-2182.

4. Fast facts. American Diabetes Association website. http://professional.diabetes.org/admin/UserFiles/0%20-%20Sean/FastFacts%20March%202013.pdf. Updated March 2013. Accessed March 30, 2014.

5. Mehr S. The link between a common type of bariatric surgery and increased alcohol use. *Am J Manag Care*. 2014;20(SP4):SP116-SP118.

6. Bariatric surgery beats medical therapy alone for managing diabetes [press release]. Washington, DC: American College of Cardiology; March 31, 2014. http://acc2014.org/wp-content/uploads/2013/11/SCHAUER_-STAMPEDE_-LBCT-NEJM_Press-Release_FINAL.pdf.

Diet Drinks Linked to Heart Trouble for Older Women

Mary K. Caffrey

Evidence linking sugar-sweetened sodas to cardiovascular damage has been the subject of studies presented by the American Diabetes Association and even *60 Minutes*.[1] Now, diet sodas are getting their turn.

At the 63rd Scientific Sessions of the American College of Cardiology held in Washington, DC, Ankur Vyas, MD, of the University of Iowa Hospitals and Clinic, Iowa City, Iowa, presented results showing that older women who drink at least 2 diet drinks per day are more likely to have a heart attack, stroke, or other cardiovascular issue.

Vyas' March 30, 2014, talk, "Diet Drink Consumption and the Risk of Cardiovascular Events: A Report from the Women's Health Initiative," involved data from 59,614 women with an average age of 62 years who were followed for an average of 8.7 years.[2]

In his presentation, Vyas said the women were divided into 4 groups based on diet drink consumption, with those who consumed at least 2 drinks per day forming 1 group; those consuming 5 to 7 drinks per week forming another; those having 1 to 4 drinks per week forming a third; and those having 0 to 3 drinks per month making up the fourth group, or reference group.

The primary outcome—a composite of incidence of coronary heart disease, congestive heart failure, heart attack, coronary revascularization procedure, ischemic stroke, peripheral arterial disease, and cardiovascular death—occurred in 8.5% of the women consuming 2 or more drinks per day, followed by 6.9%, 6.8%, and 7.2% in the other 3 groups, respectively.

Ankur Vyas, MD

Vyas said the relationship persisted after adjusting for demographic and cardiovascular risk factors, body mass index, smoking status, physical activity, and salt, cholesterol, and sugar-sweetened beverage intake. Women who consumed 2 or more diet drinks per day were younger, but their overall health was worse: they were more likely to smoke, weigh more, and have diabetes or hypertension.

Reasons for the association between higher consumption of diet soda and cardiovascular risk is unclear, but Vyas said it is possible that artificial sweeteners in the drinks may trigger "an increase in desire for sugar-sweetened, energy-dense beverages and foods due to disruption of normal feedback mechanisms." It appears that those who drink more diet sodas than average already have unhealthy lifestyles, he said, and this relationship merits further study.[3]

About 1 in 5 people in the United States consume diet drinks on a given day, according to data from the National Health and Nutrition Examination Survey (2009-2010).[4] But Vyas cautioned that this particular study only applies to postmenopausal women. To be included in this analysis, women had to have no history of cardiovascular disease and had to be alive 60 or more days from the time of data collection.[3]

A 2009 study published in *Diabetes Care* found an association between consumption of diet soda and the incidence of metabolic syndrome and type 2 diabetes mellitus, but the study cautioned that no causality could be determined.[5]

A commenter at the session noted the irony of Vyas' results: "Here we have a multibillion-dollar industry promoting health without any outcomes research," he said. **EBDM**

References

1. Caffrey MK. Does sugar cause cardiometabolic disease? Stanhope reviews the evidence. *Am J Manag Care.* 2013;19(SP7):SP247.

2. Vyas A, Rubenstein L, Robinson J, et al. Diet drink consumption and the risk of cardiovascu-lar events: a report from the women's health initiative. *JACC.* 2014;64(12, suppl A):Abstract 917-905.

3. Too many diet drinks may spell heart trouble for older women [press release]. Washington, DC: American College of Cardiology; March 29, 2014. http://acc2014.org/wp-content/uploads/2014/03/VYAS_Diet-Drinks_Consumer-Briefing-2_Press-Release_FINAL.pdf. Accessed March 29, 2014.

4. Nutrition Health and Examination Survey. CDC website. http://wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx. Updated March 27, 2014. Accessed March 30, 2014.

5. Nettleton JA, Lutsey PL, Wang Y, Lima JA, Michos ED, Jacobs DR Jr. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the multi-ethnic study of atherosclerosis (MESA). *Diabetes Care*. 2009;32(4):688-694.

Aims of ACA Get Better Reviews Than Implementation at Cardiologists' Meeting

Mary K. Caffrey

Wendell Primus, PhD, the veteran legislative aide for US House Minority Leader Nancy Pelosi, (D-CA), got right to the point when he asked those gathered for the 63rd Scientific Sessions of the American College of Cardiologists if, so far, the Affordable Care Act (ACA) was helping *them*, as opposed to their patients.

Only a pair of hands out of several hundred in the hall went up.

"So, we have our work cut out for us here," Primus said, to a sprinkle of laughs.

But for Primus, who has spent his entire career battling over healthcare, the bickering in Washington, DC, where the cardiologists held their annual meeting, and beyond the beltway is no joke. Primus, who famously dueled with then–White House Chief of Staff Rahm Emmanuel over the fine points of the ACA to the point that the two could not be in the same room,[1] today deals with its ongoing fallout—the botched implementation of HealthCare.gov, the possible loss of seats in the upcoming midterm elections, and the refusal of many governors to expand Medicaid.

Primus, the first of a roster of speakers in the March 29, 2014, presentation, "Affordable Care Act Implementation: Impact on Patients and Providers, A Town Hall Forum," began with an observation that the ACA, as a concept, is not the far-left construct it is portrayed as by its opponents. Its core elements, especially small business subsidies and the individual mandate, were featured in every Republican healthcare proposal going back to the Nixon Administration, Primus said.

Some of Primus' points were well received; there were nods at his prediction that 12 to 14 million of the nation's uninsured will end up with coverage when marketplace, Medicaid, and young adults on their parents' plans are taken into account. But the cardiologists had issues with implementation, and they had plenty of questions. In particular, they asked about items left out of the ACA, such as tort reform; questioners insisted the legal environment and insurers' red tape continue to force them to practice defensive medicine and waste time and money.

That said, there was optimism for the changes coming in medicine from the perspectives of a physician, a hospital executive, a patient, a payer, and a representative from the CMS. All agreed that the revolution in healthcare, which demands a change to payment models that reward quality, were in motion already, and that ACA is just part of that change. Thomas M. Priselac, president and CEO of Cedars-Sinai Health System in Los Angeles, California, said the ACA is far from a "national system;" rather, it set up 50 state systems.

"The ACA was not implemented in a vacuum," Priselac said. "It really reflected the broader economic circumstances that are still with us today." The ACA, he said, put in place the "levers and dials" to achieve the goals of the triple aim: lower cost, population health, and patient satisfaction.

Sean Cavanaugh, deputy director of CMS' Center for Medicare and Medicaid Innovation, is charged with giving those new payment models a try within the biggest payer of all, and he said there have been some good signs. He agreed that the rollout of ACA has not been perfect, but he said that the prior situation could not stand. In a former job at a Brooklyn hospital, many of his days were spent trying to figure out "how to keep the doors open" while taking care of high numbers of uninsured patients.

> *"The ACA was not implemented in a vacuum. It really reflected the broader economic circumstances that are still with us today."*
>
> **—Thomas M. Priselac**
> President and CEO,
> Cedars-Sinai Health System

Already, Cavanaugh said, CMS is seeing a drop in Medicare readmission rates because of quality improvement initiatives in the new accountable care organizations. These were rates that had been stuck at 19% for a very long time, and have fallen to 17%. "This improvement is being driven by many factors; some of it is by payment changes, some of it is by public reporting," he said.

Patient representative Jonathan Rintels, a longtime member of the Writers' Guild of America and a former member of its board, riveted the audience with his tale of what life was like when he lost eligibility for his union insurance and had to shop for individual coverage in the years before the ACA took effect. With an autistic son, insurance costs consumed 25% of the family income. He avoided seeking care for a cardiac condition until he collapsed on a tennis court. He worried how he would pay his daughter's college costs.

Wendell Primus, PhD

When the infamous HealthCare.gov site went live in October 2013, Rintels said of trying to sign up: "My own experience is that those reports were inaccurate. It was worse."

And, yet, after the site was overhauled, he did manage to get through and use his credit card to sign up on Christmas Eve, in time for a policy to take effect New Year's Day. He will spend 40% less than he did before. He did have to change to a new orthopedist for his tennis elbow, but he said he would do it all again.

"For all the hours I spent…" he said, "you cannot put a price on peace of mind."

Richard Salmon, MD, PhD, who is national medical executive for Performance and Improvement at Cigna, said there are elements of the ACA that are making the triple aim a reality:

- Patient engagement is requiring employers to go after opportunities to encourage employees to engage in healthy behavior, especially quitting smoking.
- Financial incentives are part of the equation.
- The change from "volume-based" to "value-based" incentives is real, but if the healthcare system is going to transform, it's going to require aligning payment incentives to bring health insurance technology to hard-to-reach places, as well as quality improvement collaboratives.
- Training of new physicians is essential.

Salmon said there's a big difference between today's reform movement and that of the health maintenance organization (HMO) movement of the 1990s, which was just about transferring risk without really changing the way medicine was practiced. "Today, the technology is better, the federal stimulus is better, and the collaboration is better," he said.

J. James Rohack, MD, former president of the American Medical Association, offered his thoughts on what he called "the good, the bad, and the ugly." What's good about the ACA? Getting rid of the ability to let insurers exclude the people who need insurance because they are sick. What's bad? Lawmakers have to figure out what to do about those who sign up for healthcare but don't pay the premium, leaving the unwitting doctor or hospital on the hook down the road. What used to be charity care is going to become bad debt, Rohack said. "If I don't have cash coming in, how do I keep the doors open?" he said.

And then there's the ugly. "We have states refusing to expand Medicaid, which doesn't cover childless adults. I come from Texas, so we have 1.6 million Texans who won't have health insurance."

Where should doctors stand on these issues? "A physician should support medical care for all people," he said. **EBDM**

Reference

1. Akers MA. In the speaker's office, a quiet liberal lion: Wendell E. Primus. *The Washington Post*. http://www.washingtonpost.com/wp-yn/content/article/2010/06/20/AR2010062003442.html. Published June 21, 2010. Accessed March 30, 2014.

To Treat or Not to Treat? Questions, Controversies in Prevention

Mary K. Caffrey

Should patients with moderately elevated levels of triglycerides be treated, even while cardiologists await the results of a trial that may provide a definitive answer?

What are "real-world" blood pressure (BP) goals for patients with type 2 diabetes mellitus (T2DM), despite what guidelines say? What about BP management for patients with chronic kidney disease (CKD)?

Finally, what is the right level of glycemic control for patients with T2DM? Should "control" mean the same thing for everyone, or does the line move depending on the patient's cardiovascular (CV) profile?

A panel of leading physicians took on these questions at the 63rd Scientific Sessions of the American College of Cardiology, held in Washington, DC, March 29-31, 2014, with the debate proving lively at times. Sanjay Kaul, MD, best characterized the spirit of the exchange when he said of Michael Miller, MD, his partner in the triglyceride debate, "Mike and I look at the same data set and come to different conclusions; it doesn't mean that Mike is right or I am right—it speaks to the weakness of the data."

Triglycerides. First, Miller, of the University of Maryland School of Medicine, Baltimore, and Kaul, of Cedars-Sinai Medical Center, Los Angeles, discussed whether medications should be routinely used to treat patients with triglyceride levels between 200 mg/dL and 500 mg/dL, with Miller asserting that there are epidemiologic, mechanistic, post hoc clinical data to support treatment.

A randomized, double-blind trial called REDUCE-IT is under way, with a primary end point of the prevention of the first major CV event. The trial involves men and women at least 45 years of age who have medical histories that include coronary heart disease or T2DM, and triglyceride levels ranging from 200 mg/dL to 500 mg/dL. The trial will compare groups taking icosapent ethyl (Vascepa) or placebo. Results are expected in 2016.[1]

With the trial under way, Miller said, "Why wait?"

There's reason to wait, Kaul said. Non-statin therapies for hyperlipidemia do not provide acceptable risk reduction benefits compared with adverse effects (this includes fish oil–based treatment). He said these should be avoided, with a few exceptions. In looking at Lovaza and Vascepa, 2 approved omega-3 fatty acids, Kaul said they were approved for patients with severely high triglyceride levels (at least 500 mg/dL) on the presumption of increased risk of pancreatitis; Kaul said there are no data to support using these agents for triglycerides at lower levels.

Stuart Zarich, MD, FACC, FAHA, FASE

> *"Tight glucose control has only been linked to a reduction in microvascular events, while its role in reducing macrovascular events has been controversial."*
>
> **— Stuart Zarich, MD**
> Bridgeport Hospital and Yale School of Medicine

Blood pressure, diabetes, and CKD. Both William C. Cushman, MD, who discussed BP goals for patients with diabetes, and George L. Bakris, MD, who outlined goals for those with CKD, offered insights into how guidelines are developed. Bakris went so far as to ask whether the now-updated Joint National Committee 7 (JNC 7) goal of having a BP at, or lower than, 130/80 mm Hg was "defensible."

