Bridging the gap between payer and provider perspectives

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Evidence-Based Diabetes Management

Drug Pipeline

What Is the Place of New SGLT-2 Inhibitors in Therapy and on the Formulary?

Stanton R. Mehr and Marj P. Zimmerman, BSPharm

Diabetes mellitus continues to be an area of robust research and development for pharmaceutical manufacturers. An estimated 26 million Americans have the disease, and an estimated 79 million US adults have prediabetes, putting direct medical costs at $116 billion.[1]

Investment ranges from the development of new therapies to control the disease, to innovations toward the so-called "artificial pancreas" for type 1 patients (T1DM), to work on preventing type 2 diabetes mellitus (T2DM) with therapies to combat obesity.

Until there is a decline in the number of patients with T2DM, both payers and the medical community will witness the introduction of a new category of agents for these patients every few years. Each new mechanism of action must then be proven in the crucible of clinical practice and in formulary decision making.

In the last cycle, the incretin mimetics, which include the dipeptidyl peptidase 4 (DPP-4s) and the glucagon-like peptide-1 (GLP-1s) were introduced and incorporated into practice and onto drug formularies. First came the GLP-1s with injectables like exanatide, and then came the DPP-4s with oral tablets like sitigliptin. The GLP-1s are thought to offer slightly better glycemic control than the DDP-4s, but some diabetics do not prefer the injectable form.

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Payer Perspective

Evidence-Based Diabetes Protocol Development: Approaches and a Case Study

Jeffrey D. Dunn, PharmD, MBA; Alexander C. Bitting, PharmD; and Alan D. Pannier, PharmD, MBA

Managed care faced an interesting dilemma in 2012 when the American Diabetes Association (ADA) released new guidelines for the treatment of type 2 diabetes mellitus (T2DM).[1] The new guidelines replaced the previous iteration that was algorithmic in its recommendations of drug therapy with one that was more individualized to the patient. While diabetes is not a one-size-fits-all disease, the new guidelines did not recommend a preferred second- or third-line medication. Many diabetic medications are still branded and associated with a relatively high cost compared with older generic medications. Furthermore, newer medications continue to come to market in these newer categories, such as DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors. Despite comparative glycated hemoglobin (A1C)-lowering data, these medications have little clinical differentiation in terms of outcomes and safety. This should allow health plans to streamline their approach in managing drugs that treat diabetes.

Jeffrey D. Dunn, PharmD

Managed care continues to evaluate efficacy, safety, and cost as part of any drug review process. However,

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Physician Interview

Managing the Transition to Adulthood With Type 1 Diabetes Mellitus

An Interview With Robert Kritzler, MD, Pediatric Endocrinologist, and Deputy Chief Medical Officer, Johns Hopkins Health Care LLC

Interview by Stanton R. Mehr

Robert Kritzler, MD, wears 2 hats: He has been a practicing physician for more than 30 years; with a specialty in pediatric endocrinology, he has seen the rise of obesity and diabetes and its effects on the healthcare system. Today, as a leader in a health plan associated with a major academic institution, he is also part of the national conversation on how to control rising costs, as more patients gain access to the system under the Affordable Care Act.

Evidence-Based Diabetes Management: **Have you observed progress in the community's efforts to address diabetes mellitus in children as a public health problem?**

Robert Kritzler, MD: There has been some progress, but we need to break the progress down into type 1 and type 2 diabetes mellitus. Pediatric endocrinologists see more type 1 disease, and I think there's been a lot of progress in terms of technology. As a clinician, many more of my young patients are using insulin pumps than in the past. Some of my patients are now using continuous glucose sensors (for continuous glucose monitoring, or CGM). As a managed care medical director, I can say that we're seeing many more requests for insulin pumps and CGM monitors. That technology is changing how we treat the patient with type 1 disease. Alone, it is, however, not the whole answer.

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Smoking and Diabetes

A new report marking the 50th anniversary of the Surgeon General's *Smoking and Health* draws stronger conclusions than ever that cigarette smoking not only aggravates diabetes, but also can be the cause. *EBDM* talks with leaders at the CDC (SP98).

Also in this issue...

Halting T1DM in its Tracks

Orphan drug status may aid research on a promising immunotherapy, which would give patients a vaccination during the preclinical "window" before the onset of type 1 diabetes mellitus (SP96).

Better Nutrition Equals Prevention

News about the Dietary Guidelines Advisory Committee, Mediterranean diets, and commentary on how school nutrition aids the fight against obesity (SP111-115).

Millen Mills Schmidt

Living With the New Pump

Our writer, diagnosed with T1DM more than 30 years ago, reviews the performance of Medtronic's Minimed 530G with Enlite (SP119).

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Victoza®—a force for change in type 2 diabetes.

[a]1.8 mg dose when used alone for 52 weeks.
[b]Victoza® is not indicated for the management of obesity. Weight change was a secondary end point in clinical trials.
[c]In the 8 clinical trials of at least 26 weeks' duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza®-treated patients.

A 52-week, double-blind, double-dummy, active-controlled, parallel-group, multicenter study. Patients with type 2 diabetes (N=745) were randomized to receive once-daily Victoza® 1