But Bakris, who noted that both he and Cushman served on the panel that developed the JNC 7 guidelines, knows that in a real-world setting, primary care physicians use some latitude in applying a guideline and will move up to 140/80 mm Hg, and so that knowledge is taken into account.

What's known now is that the patient population suffering from these diseases is aging, and these realities must now be weighed as physicians push patients toward certain goals. As Cushman noted, "strict interpretation" of randomized controlled trials would call for a goal of 150 mm Hg for the systolic BP in hypertensive patients with T2DM, but based on the more recent ACCORD trial, 140 mm Hg might be reasonable. However, it is important not to overlook the diastolic number just to push the systolic.

Darren K. McGuire, MD, MHSc

Glycemic control. Darren K. McGuire, MD, MHSc, of the University of Texas Southwestern Medical Center in Dallas, led off his case, "No Need for Tight Glycemic Control," with a product label for tolbutamide, which reads in part that the drug is "associated with increased cardiovascular mortality." As if that weren't enough to get everyone's attention, McGuire showed results from a series of studies, including the ACCORD trial,[2] that displayed what he called "discordance" between control of glycated hemoglobin (A1C) and outcomes. He acknowledged that control of A1C early on in younger patients did have favorable outcomes down the road, but older, sicker patients need flexibility in control of glycemic levels.

McGuire's comments dovetailed with comments he and others made the previous day at a session on pharmacotherapy and diabetes, where it was observed that, for all the advances in diabetes care, the field still lacks a bulletproof treatment that poses no CV risks.

Stuart Zarich, MD, FACC, FAHA, FASE, of Bridgeport Hospital and Yale School of Medicine, took the opposite position in observing the "glucose paradox." He said that although base glycemia predicts both future microvascular and macrovascular events, "Tight glucose control has only been linked to a reduction in microvascular events, while its role in reducing macrovascular events has been controversial."

Meanwhile, control of BP and use of statins to reduce lipid levels have been shown to limit macrovascular events for those with T2DM. Part of the problem is that reducing BP will have immediate positive benefits, while the other steps can take several years to show benefits, Zarich said. Conversely, some effects of intense medication therapy include weight gain or even use of additional antidiabetic drugs.

Zarich read the ACCORD results somewhat differently, observing that the lowest risk of death was seen when A1C was well controlled at 6% to 7%, with excess mortality above 7%. Mortality increased for every 1% increase in A1C above 6%, he said.

In a sense, Zarich agreed with McGuire—early treatment may work; it just takes years for the evidence to appear. This "legacy" effect, or memory, requires patience on the part of physicians and patients—not to mention those reviewing the literature. **EBDM**

References

1. Bradberry JC, Hillman D. Overview of omega-3 fatty acid therapies. *PT.* 2013;38(11):681-691.

2. The Accord to Control Cardiovascular Risk in Diabetes Study Group (ACCORD). Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545-2559.

Use of Rivaroxaban Could Trim Hospital Spending in Treating Pulmonary Embolism

Mary K. Caffrey

The "triple aim" promised by healthcare reform—better-quality care, greater patient satisfaction, at a lower cost—will play out procedure by procedure as physicians find ways to deliver better care and find savings. One such intervention is treatment for pulmonary embolism (PE), a dangerous condition that often involves a multiday stay in the hospital. A 2013 study that tracked 991 patients at Brigham and Women's Hospital in Boston found a mean stay of 4 days and a mean cost per patient of $8764 for PE treatment.[1]

Thus, a method that would trim those stays in half would explain the title of a presentation by Mohsen Sharifi, MD, at the 63rd Scientific Sessions of the American College of Cardiology (ACC) held March 29-31 in Washington, DC: "Paradigm Shift in the Treatment of Pulmonary Embolism: Safe Dose Thrombolysis Plus Rivaroxaban."

Sharifi, who practices at the Arizona Cardiovascular & Vein Clinic in Mesa, Arizona, offered a different approach to thrombolysis, which simply means treating PE with drugs to break up a blood clot. The "safe dose" approach involves an initial infusion of heparin followed by daily doses of the new oral anticoagulant rivaroxaban, which Sharifi said could trim the typical hospital stay to an average of 1.8 days for moderate or severe PE.

In his March 30, 2014, presentation, and in an accompanying abstract, Sharifi summed up the approach as "drip, dose, and discharge."[2] Findings on this approach were previously published in *Clinical Cardiology*.[3]

Mohsen Sharifi, MD

This method represents a "middle ground" to other treatment approaches that have seen results released over the past 2 years, Sharifi said. These include heparin-plus-tenecteplase, which was found to present some risk stratification challenges in the PEITHO trial.[4]

The use of EKOS ultrasound technology[5] to speed up the effects of thrombolysis was found to be effective in the ULTIMA trial, but Sharifi said the involvement of devices can drive up costs.

The results have important implications not only for the goal of keeping patients out of the hospital, but also for formulary managers. Sharifi reported his best results for patients who stayed on rivaroxaban, while a few patients who switched to warfarin for insurance reasons suffered setbacks.

Results presented at ACC involved 119 patients who were treated over a 15-month period; 101 patients had moderate and 18 had severe PE. Patients received 10 mg of tissue plasminogen activator (tPA) given as a bolus, followed by a 40-mg infusion given in 2 hours. Heparin was then infused over the next 24 hours, and rivaroxaban was started in 15-mg or 20-mg doses 2 hours after the end of heparin dosing. Oral anticoagulants continued for 30 days, with 22 patients switching from rivaroxaban to warfarin, chiefly due to cost issues.

After a mean follow-up of 14 months, no bleeding occurred in any patients on the safe-dose thrombolysis. The abstract reads, "Recurrent venous thromboembolism occurred in 3 patients who were on warfarin but in no patients who were on rivaroxaban." At the session, Sharifi said that based on these results he saw "little role for warfarin" in this type of therapy.

The best part is, "Patients go home in 2 days," Sharifi said. "That's very appealing in today's healthcare environment." **EBDM**

References

1. Fanikos J, Rao A, Seger AC, Carter D, Piazza G, Goldhaber SZ. Hospital costs of acute pulmonary embolism. *Am J Med*. 2013;126(2):127-132.

2. Sharifi M, Freeman W, Bay C, et al. Paradigm shift in the treatment of pulmonary embolism: safe dose thrombolysis plus rivaroxaban. *JACC*. 2014;64(12, suppl A):Abstract 916-07.

3. Sharifi M, Bay C, Shwartz F, Skrocki L, Safe-dose thrombolysis plus rivaroxaban for moderate and severe pulmonary embolism: drip, drug, and discharge. *Clin Cardiol*. 2014;37(2):78-82.

4. Nainggolan L. PEITHO: persuasive for thrombolysis in PE? Medscape Multispecialty. http://www.medscape.com/viewarticle/780651#2. Published March 12, 2013. Accessed March 30, 2014.

5. Ultima trial results published in *Circulation*. Vascular News. http://www.cxvascular.com/vn-venous-news/vascular-news—venous-news/ultima-trial-results-published-in-circulation/. Published January 20, 2014. Accessed March 30, 2014.

Relationship Between Cardiac Issues, Diabetes Gets Plenty of Attention

Mary K. Caffrey

From a session called "How to Navigate the Maze of Pharmacotherapy in Diabetes?" to oral abstracts and posters, the relationship between cardiac risks and the rising incidence of type 2 diabetes mellitus (T2DM) received plenty of attention March 29, 2014, at the 63rd Scientific Sessions of the American College of Cardiology, held in Washington, DC.

Diabetes now affects nearly 26 million Americans, and an estimated 35% of US adults over age 20 years have prediabetes.[1] Most of the increase has come from the rise in the number of adults and even children with T2DM; 3600 children are diagnosed each year.[1]

Drug development still seeks the "holy grail," a diabetes therapy with no side effects and CV risk reduction.

Treating diabetes has proved tricky because for many years therapies were developed with a blind spot for their cardiovascular (CV) effects; with the well-documented uproar over rosiglitazone (Avandia) in the middle of the past decade,[2] the posture of the FDA has shifted to require evaluation of CV risk for diabetes therapies.

Options for diabetes drugs abound today. Silvio E. Inzucchi, MD, of Yale School of Medicine, noted during the pharmacotherapy session that decades ago, hypertension had multiple treatment options while diabetes had comparatively few; now the situation is reversed. And yet, he said, drug development will continue because the "holy grail," a diabetes therapy that has no side effects and the benefit of CV risk reduction, "is something that has eluded us for many years."

Part of treatment means understanding that men and women present disease differently. And those differences were the focus of several presentations at a poster session Saturday morning, as the theme continued to be moving away from "one size fits all" in understanding the relationship between cardiac care and diabetes care. Among the results presented:

Gender differences in predicting CAD.[3] A study from Japan involved 813 male and 413 female subjects who underwent their first coronary angiography and had glycated hemoglobin (A1C)

levels measured from December 2008 to September 2013. Researchers measured coronary artery lesions using the SYNTAX score, a classification developed from existing measurements to classify coronary artery disease (CAD). A logistic regression analysis evaluated predictors for CAD prevalence, adjusting for age, level of hypertension, dyslipidemia, smoking, diabetes, and A1C.

Among men, A1C was an independent predictor of CAD, but among women, adjusting for diabetes eliminated the predictive value of A1C for CAD. Among men, A1C value showed a significant correlation with SYNTAX score, but there was not a significant correlation between A1C and SYNTAX score among women.

Gender, A1C, and coronary atherosclerosis. A study from Austria enrolled 1449 patients—484 women and 965 men—who did not have previously known diabetes and who underwent coronary angiography for the evaluation of stable CAD. Significant coronary atherosclerosis was diagnosed in the presence of significant coronary stenosis with lumen narrowing of at least 50%. Based on results using A1C to diagnose diabetes based on American Diabetes Association criteria, A1C was a strong predictor of coronary atherosclerosis among women, but not among men who did not have previously undiagnosed diabetes.[4]

A1C predicting CAD. The same Austrian research group investigated the power of A1C to predict future CV events by gender.[5] The same group of 1449 patients without previously known diabetes in the previous study were followed for 4.4 years. At follow-up, the incidence of CV events was 19.5% in women and 25.6% in men, corresponding to annual event rates of 4.4% and 5.5%, respectively. Among women, A1C strongly and significantly predicted CV events (adjusted odds ratio [OR] for a 1% increase in A1C was 1.69) while the association between A1C and CV events in men was weaker and statistically not significant (adjusted OR was 1.15).

Biomarkers, diabetes, and CV risk. The giant study of 12,000 patients with T2DM in the SAVOR-TIMI 53 trial found that, regardless of baseline risk, a substantial share of stable patients with this disease have signs of ongoing myocardial damage or hemodynamic stress. These conditions were strongly associated with later risk of death from myocardial infarction (MI). Biomarkers measured in the study were high-sensitivity troponin, NT-proBNP, and hsCRP for enrolled patients. Researchers found a stepwise increase in rates of CV death and MI with higher quartiles of each biomarker.[6] **EBDM**

References

1. Fast facts. American Diabetes Association website. http://professional.diabetes.org/admin/UserFiles/0%20-%20Sean/FastFacts%20March%202013.pdf. Updated March 2013. Accessed March 30, 2014.

2. Regan T. FDA mea culpa part of cautionary tale. *Am J Manag Care*. 2013;19(SP7):SP242-SP243.

3. Ikeda N, Hara H, Hiroi Y, Nakamura M. Gender specific difference of association between glycated hemoglobin and prevalence or complexity of coronary artery disease. *JACC*. 2014;63(12, suppl A):Abstract 1121-326.

4. Saely C, Vonbank A, Rein P, et al. Gender significantly modulates the association of HbA1C with angiographically diagnosed coronary atherosclerosis among subjects without previously known diabetes. *JACC*. 2014;63(12, suppl A):Abstract 1121-1336.

5. Saely C, Vonbank A, Rein P, et al. HbA1c is a significantly stonger predictor of cardiovascular event risk in women than in men among patients undergoing coronary angiography. *JACC*. 2014;63(12, suppl A):Abstract 1121-1334.

6. Scirica B, Bhatt D, Braunwald E. Prognostic implications of simultaneious biomarker assessments in patients with type 2 diabetes mellitus: observations from the SAVOR-TIMI 53 trial. *JACC*. 2014;63(12, suppl A):Abstract 1121-1337.

Study Answers Long-Standing Question About Metformin After Heart Attack

Mary K. Caffrey

Metformin, the go-to drug for patients with a diagnosis of type 2 diabetes mellitus (T2DM), may help control glycated hemoglobin (A1C) levels, but according to a new study from the Netherlands, metformin does not help prevent heart failure in patients who have had a heart attack and do not have T2DM.[1]

The study was presented March 31, 2014, at the final late-breaking session of the 63rd Scientific Sessions of the American College of Cardiology (ACC), held in Washington, DC. It answered a question that some researchers have wondered about, given that some studies have suggested that metformin's protective effects go beyond its ability to lower glucose levels.

Although the session was jointly sponsored by the ACC and the *New England Journal of Medicine,* the metformin study was simultaneously published in the *Journal of the American Medical Association.*[1]

Lead author and presenter Chris P.H. Lexis, MD, of the University Medical Center Groningen, Netherlands, said the study was designed to find out whether metformin would benefit patients who had suffered a heart attack but who would not be candidates for metformin because they did not have diabetes. Animal studies had shown that metformin preserved the ability of the heart to pump blood through the body after myocardial infarction (MI), which left researchers wondering if the same was true in humans. If so, metformin could be prescribed for patients who have had a heart attack to prevent heart failure after an MI.

> *"It is noteworthy that metformin started early after heart attack did not adversely affect kidney function and was well tolerated."*
>
> **—Chris P.H. Lexis, MD**

In the study, 380 patients who had experienced an MI and had percutaneous coronary intervention (PCI) were randomized to receive either 500 mg of metformin twice daily or placebo, in addition to normal standard of care. Patients who had already received a diagnosis of T2DM or who were coronary bypass candidates were excluded. The median age of patients was 59 years.

The primary end point of the study was left ventricular ejection fraction, a measurement that describes the percentage of blood leaving the heart each time it contracts. This measure is key after MI, which can reduce the left ventricle's ability to pump blood through the body. The measurement was taken by magnetic resonance imaging, 4 months after each patient's MI. Results showed that the metformin group's fraction was 53.1%, compared with 54.8% for the placebo group, which Lexis said was not statistically significant.

Lexis said that while the results will not change clinical practice for patients without diabetes, they do show that metformin is safe for patients who have suffered ST-elevated myocardial infarction, or STEMI. "It is noteworthy that metformin started early after heart attack did not adversely affect kidney function and was well tolerated," he said. So, our findings do not preclude the use of metformin to treat diabetes in this setting."[2] **EBDM**

References

1. Lexis CPH, Iwan CC, van der Horst EL, et al. Effect of metformin on left ventricular function after acute myocardial infarction in patients without diabetes: the GIPS-III randomized clinical trial [published online March 31, 2014]. *JAMA*.

2. Metformin fails to reduce heart failure after heart attack [press release]. Washington, DC: American College of Cardiology; March 31, 2014. http://acc2014.org/wp-content/uploads/2013/11/LEXIS_GIPSIII_LBCT-NEJM_Press-Release_FINAL.pdf.

The Persistent Complication of Hypoglycemia in Diabetics

Surabhi Dangi-Garimella, PhD

Hypoglycemia, also referred to as insulin reaction or insulin shock, is defined as abnormally low glucose in the blood (low blood sugar), usually below 70 mg/dL. The condition is usually associated with several symptoms, including shakiness, nervousness, sweating, chills and clamminess, dizziness, hunger and nausea, confusion, weakness, sleepiness, seizures, and losing consciousness. Severe hypoglycemia can cause accidents, injuries, coma, and may even prove fatal.[1] Recent studies have associated severe hypoglycemia as a risk factor for dementia, falls, fractures, and heart attacks.[2]

The simplest solution under hypoglycemic conditions is to provide a sugar source to the patient. However, managing the condition can prove especially challenging in individuals who are hypoglycemic without any evident symptoms, defined as *hypoglycemia unawareness*. Patients suffering from *hypoglycemia unawareness* would be difficult to wake from sleep if they do get hypoglycemic at night. This condition is most commonly observed in individuals who experience frequent episodes of hypoglycemia, among chronic diabetics, or in those with tightly controlled diabetes.[1]

However, a collaborative study between Kaiser Permanente and Yale University School of Medicine, published last year in the journal *Diabetes Care*, revealed that hypoglycemia can also affect those with poorly controlled diabetes. The authors stated that nearly 11% of the more than 9000 responders who had participated in the survey had experienced hypoglycemia, independent of blood sugar control.[3]

Two recent papers in *Diabetes*, a collaboration between 2 laboratories at the Department of Biological Sciences, University of Southern California, delved into the details of the feedback signals received by the brain following a drop in blood sugar in hypoglycemic diabetics. Their research identified a startling difference in neuronal firing between slow-onset hypoglycemia and rapid-onset hypoglycemia.[4,5]

The authors on the papers published in *Diabetes*. From left, Casey Donovan, PhD, MaryAnn Bohland, PhD, Anne Jokiaho, PhD, Alan Watts, DPhil.

Disease Burden on Healthcare

A study conducted by the pharmaceutical company Novo Nordisk, in association with the health technology assessment company Heron Evidence Development, identified that a greater number of comorbidities (excluding dyslipidemia) were prevalent in hypoglycemic diabetic patients than in their matched controls, diabetics who had not presented with any hypoglycemic events. A majority (97%) of the patients were persons with type 2 diabetes mellitus (T2DM) who were documented to have required medical attention during 2009. The analysis, presented at the meeting of the International Society for Pharmacoeconomics and Outcomes Research, showed that patients experiencing hypoglycemic events had significantly higher all-cause annual healthcare costs over controls ($32,337 vs $19,786). The study identified nonsurgical inpatient costs as the primary driver of the significant difference between the cohorts. On the contrary, controls had higher outpatient costs over the controls.[6]

Another study evaluating the cost of hypoglycemia in 536,581 patients with T2DM estimated the total cost during a 4-year study period (2004-2008) at $52,223,675, accounting for 1% of all inpatient costs, 2% of emergency department (ED) costs, and 0.3% of outpatient costs. The average costs for hypoglycemia visits were high for an inpatient admission ($17,564) compared with an outpatient visit ($394), which mirrored the findings of the Novo Nordisk study.[7] The authors reiterated the need for continued vigilance and efforts to develop strategies to curb these avoidable costs. Analysis of ED visits for insulin-related hypoglycemia over a 5-year period found that the United States healthcare system had forfeited $600 million, excluding hospitalization costs.[8]

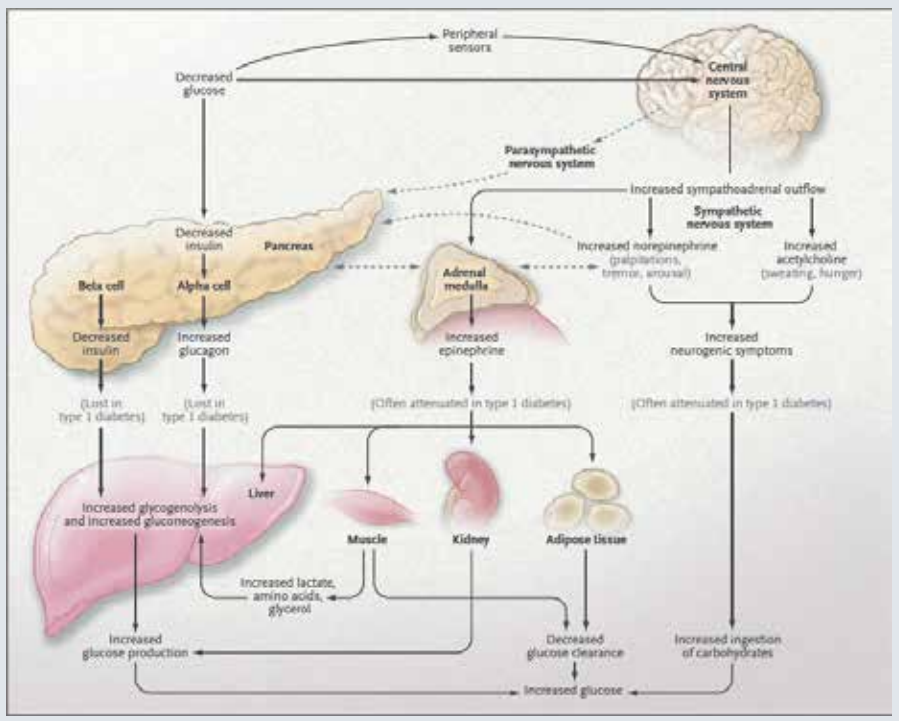
What Prevents the Brain From Generating Feedback Compensation in Diabetics?

Patients suffering from type 1 diabetes mellitus as well as T2DM often face a recurring issue in disease management: *iatrogenic hypoglycemia*. It is defined as an abnormally low plasma glucose concentration that exposes the individual to potential harm, a definition coined by a joint work group of the American Diabetes Association and The Endocrine Society.[9]

Normally, following a drop in the blood glucose level, the body compensates by reducing insulin secretion (which lowers glucose) and increasing glucagon secretion (which increases glucose) by the pancreas, along with increasing epinephrine secretion by the adrenal gland. These physiological responses prompt the behavioral response of carbohydrate ingestion prompted by neurogenic symptoms that originate from a sympathetic neural response (**Figure 1**). Altogether, a continuous supply of glucose to the brain is ensured.[10]

In diabetics, however, due to the lack of insulin-producing pancreatic beta cells, the feedback mechanisms that regulate insulin levels are obsolete. So the exogenously administered insulin is regulated merely by absorption and clearance. Additionally, the pancreas fails to secrete increased glucagon

Figure 1. Physiological and Behavioral Defenses Against Hypoglycemia in Humans[10]



Under normal physiological conditions, a drop in plasma glucose levels inhibits insulin production while stimulating increased production of glucagon and epinephrine. This in turn induces glucose production. Additionally, peripheral sensors stimulate the central nervous system, and the resultant neurogenic symptoms promote an increased intake of carbohydrates.

and the adrenal gland fails to increase epinephrine production (**Figure 2**). Together, these compromised physiological conditions in patients with diabetes result in a defective glucose counter-regulatory response (CRR) and increases their risk of hypoglycemic episodes at least 25-fold. Additionally, lack of symptoms of hypoglycemia due to attenuation of the sympathoadrenal response results in *hypoglycemia unawareness*, further increasing the risk of severe hypoglycemia 6-fold or more.[10]

Recent Findings

The results alluded to earlier, published in the journal *Diabetes*, teased out the exact mechanism of failure of the sympathoadrenal CRR in a rat model.

It has been long known that the rate of fall of blood glucose determines the participation of the brain (central nervous system) versus the peripheral nervous system to activate the CRRs. Rapid-onset hypoglycemia results in the activation of the brain glucosensing elements (hindbrain), whereas slow-onset hypoglycemia stimulates participation by the portal-mesenteric vein (PMV). However, the specific role of catecholamine neurons of the hindbrain in glucosensing has not been clear. In this paper, the authors highlighted that catecholamine neurons stimulate sympathoadrenal CRR during slow-onset hypoglycemia and that rate of onset is a major determinant of the mechanism adopted for the CRR.[4] The second study demonstrated that peripheral glucosensory response from the PMV is essential for activation of a complete CRR during slow-onset hypoglycemia.[5]

The lead authors on the 2 papers, Casey Donovan, PhD, professor and section head, human and evolutionary biology, Department of Biological Sciences at the University of Southern California, and Alan Watts, DPhil, professor in the same department, said in an e-mail response, "While it's been postulated that these various glucose-sensing loci constitute an extended neural network responsible for mediating the hypoglycemic CRR, there was not substantial evidence. These 2 papers now provide the first evidence demonstrating the existence of such a network. Specifically, we show that PMV glucose sensing input is critical for the activation of hindbrain neurons during slow-onset hypoglycemia and the subsequent CRR." They further pointed out that results from their neuronal activation data suggest that distinct neural networks are in play during rapid- vs slow-onset hypoglycemia. "The fact that hypoglycemia generally develops slowly in insulin-dependent diabetics points to the importance of fully understanding the functional organization of these glucose-engaged neural networks," say the authors.

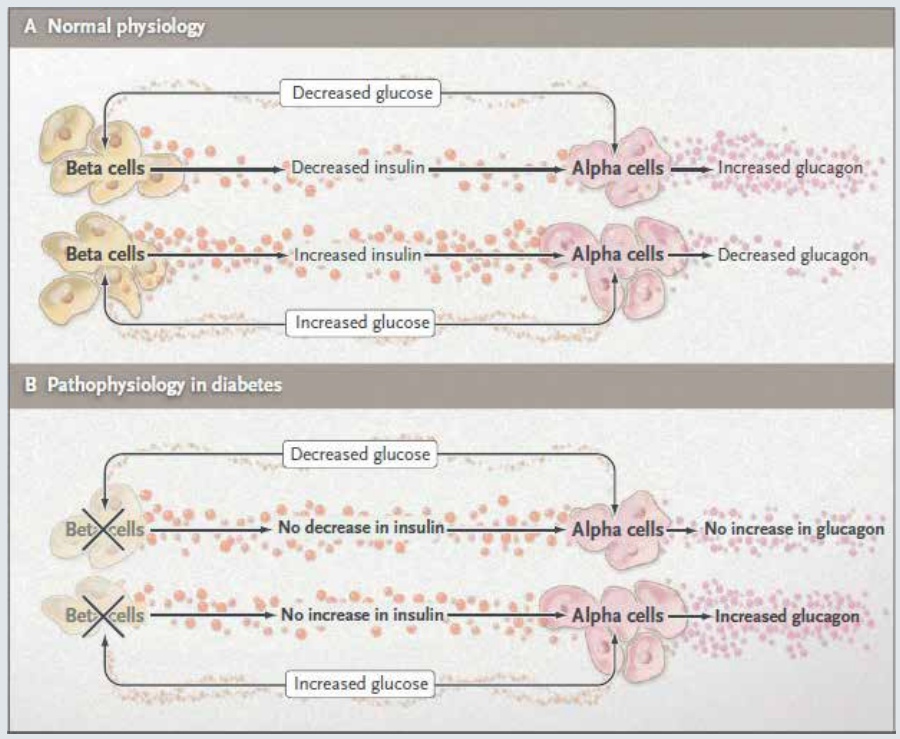
Philip E. Cryer, MD, Irene E. and Michael M. Karl Professor of Endocrinology and Metabolism in Medicine, Washington University School of Medicine, and a past president of the American Diabetes Association, summarized the significance of these findings in an e-mail: "The reports…provide evidence that signals from the periphery (eg, from the PMV) travel through the brain stem to the hypothalamus to mediate the sympathoadrenal response to relatively slowly developing hypoglycemia in rats.

"As developed in some detail,[10] the mechanism of the attenuated sympathoadrenal response to hypoglycemia that follows recent antecedent hypoglycemia occurs during sleep or follows earlier exercise and characterizes hypoglycemia-associated autonomic failure; however, its increased risk of iatrogenic hypoglycemia in diabetes is not known. It could directly involve the CNS (central nervous system) or the afferent or efferent components of the sympathoadrenal system." Cryer believes that understanding the physiology of this response could contribute to an improved understanding of the hypoglycemic episodes in diabetics.

A better handle on the mechanism of this avoidable phenomenon, via improved research efforts, is definitely the need of the day. **EBDM**

Two recent papers in Diabetes delved into the details of the feedback signals received by the brain following a drop in blood sugar in hypoglycemic diabetics. The research identified a startling difference in neuronal firing between slow-onset hypoglycemia and rapid-onset hypoglycemia.

Figure 2. Compromised Regulatory Response in Diabetic Patients[10]



Beta-cell failure compromises downstream alpha-cell glucagon secretion despite a drop in glucose levels in patients with diabetes.

References

1. Hypoglycemia. The American Diabetes Association website. http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html. Accessed April 23, 2014.

2. Severe low blood sugar occurs often in patients with type 2 diabetes [press release]. Oakland, CA: Kaiser Permanente; July 30, 2013. http://share.kaiserpermanente.org/article/severe-low-blood-sugar-occurs-often-in-patients-with-type-2-diabetes/. Accessed April 23, 2014.

3. Lipska KJ, Warton M, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the diabetes and aging study. *Diabetes Care*. 2013;36(11):3535-3542.

4. Jokiaho AJ, Donovan CM, Watts AG. The rate of fall of blood glucose determines the necessity of forebrain-projecting catecholaminergic neurons for male rat sympathoadrenal responses [published online April 16, 2014]. *Diabetes*. doi:10.2337/db13-1753.

5. Bohland M, Matveyenko AV, Saberi M, Khan AM, Watts AG, Donovan CM. Activation of hindbrain neurons is mediated by portal-mesenteric vein glucosensors during slow-onset hypoglycemia [published online April 11, 2014]. *Diabetes*. doi:10.2337/db13-1600.

6. Pietri G, Kennedy K, Goldhammer M, Bouchard J. The cost of severe hypoglycemic events in diabetes: a retrospective claims database study. Poster presented at: ISPOR 17th Annual International Meeting; June 2012; Washington, DC. http://www.ispor.org/research_pdfs/40/pdffiles/PDB37.pdf. Accessed April 24, 2014.

7. Quilliam BJ, Simeone JC, Ozbay AB, Kogut SJ. http://www.ajmc.com/publications/issue/2011/2011-10-Vol17-n10/AJMC_11oct_Quilliam_673to680#sthash.A0WyNwqV.dpuf. *Am J Manag Care*. 2011;17(10):673-680.

8. Busko M. Insulin-related hypoglycemia: common, costly, preventable. Medscape. http://www.medscape.com/viewarticle/821764. Published March 11, 2014. Accessed April 24, 2014.

9. Seaquist ER, Anderson J, Childs B. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36(5):1384-1395.

10. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med*. 2013;369:362-372.

Inhaled Insulin's Long Journey to Commercialization
(continued from cover)

body, it must also be practical. An insulin product must be easy to use and small enough to carry around for use when needed.

Results have been mixed. Pfizer achieved FDA approval of its product Exubera in 2006 with considerable fanfare and lofty sales expectations of $2 billion a year, but then withdrew the product a year later, taking a $2.6-billion corporate charge.

Pfizer's Exubera was successful in clinical trials. The real world was another story. Exubera did deliver insulin deep into the lungs. However, the delivery system was 1 foot long, ungainly, and much too large to fit into a purse. Dose adjustment was time consuming (selection of a specific dose was not possible) and required more patient education than Pfizer anticipated. A series of blisters needed to be inserted into the device, followed by activation of an air pump. Needless to say, this was not a discreet activity.[2]

Patients with T1DM avoided using it, but providers also avoided prescribing it. Mark Feinglos, MD, professor of medicine, and division chief, endocrinology, metabolism, and nutrition at Duke University, commented, "What really caused Exubera's failure was that in order to put people on it you had to explain to them how to use it very carefully, and pulmonary function tests had to be done. It was very labor intensive." The average primary care physician had too little time to invest in this new therapy.

Pfizer soon realized the magnitude of the gap between sales expectations and reality, and Exubera was withdrawn at the end of 2007. To complicate matters, a connection (somewhat tenuous) was drawn between use of Exubera and subsequent cases of lung cancer. In 2008, 6 cases of lung cancer were reported in patients who used Exubera (and also smoked) versus 1 patient using a control inhaler. Although the numbers were not statistically significant, and causation has not been established, the possibility of a connection between lung cancer and inhaled insulin made later efforts to popularize inhaled insulin challenging.

Some researchers believe inhaled insulin is mediated through IGF-I receptor activation by high local concentrations of inhaled insulin that become lodged in bronchial tissue.[3] Pfizer's experience helped scuttle the developmental work of 2 other manufacturers (Lilly and Novo Nordisk) whose inhaled insulin technologies were in late-stage trials.[1]

> ***"It appears to me like [Pfizer] didn't do enough market research, because Exubera was inconveniently large, drawing even more attention to the user than an insulin injection would. I think Afrezza has addressed this fairly well with its inhaler."***
>
> **— Manny Hernandez**
> Diabetes Hands Foundation

Afrezza on the Verge

MannKind, which was also working on its inhaled insulin product Afrezza, continued efforts and filed a new drug application in March 2009 for use with its first-generation MedTone inhaler.

Manny Hernandez, president of the Diabetes Hands Foundation as well as AskManny, told *Evidence-Based Diabetes Management,* "I think it is fair to say that the Exubera failure made the demands on and the expectations for Afrezza higher. We want to make sure that the new drugs are safe and effective for patients.

"Judging from the form factor of the Exubera inhaler," Hernandez continued, "it appears to me like [Pfizer] didn't do enough market research, because Exubera was inconveniently large, drawing even more attention to the user than an insulin injection would. I think Afrezza has addressed this fairly well with its inhaler."

Afrezza uses an ultra-rapid-acting formulation, and it showed promise in initial clinical trials. It comprises insulin formed into particles 2 to 3 µm in diameter, which are then lyophilized into a dry powder for inhalation. The insulin used is a type of regular human insulin. Unlike regular insulin, the dry form does not require refrigeration.

Afrezza proved to be at least equivalent in combination with insulin glargine to multiple daily injections with an intermediate-acting insulin and basal insulin.[4] Additionally, it did not interfere with pulmonary function.[5] However, the FDA issued a complete response letter requiring additional information. MannKind resubmitted the application in early 2010 (but this time with a smaller, second-generation inhaler called Dreamboat). FDA rebuffed the manufacturer again in January 2011, requesting 2 additional clinical trials.[6] This time, the FDA also required comparisons of Afrezza's Dreamboat inhaler with the MedTone Inhaler, to better understand whether clinical studies using the original inhaler could be applied to FDA decision making with the new inhaler. The new "bridging" study would assess not only "performance characteristics, usage, handling, shipment, and storage," but safety information and proposed user training.[6]

Bottom left, MannKind's Afrezza and its Dreamboat inhaler. Top right, the delivery system of Exubera.

The 2 clinical trials posted positive results. The first study evaluated the inhaled insulin in 2 inhaler types (its older MedTone inhaler and newer-generation Dreamboat inhaler) compared with rapid-acting insulin aspart mealtime injections, in a 12-week observational, open-label study design for 518 patients with T1DM. All patients were first optimized on a basal insulin regimen. The study results established similar levels of glycated hemoglobin (A1C) reduction for both insulin aspart and Afrezza and its next-generation inhaler. However, Afrezza was associated with a reduction in fasting blood glucose (FBG) levels, whereas aspart was associated with increased FBG concentrations. The frequency of all hypoglycemia events favored Afrezza and its next-generation inhaler, but there was no significant difference in severe hypoglycemic events. Patients experienced a mean weight loss of 0.4 kg in the Afrezza Dreamboat group, compared with a 0.9 kg weight gain in the insulin aspart group.[7]

Next, Afrezza was tested against oral therapy alone in a double-blind, placebo-controlled study of 353 patients with type 2 diabetes mellitus (T2DM) whose disease was uncontrolled on metformin with or without a second or third oral medication. Participants were given their oral therapy in addition to either Afrezza or an identical inhaler with placebo microspheres.

Over 24 weeks of treatment, Afrezza therapy was associated with significantly lower mean A1C concentrations (0.82- vs 0.42-point reduction in the inhaled insulin and oral therapy groups, respectively [P <.0001]) and 30% of the Afrezza group reaching A1C levels of 7.0% or below compared with 19% of the oral therapy group (P <.0005). Sixteen percent of those using inhaled insulin attained an A1C level of no greater than 6.5% compared with 4% of those assigned to receive oral therapy (P <.0021). Patients receiving Afrezza had a higher rate of mild to moderate hypoglycemia (but no patient discontinued as a result of this side effect) and experienced a mean weight gain of 0.5 kg.[8]

In October 2013, MannKind filed its

third new drug application for Afrezza. The FDA's internal staff compiled an internal report indicating that some problems still existed and that claims of noninferiority to insulin aspart could not be supported. However, on April 1, 2014, the FDA's Advisory Committee voted 13-1 to recommended approval for its use in T1DM and 14-0 for use in T2DM.[9] The FDA then delayed the product's prescription drug user fee act date (PDUFA) from April 15 to July 15, 2014, the deadline for the latest (or final) chapter in MannKind's long, difficult trek to approval.

However, as MannKind spent nearly $1.5 billion on the journey to approve Afrezza, industry consultants doubt that it has the capital to market the product.[9,10] Undoubtedly, MannKind will need a marketing partner, and with some major players withdrawing from the inhaled insulin market, the company may find this challenging.

Even if it does receive approval and find a commercialization partner, MannKind shouldn't expect patients to run to therapy, said Tenderich, who has T1DM. "With any new formulation, we don't really know what the long-term effects will be, like how it may affect the lungs," she said. "The FDA is doing its best to mitigate those concerns, but it may take 5 to 15 years of real-world experience to find out how safe it actually is." She also pointed out that for patients such as herself with T1DM, "We need more precision dosing for the most part, matched to the amount of carbs we eat. It's hard to believe that we can get this precise level of dosing, but we're being told otherwise."

A Patient's Opinion of Unmet Need

What is the sweet spot for the inhaled insulin market? *Evidence-Based Diabetes Management* interviewed Manny Hernandez, president of the Diabetic Hands Foundation and @Ask Manny, about the market for Afrezza.

EBDM: What is the gap in care that an inhaled insulin might fill?
Hernandez: A very important number of people with type 2 diabetes have avoided "getting to" insulin for years... in no small part because it's injected. I can't blame them. I was misdiagnosed with type 2 diabetes back in 2002, and eventually correctly diagnosed as having type 1 (and had to start injecting insulin). It does change you: life is never the same after you have to start taking shots. When you know life without shots, it's much harder to start them.

In the case of someone with type 1, there's no option. In the case of so many people with type 2 disease, while there may be options earlier on, there can be a point where it may be ideal to include insulin as part of the treatment. But the "psychological insulin resistance" can be so strong that the person cannot get past it, getting essentially stuck in a place of poorer control, and potentially leading to complications.

This is where inhalable insulin can disrupt things. I do believe we can see a deep impact in terms of control. The 1 thing I look forward to seeing is that it can be affordable to patients who most need it; so another important element to consider is the reimbursement side of things...but that's a whole other story.

If the inhaled insulin is just as effective as its injected counterpart, to me the fact that it doesn't need to be injected makes it a very important option to offer to patients.

EBDM: If the FDA does approve Afrezza in July, how do you think patients will react?
Hernandez: If the drug is approved, it will still be a while before it is actually available to patients broadly. Distribution can be challenging. However (assuming it's approved), once it's available, the people at MannKind will need to spend important time and energy raising awareness around the new treatment option, because it's not going to simply be a new insulin, but an altogether new type of insulin delivery that doesn't involve injections.

I think an important percentage of patients (especially people with type 2 diabetes) will ask their physicians to look into this. I certainly hope physicians listen...but first let's see what happens in July.

An Experienced Dancer in the Wings

A relatively new (but not *that* new) player in the inhaled insulin development drama is Dance BioPharm. Started in 2010 by members of the team involved with Pfizer's Exubera, Dance is working on a pocket-sized electronic insulin inhaler. This product (dubbed Adagio) has finished phase 2 trials (its clinical trial information has not been publicized) and is awaiting the beginning of its pivotal phase 3 testing. According to Dance's website, insulin is provided as a liquid not a powder in Adagio, and drops are deposited into a reservoir on the top of the device for use at mealtimes.

Evidence-Based Diabetes Management contacted John Patton, PhD, CEO of Dance BioPharm, but he indicated that he could not comment because his company was preparing for an initial public offering.

If You Build It, Will They Come?

Should it be approved, MannKind believes that its product will retail for somewhere between $100 to $200 per inhaler. From the patient's point of view, Tenderich believes that the needleless attribute of inhaled insulin may be a bit less attractive than proposed. If this product is to be used in patients requiring basal insulin, a daily injection is still needed, "and for most of us with type 1, the needles are so tiny, and they aren't the biggest issue," she said. "This may be more appealing to the type 2 patient, for the crowd who is worried about injecting," Tenderich said. "In any case, patients are pretty savvy these days, and they will want to know about the side effects, and of course, whether their insurance will cover the therapy, and how much will it cost them."

Feinglos agreed that Afrezza may be a better bet for patients with T2DM, but for a different reason. "The absorption is a very small percentage of what you give, so it's really good for people with type 2 diabetes who need a boost in insulin," Feinglos said. "But for someone with type 1 diabetes who happens to be very sensitive to insulin and needs to make very small changes in dose, it might not be the right thing for them" despite the advantages of the inhaler over injections.

He pointed out that providers have concerns with Afrezza that are similar to those with the original approval of Exubera. "The education and testing challenges for the physician's office remain," reminded Feinglos. "But how do you get around the problem of physicians actually prescribing it? Again, remember that most people with diabetes are cared for by primary care physicians, not by specialists. And you know very well how limited is the amount of time that the primary care physicians have. And not all of them have educators in the practice, not even group practices necessarily have educators. So how do you get people onto a drug like this and how do you monitor them successfully? That's where the problem may well come up again." **EBDM**

References

1. Kling J. Dreamboat sinks prospects for fast approval of inhaled insulin. *Nat Biotechnol.* 2011; 29:175-176.

2. Heineman L. The failure of Exubera: are we beating a dead horse? *J Diabetes Sci Technol.* 2008;2(3):518-529.

3. Mayer P, Reitzenstein U, Warnken M, Enzmann H, Racké K. Insulin action on H292 bronchial carcinoma cells as compared to normal bronchial epithelial cells. *Pulm Pharmacol Ther*. 2012;25(1): 104-114.

4. Rosenstock J, Lorber DL, Gnudi L, et al. Prandial inhaled insulin plus basal insulin glargine versus twice daily biaspart insulin for type 2 diabetes: a multicentre randomised trial. *Lancet*. 2010;375:2244-2253.

5. Raskin P, Heller S, Honka M, et al. Pulmonary function over 2 years in diabetic patients treated with prandial inhaled Technosphere Insulin or usual antidiabetes treatment: a randomized trial. *Diabetes Obes Metab*. 2012;14:163-173.

6. MannKind Corporation receives complete response letter from the FDA for AFREZZA(R) [press release]. Valencia, CA: MannKind; January 11, 2011. http://www.news.mannkindcorp.com/phoenix.zhtml?c=147953&p=irol-newsArticle&ID=1517413&highlight=. Accessed April 22, 2014.

7. Mannkind reports positive data from a phase 3 clinical study of Afrezza in patients with type 1 diabetes [press release]. Valencia, CA: MannKind; August 14, 2013. http://www.news.mannkindcorp.com/phoenix.zhtml?c=147953&p=irol-newsArticle&ID=1847570&highlight=. Accessed April 23, 2014.

8. MannKind reports positive data from a phase 3 clinical study of AFREZZA in patients with type 2 diabetes [press release]. Valencia, CA: FierceBiotech; August 14, 2013. http://www.fiercebiotech.com/press-releases/mannkind-reports-positive-data-phase-3-clinical-study-afrezza-patients-type-1#ixzz30JdsWpur. Accessed April 22, 2014.

9. Pollack A. Inhaled insulin clears hurdle toward F.D.A. approval. *The New York Times,* April 1, 2014. http://www.nytimes.com/2014/04/02/health/inhaled-insulin-clears-advisory-hurdle-toward-fda-approval.html?_r=2. Accessed April 28, 2014.

10. Carroll J. Questions on MannKind's inhaled insulin PhIII data cloud Afrezza's future. Fierce Biotech; August 15, 2013. http://www.fiercebiotech.com/story/questions-mannkinds-inhaled-insulin-phiii-data-cloud-afrezzas-future/2013-08-15#ixzz30NVLOcKm. Accessed April 28, 2014.

Role of Bioinformatics
(continued from cover)

tionally, sequences from issued patents are submitted by the US Patent and Trademark Office.[3] Despite the open access to this database, researchers all over the world have actively contributed to building up the resource, realizing the vast potential of this knowledge-sharing database. The information either goes to GenBank or is submitted through its European counterpart, the European Bioinformatics Institute (EBI), or its Japanese counterpart, the DNA Data Bank of Japan (DDJB).[4] All the leading journals need researchers to submit their sequences to GenBank and cite the corresponding access number in the published article. The new sequences can be directly submitted to EBI, DDJB, or GenBank, and the 3 databases are synchronized daily for easy access to all the information on all 3 databases. The data are virtually in real time, with minimal delay in access to the latest data, free of cost.

Other commonly used nucleotide databases include the European Molecular Biology Laboratory (EMBL; EBI is run by EMBL), SwissProt, PROSITE, and Human Genome Database (GDB).[5] Taken together, these databases are essentially a *bioinformatics* tool that helps integrate biological information with computational software. The information gained can be applied to understand disease etiology (in terms of mutations in genes and proteins) and individual variables, and ultimately aid drug development.

According to the National Institutes of Health Biomedical Information Science and Technology Initiative, bioinformatics is defined as "research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral, or health data, including those to acquire, store, organize, archive, analyze, or visualize such data."[6]

Development of GenBank

Initially called the Los Alamos Sequence Database, this resource was conceptualized in 1979 by Walter Goad, a nuclear physicist and a pioneer in bioinformatics at Los Alamos National Laboratory (LANL).[7] GenBank followed in 1982 with funding from the National Institutes of Health, the National Science Foundation, and the Departments of Energy and Defense. LANL collaborated with various bioinformatics and technology companies for sequence data management and to promote open access communications. By 1992, GenBank transitioned to being managed by the National Center for Biotechnology information (NCBI).[8]

Submissions to the database include original mRNA sequences, prokaryotic and eukaryotic genes, rRNA, viral sequences, transposons, microsatellite sequences, pseudogenes, cloning vectors, noncoding RNAs, and microbial genome sequences. Following a submission (using the Web-based BankIt or Sequin programs), the GenBank staff reviews the documents for originality and then assigns an accession number to the sequence, followed by quality assurance checks (vector contamination, adequate translation of coding regions, correct taxonomy, correct bibliographic citation) and release to the public database.[3,8]

How Are Researchers Utilizing This Database?

BLAST (Basic Local Alignment Search Tool) software, a product of GenBank, allows for querying sequence similarities by directly entering their sequence of interest, without the need for the gene name or its synonyms.[4] An orphan (unknown) or de novo nucleotide sequence, which may have been cloned in a laboratory, can gain perspective following a BLAST search and a match with another, better-characterized sequence in the database. Further, by adding restrictions to the BLAST search, only specific regions of the genome (such as gene-coding regions) can be examined instead of the 3 billion bases.[4] BLAST can also translate a DNA sequence to a protein, which can then be used to search a protein database.

BLAST, which was developed at NCBI, works only with big chunks of nucleotide sequences, and not with shorter reads, according to Santosh Mishra, PhD, director of bioinformatics and co-director of the Collaborative Genomics Center at the Vaccine and Gene Therapy Institute (VGTI) of Florida. Mishra, who worked as a postdoctoral research associate with Goad at LANL, was actively involved in developing GenBank. His work contributed to the generation of the "flat file" format, and he also worked on improving the query-response time of the search engine. Additionally, he initiated the "feature table" in GenBank—the documentation within that helps GenBank, EMBL, and DDJB exchange data on a daily basis.

According to Mishra, the STAR aligner, developed at Cold Spring Harbor, works better with reference sequences, while Trinity, developed at the Broad Institute in Cambridge, Massachusetts, is useful for de novo sequences. (The Broad Institute made news last month with its work on identifying gene mutations that prevent diabetes in adults who have known risk factors, such as obesity.)

Advantages and Disadvantages of the GenBank Platform

The biggest single advantage of GenBank is the open-access format, which allows for a centralized repository in a uniform format. The tremendous amount of data generated by laboratories (such as from microarrays and microRNA arrays) cannot be published in a research article. However, the data, tagged and uploaded on GenBank, can be linked to the journals' websites and the links can be provided in the print versions of the articles as well.[4]

On the flip side, the biggest advantage of being an open-access platform is also the biggest disadvantage of the software. There's always the probability of scientists registering faulty genetic sequences on the website, which will not be caught unless they are peer reviewed. Despite the incorporation of several quality control mechanisms into the system, reuse of the data by other scientists alone can help discover glitches in the existing data. Additionally, GenBank encourages its users to submit feedback and update records, which unfortunately is not a very proactive process.[4]

Bioinformatics and Pharmacogenomics in Drug Discovery/Development

Accelerating the drug development process saves costs for the pharmaceutical industry, especially with the way the industry functions today. The company that discovers or invents a new chemical entity, which could metamorphose into a new drug candidate, can squeeze the maximum profit out of the drug before the patent expires and competitors catch on. Essentially, companies jump at every opportunity to accelerate any aspect of the discovery/development process. Resources like the GenBank and EBI are data mines that can speed up the entire process in the following ways:

Target identification: Drug candidates can be identified (following a high-throughput screen of chemical libraries) and developed only after a "druggable target" is discovered for a disease condition. Typically, about 1 in 1000 synthesized compounds will progress to the clinic, and only 1 in 10 drugs undergoing clinical trials reaches the market.[9] Optimizing/validating a target is essential due to the prohibitively high cost of conducting trials, and the potential targets for drug discovery are increasing exponentially.[10] By mining and storing information from huge data sets, like the human genome sequence, the nucleotide sequence of the target proteins has become readily available, as has the potential to identify new targets. This can exponentially increase the content of the drug pipelines of pharmaceutical companies.[10]

According to Arathi Krishnakumar, PhD, a protein biochemist and a senior research investigator with the department of Exploratory Biology and Genomics, Bristol-Myers Squibb (BMS), "For compounds that have no obvious targets from a typical phenotypic screening, proteomics offers tools for target identification or target deconvolution. Monitoring the global phosphorylation status of proteins that are downstream of tyrosine kinase inhibitors—also termed phosphoproteomics—is a very attractive tool that can also be used for target as well as biomarker identification. These events can be used as reporters (biomarkers) for specific upstream kinase(s)."

The biggest advantage of being an open access platform is also the biggest disadvantage of the software. Errors are always a possibility.

The previous issue of *Evidence-Based Diabetes Management* reported on the identification of a mutation in the gene *SLC30A8* that protected individuals from developing T2DM. The mutation was identified by genetic tests conducted in more than 150,000 individuals, a multi-collaborative effort between the Broad Institute, Massachusetts General Hospital, Pfizer, and Amgen.[11]

Target validation: Establishing a robust association between a likely target and the disease, to confirm that target modulation translates into a beneficial therapeutic outcome, would not only validate the drug development process but also help absorb the risks associated with clinical trial failure of the molecule being developed.[10]

Says Krishnakumar, "Target validation is typically done with knock-out or knock-down of the proposed target using RNAi and then monitoring the disease phenotype in relevant cellular

models. Proteomics tools are also highly valuable in monitoring specific events on proteins like post translational modifications, including phosphorylation, methylation, oxidation, etc, new product generation, degradation products, protein-protein interaction, etc, all of which could be direct or indirect consequences of target activation or engagement."

Cost reduction: The drug development process is not just lengthy (product development can take 10 to 15 years[9]), but prohibitively expensive as well. Averaging $140 million in the 1970s, the cost of developing a drug was estimated at a whopping $1.2 billion in the early 2000s,[12] and a recent *Forbes* analysis estimated the cost at $5 billion.[13]

Worth noting is that the final cost of any drug, which includes the total costs from discovery to approval, includes the cost of absorbing all the clinical trial failures.[10] Clearly, bioinformatics tools improve the efficiency of target discovery and validation processes, reduce the time spent on the discovery phase, and make the entire process more cost-effective.

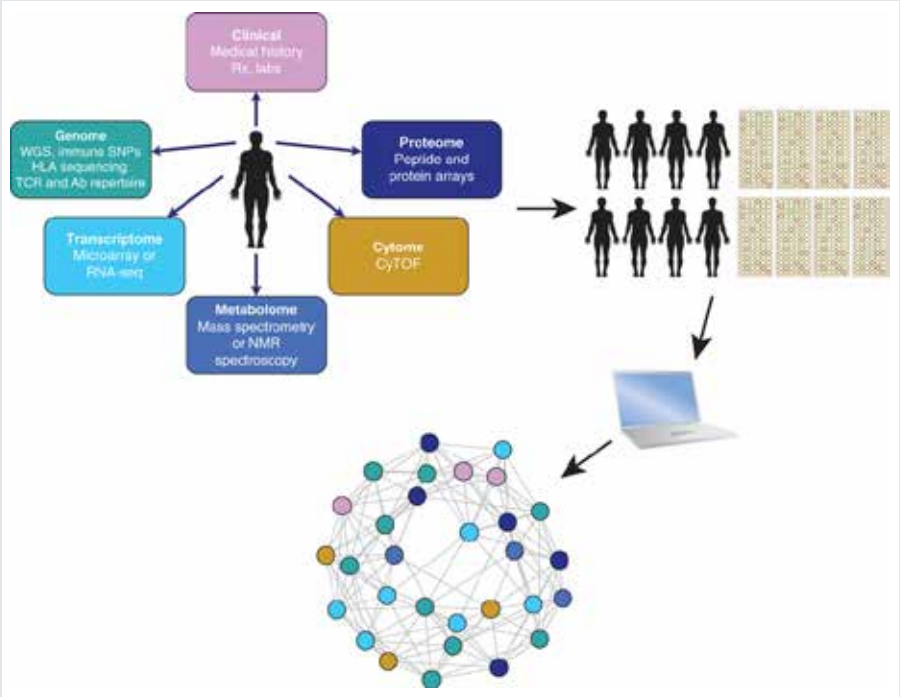
Mishra believes GenBank is a good starting point in the drug discovery process. When a new sequence (of known or unknown function) is identified/isolated in the laboratory, a GenBank search will help identify homologues (human or in other organisms) with a 70% to 80% match. Functional studies would then ensue, along with cell and tissue distribution studies.

Industry Partnerships

With the value of personalized medication gaining acceptance, the study of *pharmacogenomics* (genetic variants that determine a person's drug response; one size does not fit all) is extremely helpful to tailor the optimal drug, dose, and treatment options for a patient to improve efficacy as well as avoid adverse events (AEs).[10] According to the Agency for Healthcare Research and Quality of the HHS, AEs annually result in more than 770,000 injuries and deaths and may cost up to $5.6 million per hospital.[14]

To this end, EMBL-EBI is actively involved in industry partnerships (the partnerships were initiated in 1996), which include Astellas, Merck Serono, AstraZeneca, Novartis, GlaxoSmithKline, BMS, and several others.[15] With the high-throughput data that research and development (R&D) activities generate, open-source software and informatics developed by organizations like the GenBank and EBI could greatly improve efficiency and reduce the cost of drug discovery and development.

Figure. Integrating Bioinformatics With Biology for Precision Medicine



Source: *Nature Immunol*. 2014,15:118-127.

Translational Bioinformatics and Precision Medicine

Healthcare today is primarily symptom driven, and intervention usually occurs late in the pathological process, when the treatment may not be as effective. Identifying predisease states that could provide a window into the forthcoming risk of developing a disease, identifying reliable markers, and developing useful therapies would be the key to managing disease treatment[16]—not just to improve efficiency but also to reduce healthcare costs, which it is estimated will steadily increase and by 2022 account for 19.9% of the gross domestic product (GDP).[17]

With *precision medicine* or *personalized medicine*, molecular profiles generated from a patient's genomic (coupled with other "-omics" such as epigenomics, proteomics, and metabolomics) information could help accurately drive the diagnostic, prognostic, and therapeutic plans, tailored to the patient's physiological status. Predictive models can also be developed for different biological contexts, such as disease, populations, and tissues.[15] However, the deluge of data generated by bioinformatics tools requires a framework to regulate, compile, and interpret the information. Most importantly, the key stakeholders (government, research industry, biological community, pharmaceutical industry, insurance companies, patient groups, and regulatory bodies[17]) that would drive the widespread acceptance and implementation of precision medicine need to be brought up to speed with the enormous progress made in the field and the promise it brings. There would also be a revolutionary change in the approach to conducting clinical trials—the phase 3 studies conducted in the target population could focus on a more select patient group, which could improve both clinical and economic efficacy.[18]

At BMS, Krishnakumar's group actively provides support to clinical trials by developing assays for clinical samples. When it comes to administration of biologics such as antibodies, individual variations such as expression levels of various proteins and their affinity for an antibody necessitate dose-titration in order to *personalize* treatment to improve efficacy.

The developing field of *translational bioinformatics* creates a platform to bring all the data together, which can then be used to generate a treatment plan personalized to a patient (**Figure 1**). It has been defined as "the development of storage, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data into proactive, predictive, preventative, and participatory health."[15] The primary goal of translational bioinformatics is to connect the dots and develop disease networks that can be used as predictive models. In other words, *harmonization* of the data from different sources (genome, proteome, transcriptome, metabolome, and patient's pathological data) could help in making better-informed treatment decisions.

Within medical R&D, a commonly held belief is that cures for diseases could be found residing within existing data, if only the data could be made to give up their secrets.[19] The current status of the scientific, medical, and healthcare fields is that experts in each field have set their minds on developing the best technologies; unfortunately, the technologies are compartmentalized and they work in parallel. The great need, which has been recognized and implemented in limited areas, is to create platforms where the data can be merged to produce meaningful outcomes.

Data Integration Platforms to Boost Evidence-Based Decisions

Implementing these huge changes would necessitate that physicians and providers be more adept at interpreting molecular data, which essentially requires improved education models that include relevant courses during graduate training. Also, development of software that can interpret the data would provide a tremendous advantage to researchers, clinicians, scientists, pathologists, and maybe patients as well.

An application developed by Remedy Informatics, TIMe, boosts the process further. TIMe merges data, registries, applications, analyses, and any other relevant content. TIMe promises to enable faster, more informed decisions in clinical practice, research, and business operations. It also is expected to improve treatment effectiveness, quality of care, and patient outcomes.[20]

In Europe, a collaborative project (DIRECT) was initiated in 2012 by 4 pharmaceutical companies and 21 academic institutions, with the objective of stratifying diabetic patients based on biomarker identification, which would allow targeted intervention, monitor treatment response, conduct stratified trials, and identify nonresponders or those who might be intolerant to treatment.[21] The pharmaceutical companies participating in this effort include sanofi-aventis, Eli Lilly, Servier, and Novo Nordisk. DIRECT, in turn, constitutes 1 of 3 consortia under development by the Innovative Medicines Initiative (IMI). IMI, a partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations, includes DIRECT, IMIDIA (to slow disease progression by

improving beta-cell function), and SUMMIT (developing surrogate markers for late-stage micro- and macro-vascular complications), collaborative efforts aimed to develop novel individualized therapies with improved efficacy and safety.[22]

Applications of Translational Bioinformatics

Once the genomic and/or proteomic data have been generated, what next? How are providers employing these data to their advantage and to guide treatment? There are several reports on clinical studies that are being successfully conducted on the foundation of precision as well as evidence-based medicine.

Researchers at the University of Southampton have developed a blood test that identifies young children at risk for developing obesity. The test, to be conducted in children as young as 5 years, differentiates between those with high body fat and those with low body fat when they grow older. This test, which identifies epigenetic changes (DNA methylation), showed that a 10% increase in DNA methylation at age 5 years translates into 12% more body fat by the time the children are 14 years old, independent of gender, physical activity, or their timing of puberty. The principal investigators on the study believe that identifying at-risk children could help make lifestyle modifications early on to help disease management.[23]

Genetic analysis using genotyping and sequencing techniques in a family of type 1 diabetes mellitus (T1DM) patients resulted in the identification of a mutation in the *SIRT1* gene, which produces a defunct SIRT-L_{107}P protein. Essentially, the study identified that the mutant protein was responsible for an autoimmune disorder in the family: 4 members suffered from T1DM and 1 developed ulcerative colitis. Overexpression of SIRT-L_{107}P in beta cells in vitro resulted in an increased expression of nitric oxide, the cytokine TNF-α, and the chemokine KC, compared with the controls. Additionally, *SIRT1* knockout mice were more susceptible to islet destruction and hyperglycemia following induction of pancreatic insulitis.[24] The study provides a foundation for the application of SIRT1 activators, already under development for aging and other metabolic disorders, in T1DM therapy.

Bioinformatics studies have also yielded microRNAs, which are small (~22 nucleotides), noncoding RNA molecules that can repress the transcription of messenger RNA (mRNA) or promote its degradation, thereby silencing gene expression.[25] Initially thought of as "junk" sequences on the DNA since they are non-coding nucleotides, miRNAs (about 24,521 listed in miRBase, a database maintained by the University of Manchester[26]) have now found their place in clinical trials as biomarkers (cancer,[27] multiple sclerosis,[28] psoriasis[29]) and are also being developed as "drugs" by companies like Mirna Therapeutics Inc.[30]

The "Adaptive" Clinical Trial Design

The 'omic' revolution has also had a tremendous impact on clinical trial design. The FDA definition of an adaptive clinical study is "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data from subjects in the study."[31] The trial design includes interim analysis points that would allow researchers to alter the trial (treatment dose or schedule, randomization) based on results from earlier study participants. Two of the 20 ongoing adaptive trials recently published positive results.

The adaptive design was implemented in a phase 2/3 study of dulaglutide, a once-weekly glucagon-like peptide analogue being developed for T2DM. Stage 1 of the trial included an adaptive dose-finding design that could lead to dose selection or early termination due to futility. The trial was expected, should the dose selection be achieved, to enter the second stage to continue evaluation of the selected doses. Completion of the 2 stages was expected to serve as a confirmatory phase 3 trial.[32]

A software company, Aptiv Solutions, has developed 2 different softwares: FACTS for the design and simulation of early-phase adaptive clinical trials, and ADDPLAN DF for early-phase dose-finding studies.[33]

Genetic Testing to Determine Disease Susceptibility

Genetic testing for T1DM and T2DM is possible. Expression of HLA-DR3 or HLA-DR4 in Caucasians, HLA-DR7 in African Americans, and HLA-DR9 in Japanese have been identified as markers for increased susceptibility to T1DM.[34] Recent studies have also identified a mutation in SIRT1 in T1DM patients, as referred to earlier.[24] Several T2DM susceptibility genes have been identified, including *PPARγ*, *ABCC8*, *KCNJ11*, and *CALPN10*, while maturity-onset diabetes of the young has been associated with a host of other genes.[35]

Then you have J. Craig Venter, PhD, a biologist and entrepreneur, who competed with the Human Genome Project to sequence the human genome and who recently announced the launch of a new company, Human Longevity. The company plans to sequence 40,000 human genomes per year to gain insights into the molecular causes of aging and age-associated diseases such as cancer and heart disease.[36]

The Healthcare Equation

Insurance companies are rapidly adapting to this changing scene of "big data" in their own right. Back in 2011, Aetna announced a partnership with the Center for Biomedical Informatics at Harvard Medical School with the aim of improving the quality and affordability of healthcare (healthcare informatics). The researchers at Harvard aimed to:

- Evaluate the outcomes of various treatments for specific conditions based on quality and cost
- Determine factors that predict adherence for chronic diseases
- Study how claims data and clinical data, available through electronic health records, can best be used to predict outcomes
- Improve the ability to predict adverse events through a proactive study of claims and clinical data.[37]

The possibilities are enormous, with application in all disease fields. Translational bioinformatics integrates the various data sources and paves a path for precision medicine that would be immensely valuable to all stakeholders (patients, pharmaceutical companies, scientists, and physicians) alike. **EBDM**

References

1. Statistics about diabetes. American Diabetes Association website. http://www.diabetes.org/diabetes-basics/statistics/infographics.html. Accessed April 28, 2014.

2. Medicines in development: diabetes. PhRMA website. http://www.phrma.org/sites/default/files/pdf/diabetes2014.pdf. Accessed April 28, 2014.

3. Benson DA, Clark K, Karsch-Mizrachi I, Lipman DJ, Ostell J, Sayers EW. GenBank. *Nucleic Acids Res.* 2014;42:D32-D37.

4. McEntyre J, Lipman J. GenBank - a model community resource? *Nature*. http://www.nature.com/nature/debates/e-access/Articles/lipman.html. Published 2007. Accessed February 27, 2013.

5. Bioinformaticsweb website. http://bioinformaticsweb.net/data.html. Accessed March 5, 2014.

6. NIH working definition of bioinformatics and computational biology. National Institutes of Health website. http://www.bisti.nih.gov/docs/CompuBioDef.pdf. Accessed March 5, 2014.

7. Walter Goad papers. American Philosophical Society website. http://www.amphilsoc.org/mole/view?docId=ead/Mss.Ms.Coll.114-ead.xml. Accessed March 4, 2014.

8. The GenBank submissions handbook. NCBI website. http://www.ncbi.nlm.nih.gov/books/NBK51157/. Accessed March 4, 2014.

9. Tamimi NA, Ellis P. Drug development: from concept to marketing! *Nephron Clin Pract.* 2009;113(3):c125-c131.

10. Katara P. Role of bioinformatics and pharmacogenomics in drug discovery and development process. *Netw Model Anal Health Inform Bioinforma*. 2013;2:225-230.

11. Caffrey MK. Study on protective gene mutations for T2DM appears to have strong implications for drug development. *Evidence-Based Diabetes Management*. 2014;20(SP4):SP102.

12. 2013 profile: pharmaceutical research industry. PhRMA website. http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf. Accessed March 6, 2014.

13. Herper M. The cost of creating a new drug now $5 billion, pushing big pharma to change. *Forbes* website. http://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/. Published August 11, 2013. Accessed March 6, 2014.

14. Reducing and preventing adverse drug events to decrease hospital costs. Agency for Healthcare Research and Quality website. http://www.ahrq.gov/research/findings/factsheets/errors-safety/aderia/index.html. Accessed March 10, 2014.

15. Industry partnerships. The European Bioinformatics Institute website. http://www.ebi.ac.uk/industry. Accessed March 5, 2014.

16. Readhead B, Dudley J. Translational bioinformatics approaches to drug development. *Adv Wound Care (New Rochelle)*. 2013;2(9):470-489.

17. National health expenditure projections 2012-2022. CMS website. http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/proj2012.pdf. Accessed March 10, 2014.

18. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. *NEJM*. 2012;366(6):489-491.

19. Kennedy GD. Enterprise informatics: key to precision medicine, scientific breakthroughs, and competitive advantage. Remedy Informatics; 2013.

20. TIMe™ – the informatics marketplace. Remedy Informatics website. http://remedyinformatics.com/mosaic-platform/time-the-informatics-marketplace/. Accessed March 14, 2014.

21. DIRECT - innovative medicines initiative: DIabetes REsearCh on patient straTification. DIRECT website. http://www.direct-diabetes.org/index.php. Accessed April 28, 2014.

22. The IMI diabetes platform. IMI website. http://www.direct-diabetes.org/news-events/flyer-screen-einzelseiten.pdf. Accessed April 28, 2014.

23. Blood test may help predict whether a child will become obese. ScienceDaily website. Published March 25, 2014. Accessed April 15, 2014.

24. Biason-Lauber A, Böni-Schnetzler M, Hub-

bard BP, et al. Identification of a SIRT1 mutation in a family with type 1 diabetes. *Cell Metab*. 2013;17(3):448-455.
25. Cortez MA1, Ivan C, Zhou P, Wu X, Ivan M, Calin GA. microRNAs in cancer: from bench to bedside. *Adv Cancer Res*. 2010;108:113-157.
26. miRBase: the microRNA database. miRBase. http://www.mirbase.org/. Accessed March 14, 2014.
27. The role of microRNA-29b in the oral squamous cell carcinoma. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT02009852?term=microRNA&rank=1. Accessed March 14. 2014.
28. A pilot study to assess microRNA biomarkers in early and later stage multiple sclerosis. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01737372?term=miRNA+multiple+sclerosis&rank=1. Accessed March 14, 2014.
29. miRNAs and mRNAs in Psoriasis. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01604902?term=miRNA+psoriasis&rank=1. Accessed March 14. 2014.
30. Bader AG, Lammers P. The therapeutic potential of microRNAs. *Innov Pharm Technol*. http://www.mirnarx.com/pdfs/The%20Therapeutic%20Potential%20of%20microRNAs.pdf. Published March 2011. Accessed March 14, 2014.
31. Guidance for industry: adaptive design clinical trials for drugs and biologics. FDA website. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf. Published February 2010. Accessed March 27, 2013.
32. Geiger MJ, Skrivanek Z, Gaydos B, et al. An adaptive, dose-finding, seamless phase 2/3 study of a long-acting glucagon-like peptide-1 analog (dulaglutide): trial design and baseline characteristics. *J Diabetes Sci Technol*. 2012;6(6):1319–1327.
33. Design & simulation software. Aptiv Solutions website. http://www.aptivsolutions.com/adaptive-trials/early-phase-design/design-simulation-software/. Accessed April 28, 2014
34. Genetics of diabetes. American Diabetes Association website. http://www.diabetes.org/diabetes-basics/genetics-of-diabetes.html. Accessed April 28, 2014.
35. Genetics and diabetes. World Health Organization website. http://www.who.int/genomics/about/Diabetis-fin.pdf. Accessed April 28, 2014.
36. Pollack A. A genetic entrepreneur sets his sights on aging and death. *The New York Times*. March 5, 2014:B1.
37. Aetna and the center for biomedical informatics at Harvard Medical School announce research collaboration [press release]. Hartford, CT: Aetna; November 17, 2011. http://newshub.aetna.com/press-release/health-care-professionals-and-networks/aetna-and-center-biomedical-informatics-harvard. Accessed March 14, 2014.

Stress, Diabetes, & Treatment

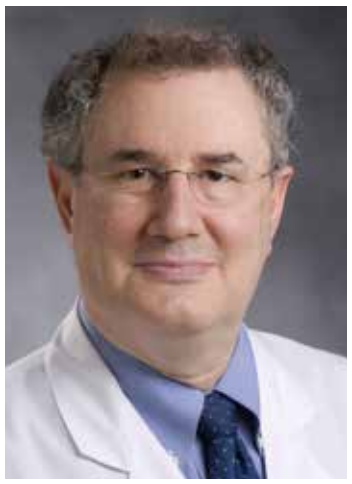
Interview With Mark Feinglos, MD, and Richard Surwit, PhD

(continued from cover)

and the anatomy but they don't think about the brain's involvement in disease. Then there are other groups of physicians and care providers—and I believe endocrinologists are part of this group—who more often consider the role that brain and behavior play in diabetes care. You see evidence of that in the steady stream of articles on the topic appearing in the specialty journals and in the journals related to nursing care or the ancillary health professions. Unfortunately, most physicians tend to not think quite as much about behavior issues.

EBDM: **I haven't seen too many articles recently relating levels of stress to diabetes.**

Feinglos: The reasons for this are: (1) It's a complex area—what does stress mean? Everybody lives with some kind of stress; (2) It's time consuming to delve into how much stress a patient has and how that is interacting with someone's diabetes. As you know, most physicians don't have a great deal of time in today's office environment; (3) Once you've even taken that time, how do you treat it? Richard and I have thought about that for a long time and have looked at both behavioral and pharmacological ways of thinking about those issues. But it's very complicated. We're frequently asked by attorneys whether a stressful event, like an auto accident, can trigger the onset of diabetes. What is more likely is that a stressful situation will not cause diabetes, but the event in the presence of underlying diabetes increases stress hormone levels, which raises glucose levels, perhaps more so in someone with diabetes.


Mark Feinglos, MD

Surwit: The direction of the work that Mark and I have been doing for over 30 years has led us to look at how the brain and the central nervous system are involved in the etiology of diabetes, and not just in terms of stress. That's the thrust of what we're doing now. The fact that diabetes is a stress-responsive disease, as are other diseases like high blood pressure, suggested to us a long time ago that there may be something wrong in the neurologic control of blood glucose that makes a person susceptible to developing diabetes. Let me give you a specific example from some of our recent work. We have shown that, in some groups, epinephrine (adrenaline), a classic stress hormone circulating in the body, interacts with central adiposity in producing elevated fasting blood sugar levels. Lean people with high levels of epinephrine don't seem to have this problem. However, obese people who have low levels of epinephrine (whom you might say are not stress responsive, or are relatively laid back) don't demonstrate this abnormality in blood sugar.

So there may be an interaction between the factors that create obesity—and those are probably numerous—and the activity of the autonomic nervous system in producing abnormalities in blood glucose concentrations. We don't really know what fraction of patients with type 2 diabetes mellitus (T2DM) is affected by this interaction.

What's more interesting to us at this point is not so much that people with diabetes will show exacerbations of diabetes when they're under stress, but rather, what does that tell us about the pathophysiology of diabetes in general? That suggests to us that certain drugs commonly used for other things might actually be helpful in the management of people with T2DM, particularly the significant group that is obese.

EBDM: **What role does insulin resistance play in that interaction, and does the brain, directly or indirectly, regulate insulin resistance?**

Surwit: The simplified explanation is that when adrenalin interacts with fat mass, it elevates free fatty acids, which then stimulate the liver to produce more sugar—essentially creating insulin resistance.

Feinglos: And this isn't an abnormal response—it's the old fight-or-flight response. If you're running or fighting, you need a source of energy. These hormones help you release energy from the liver and put it just where you need it. In that scenario, insulin resistance isn't necessarily abnormal, but it's an exacerbation of what was designed through evolution as a normal response.

Surwit: The idea that stress only affects people with a proclivity to the disease—in this case, people with substantial central adiposity—is not new. In fact, that's probably true for every disease linked to stress. Stress will not cause hypertension or irritable bowel syndrome in and of itself. If someone has an autoimmune disease affecting the gastrointestinal system, that person will be more susceptible to the effects of stress. Stress should be viewed as working through one of the lesions, if you will, that predisposes a person to disease. Not something that causes disease de novo.

EBDM: **In your research, you found certain subgroups that seem to have a greater stress response than other groups.**

Surwit: Right. We found this to be the case for African American women. There are 2 possible reasons why African American women have a greater problem with this. One is that they have much higher levels of central adiposity than either Caucasian women and men or African American men. As a group, they have high levels of central adiposity. The other potential contributing factor that could play a role is that they have more sensitive beta-adrenergic receptors, which lead to the release of free fatty acids and are stimulated by adrenalin. So those 2 factors are probably conspiring to make them more susceptible.

Feinglos: What we're seeing is not unusual in other diseases: an interaction of a genetic predisposition with factors that will bring out that genetic predisposition.

EBDM: **In this same research, I found it interesting that you measured hostility, or markers of hostility. Is that a proxy for stress levels?**

Surwit: I don't really know. Hostility is defined by a 27-item scale that was de-

rived from the Minnesota Multiphasic Personality Inventory. The scale tends to describe people who are relatively untrusting of what's going on around them. That more defines suspiciousness than it does hostility, although that's the name the scale was given.

We don't really understand why that is related, particularly in African American women, to abnormalities in blood glucose levels. It may be related to the fact that they are more responsive to high epinephrine levels, that their autonomic nervous systems are more attuned to the fight-or-flight response. But that's an open question. It's an observation we and other groups have seen on multiple occasions. Exactly what it means and why it's more common in African American women is not clear at this point.

Stress Management and Diabetes Care

EBDM: **Let's take this link between stress and glucose management into the physician's office. What does the doctor or nurse educator tell the patient with diabetes about stress in the management of the disease? What should patients do about it?**

Feinglos: I wish there were a simple answer to that. Someone who takes the time to question patients about environmental stressors will often find fertile territory. But everyone has stress. Some people live in a much more stressful environment than others and you can't necessarily change the environment. Nor do you want to put all kinds of people on pharmacologic therapies to alter their cognitive responses to stress.

Beyond attempting behavioral approaches to modifying stress, making people aware of what's happening is important. If they can't avoid the stress, they can modify their diabetes treatment to better cope with it. For example, if you know your blood sugar level is rising because of stress, you should try to bring your stress level down, knowing that this will positively affect your glucose concentrations. If that is not possible, it may be necessary to modify the medication regimen for periods of increased stress.

Surwit: The system for payment of services in medicine and psychiatry is really tying our hands, because we can't see people and bill them for a couple of sessions and teach them stress management for their diabetes unless they carry an outright psychiatric diagnosis. Most people with minor stress problems don't have that diagnosis.

One of the things that we're looking at now is using the beta-blocking drug carvedilol as a way of helping people whose glucose levels are more sensitive to stress. The drug may have very positive effects on glucose concentrations in these patients, because it blocks the mobilization of free fatty acids caused by adrenalin release. Mark and I are trying to get this study funded. If carvedilol works as we hope, we would have a very low cost intervention that wouldn't make people drowsy or affect their cognitive function, but could blunt their glucose response to stress quite significantly.

Feinglos: Realize that at this point, our ideas are unencumbered by data! We have to be a little careful about that.

Surwit: Data do exist on carvedilol's unique properties, and it has been shown to improve glucose tolerance in people with diabetes being treated for hypertension as well. The problem is that nobody has taken a look at whether this works particularly well in people with high central adiposity, which is what our hypothesis would suggest. And we don't suggest using other β-blockers, like metoprolol or propranolol. Carvedilol blocks α-adrenergic receptors as well as β receptors. That prevents the reduction in insulin secretion that occurs when giving another β-blocker. We think this is a promising avenue.

EBDM: **It sounds like this approach might be more appropriately categorized as a treatment for the metabolic syndrome than specifically for T2DM.**

Surwit: That could possibly be the case. We've been trying to get the National Institutes of Health to fund the study for 6 years now. And people either tell us, "It won't work" or "Everybody knows it will work." Meanwhile, we haven't yet obtained grant support. If the drug had still been on patent, we might have gotten the manufacturer (GlaxoSmithKline) to fund it. There's no commercial interest now that carvedilol is sold as a generic.

EBDM: **Has any research been done on the effect of anti-anxiety drugs to reduce stress in patients with diabetes?**

Feinglos: We looked at that ages ago, both in animal models that we developed and in humans. First of all, we can't put everyone on anti-anxiety drugs.

Surwit: We evaluated the benzodiazepines. The one that we've studied most was alprazolam (Xanax). The first problem is that people develop a tolerance to it. The second problem, as Mark alluded to, is that it does produce sedation…

Feinglos: …and it has an addictive potential. It wasn't really a good idea. We tried to demonstrate that using it would modify stress and affect glucose levels, and it did. Which is very nice, but you can't use that as treatment long term in large numbers of people.

Some Early Clues to the Relationship Between Fat Intake and Glucose Management

EBDM: **Both of you have been evaluating this area for a long time. How did your interest begin?**


Richard Surwit, PhD

Surwit: In 1977 or 1978, when I first came to Duke, I was brought in to run the stress management unit of the department of psychiatry. Mark sent me a consult for a patient with type 1 diabetes who was in very poor control, wanting to know if we could do anything to help her. I said I'd never worked with people with diabetes before. We tried stress management techniques, and this woman's glycemic control responded very dramatically. Then we tried it with another patient, who also responded dramatically. So we decided we might be on to something here.

Feinglos: In the late 1980s, we decided to look at this effect in animal models, the Black 6 mouse (also called the BL/6J mouse) which, being the strain on which the mutation is based, everybody thought was a control for the ob-ob mouse, a genetic model of obesity and diabetes. We discovered that this mouse in and of itself was susceptible to developing both significant obesity and T2DM if we fed it a diet with American junk food (basically cookie dough, containing lard and sugars). We asked ourselves, how would we make a susceptible mouse diabetic? We decided to feed it exactly what the American population eats. It worked. We published that in 1988. We learned that other strains of mice were not as responsive. On further study, it was clear that epinephrine was one of the mechanisms involved in this phenomenon, and it interacted with adiposity. Then we tried to identify the genes that were responsible for this particular problem.

Surwit: When we fed the mice pure sugar, it didn't do a thing to their blood sugar. Fat was the culprit.

The idea that sugar causes diabetes at least in rodents is clearly false. It doesn't happen. We published a study in 1997 in the *American Journal of Clinical Nutrition,* which showed that if we fed women trying to lose weight a hypocaloric diet that was 50% sucrose, they didn't have any problems either. They lost weight just fine. So we're not big proponents of the sugar theory of obesity and diabetes.

We think fat is really the culprit. And when you have a high fat diet, adding sugar makes it worse. But in the absence of fat, sugar and other simple carbohydrates are relatively benign. So I think people have really been paying too much attention to sugar and not enough to fat intake. The data to support the nefarious effects of sugar in the absence of fat are just not there. But it's trendy.

Feinglos: A couple of large epidemiologic studies looked at the high intake of sugars in the population and found some correlations to cardiovascular mortality. But nobody has ever demonstrated that high sugar intake causes diabetes, despite the common wisdom. In the countries experiencing the worst epidemics of new-onset diabetes, China and India, for example, it is usually the result of increased affluence and the concurrent change in diet, the addition of more animal proteins and fats. Remember, the residents of those countries have been eating high-carb diets to begin with.

Surwit: As it's consumed in poorer sections of Asia, rice has a higher glycemic index than sugar. Yet, in clinical studies, rice actually lowers blood glucose in the absence of fat.

We have a famous diet program here in Durham—the Rice Program. Patients with diabetes eat nothing but Uncle Ben's converted rice—no fat, no animal protein. In the first 2 days, we see enormous drops in blood sugar levels.

Feinglos: The Atkins diet proponents will show you how they get big drops in blood glucose concentrations with a very high fat and high-protein diet but no carbohydrates. I think the underlying point is that it's the combination of uncontrolled caloric intake and the nature of the nutrient that really gets you into trouble.

EBDM: **It sounds to me as if even more counseling needs to be done for a patient with diabetes. This cannot possi-**

bly be accomplished in the 10-minute office visit.

Feinglos: That's the seminal problem. There's a huge burden of diabetes in this country as well as others. There aren't very many endocrinologists, so most people with diabetes have to be treated by family physicians or general internists. These physicians have very limited amounts of time. Some of them don't have specific diabetes educators associated with their practice. So the care of diabetes, which is very labor intensive and very expensive, is difficult to accomplish.

The Role of Caffeine in Diabetes

EBDM: **We're talking about nutritional factors and their effect on glycemic control and glycemic response. Both of you have done a good deal of research recently on caffeine and caffeine's effect on diabetes. What have you learned?**

Feinglos: One of our colleagues, Jim Lane, has been interested in caffeine's effect on blood pressure for a very long time. We started talking about the idea that it would be important to take a look at what caffeine might do to blood glucose levels. We know that caffeine sensitizes the body to the action of epinephrine. Many very large epidemiologic studies show that if you drink a lot of coffee, there is a lower risk of developing diabetes. Those large epidemiologic studies don't tell you what happens to people who drink caffeine but who already have abnormal glucose levels.

Surwit: They don't even separate out people drinking decaffeinated from caffeinated coffee. Coffee also contains all kinds of flavonoids, which may have beneficial effects.

The work that we've done with Dr Lane clearly demonstrated that when you give caffeine pharmacologically, it makes glucose tolerance worse both in healthy people and in those with T2DM. It does so by sensitizing adrenergic receptors to stimulation by adrenalin, as well as by stimulating adrenalin's release. We've been trying to get funding to do large-scale trials on the effect of eliminating caffeine from the diet of patients with diabetes. Again, we're greeted by comments like, "Everybody drinks coffee; it couldn't be bad for you."

Feinglos: Where it's really important isn't even necessarily for adults drinking coffee but for kids with a predisposition to T2DM. Many of them drink a liter a day of caffeinated soft drinks.

Surwit: Or even worse than that, the energy drinks, which are just concentrated caffeine.

EBDM: **Do you think that the day will come when you have patients with T2DM or younger patients with prediabetic conditions who will be advised to avoid caffeine altogether?**

Feinglos: We do that in the clinic now. We always ask them about their caffeine intake. In people with poorly controlled diabetes, the first thing we tell them is to cut back on the caffeine. Very often, we'll see a significant improvement in glucose levels without taking any other action.

EBDM: **What is the range of glucose level improvement that you see with this action alone?**

Feinglos: In the studies that we've done, fasting glucose levels don't change very much, but postprandial levels may drop 20% or more. To put that in context, that sort of reduction caused by an investigational drug will ordinarily be enough for the FDA to approve its use.

EBDM: **There's obviously good reason to follow up on this research, despite the opposition of Starbucks!** **EBDM**

Evidence Builds on Yoga, but No Reimbursement Yet

Mary K. Caffrey

More than 80 yoga practitioners, in leggings and tank tops, squeezed into the meeting room at the Hilton in Midtown Manhattan at *Yoga Journal* LIVE! on April 27 to hear about a study funded by Aetna[1] on how yoga therapy improved a host of health measurements related to stress.

Six days later, just a few blocks away, leading physicians with the American Psychiatric Association (APA) urged reporters covering their 167th Annual Meeting at the Jacob K. Javits Center to check out the latest research on the practice. Yoga was prominently featured in APA's special program track, "Complementary, Alternative, and Integrative Medicine in Psychiatry."[2]

No one will confuse a *Yoga Journal* conference with a professional medical meeting, but the juxtaposition of settings for presenting evidence-based results speaks to a larger phenomenon: yoga, and yoga therapy in particular, has gained notice as medicine looks for new, low-cost tools to help patients fight diabetes mellitus, obesity, cardiovascular disease, and mental health disorders.

Interest and studies are increasing each year. In 2003, there were 56 peer-reviewed studies that included the word "yoga" in the title on PubMed; in 2013, there were 384. There is now an International Association of Yoga Therapists, which is a credentialing body with higher requirements than are needed to teach yoga. There's also an *International Journal of Yoga Therapy*, which was accepted on PubMed in 2011.

Aetna's interest in the yoga study comes as the insurer seeks ways to address the health consequences of stress: the costs of treatment for metabolic disease, increased used of employee assistance programs (EAPs) for alcohol and substance abuse, and more general impacts such as lost productivity, according to Paul Cappola, who heads Aetna's employee wellness program.

What sets the 2012 Aetna study apart is that it was funded by a national health insurer, which raises the question: as yoga practice and yoga therapy become more common, will payers start allowing reimbursement?

A few nurses who also teach yoga attended the *Yoga Journal* presentation by Gary Kraftsow, and they peppered members of Kraftsow's American Viniyoga Institute with questions about payment during a break. One cardiovascular nurse was especially eager to bring her patients the techniques, which involved breathing exercises and alignment poses of increasing duration.

Aetna funded the study after its chief executive took up yoga following a skiing accident, and transferred the findings to an employee wellness program that the company touts to other employers as a way to improve employee health and increase productivity. So far, results supplied by Aetna show positive results, with participants seeing statistically significant improvements in 5 areas:

- Triglycerides. Among participants, 85.5% were in appropriate range (less than 150 mg/dL); 74.0% were in appropriate range before the program started.
- High blood sugar (glucose). Among participants, 84.7% were in appropriate range (less than 100 mg/dL); 76.3% were in appropriate range before program started.
- Low high-density lipoprotein, or "good," cholesterol. Among the participants, 76.3% were in appropriate range (more than or equal to 50 mg/dL for women and 40 mg/dL for men); 61.8% were in appropriate range before the program started.
- Blood pressure. Among participants, 93.9% were in appropriate range (lower than or equal to 130/85 mm Hg); 77.1% were in appropriate range before the program started.
- Waist circumference. Among participants, 21.4% were in appropriate range (less than or equal to 35 inches for women and 40 for men); 9.2% were in appropriate range before the program started.
- Body mass index (BMI). Among the participants, there was a statistically significant improvement in BMI, with 8.3% achieving the appropriate range (lower than 30 kg/m^2), compared with 21.7% who were in the appropriate range before the program started.

Despite all this, Aetna is proceeding slowly. "We're continuing to evaluate the data," Cappola said. "We are making sure the results we have are evidence-based."

While there is no timetable for reimbursement, "We are moving in that direction," he said. "There's greater acceptance. The real evidence is coming in, and employers are starting to be more open-minded. We have the true believers, and we have the skeptics." **EBDM**

References

1. Kusnick C, Kraftsow G, Hilliker M. Building bridges for yoga therapy research: the Aetna, Inc., mind-body pilot study on chronic and high stress. *Int J Yoga Therap.* 2012;(22):91-92.

2. American Psychiatric Association website. Scientific program for 167th Annual Meeting, May 3-7, 2014. http://www.intpsychiatry.com/uploads/7/0/8/6/7086290/annual_mtg_caim_track_web.pdf. Accessed May 7, 2014.

THE AMERICAN JOURNAL OF MANAGED CARE

ACO and Emerging Healthcare Delivery Coalition

Background

As ACOs and other emerging delivery and payment models evolve and move away from traditional fee-for-service system models towards cost-effective and value-based care, the need to understand how these models will evolve is critical to building long term strategic solutions. The mission of the coalition is to bring a diverse group of key stakeholders together, including ACO providers, payers, IDNs, specialty pharmacy and pharmaceutical manufacturers to work collaboratively to build solutions and improve the quality and overall outcomes of patient care.

Coalition Goals

- Gather insights of current "real-world" best practices and strategies for care management interventions
- Gather insights of current ACO physician challenges and best practices in executing successful ACOs, as well as new healthcare delivery models, including the impact of incentive structures for ACO providers–implementation strategies and measurement
- Identify operational lessons and best practices, including key components of transitions-of-care programs; patient and physician engagement; quality measures; formulary decisions; and protocol development.
- Translate key findings into actionable solutions for key stakeholders

Key Stakeholders

- ACO Providers
- Payers
- Integrated Delivery Networks
- Specialty Pharmacy
- Pharmaceutical Manufacturers

Deliverables

- **Participation in two live working group sessions with coalition members:**
  - Free registration for live interactive meeting with Industry leaders across ACOs, payers, IDNs, specialty pharmacy and pharmaceutical manufacturers
  - Opportunity for exclusive breakout sessions with coalition members
- **Two virtual meetings with coalition members - free registration**
- **Ongoing collaboration opportunities with coalition members:**
  - Monthly executive interchanges with thought leaders (includes Q&A)
  - Active participation and proprietary questions in pulse surveys
- **Complimentary subscriptions:**
  - The *American Journal of Managed Care*
  - The *American Journal of Accountable Care* quarterly publication
  - **ACO and Emerging Healthcare Delivery Coalition** newsletter
- **Additional discounts:**
  - Free registration to The *American Journal of Managed Care* live events
  - Discount on HRA syndicated managed care studies and inclusion of 5 proprietary questions in 2014
- **Company/brand advertisements:**
  - The *American Journal of Managed Care*
  - The *American Journal of Accountable Care* quarterly publication
  - **ACO and Emerging Healthcare Delivery Coalition** newsletter
- **Expedited peer review for submissions to AJAC**
- **Additional Resources:**
  - Development of training modules: live, on-line, etc
  - Development of patient education
  - Access to ACO portal resource center within AJMC.com

AJMC's **ACO and Emerging Healthcare Delivery Coalition** is the premier managed care alliance for ACOs, payers, IDNs, specialty pharmacy and pharmaceutical companies. This coalition provides the platform for diverse stakeholders to collaborate and interact regarding the current and evolving healthcare delivery models–to build strategies and solutions, in addition to developing enduring materials to ensure continuous engagement and innovation for all alliance members.

Despite your efforts to control excess glucose in type 2 diabetes, SGLT2 keeps reabsorbing it back into the bloodstream[1]

- SGLT2 (sodium glucose co-transporter-2) reabsorbs 90% of glucose through the kidneys
- In patients with type 2 diabetes, glucose reabsorption is increased
- Increased glucose reabsorption helps perpetuate hyperglycemia

Learn more at www.SGLT.com

Boehringer Ingelheim

Lilly

Reference: 1. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790.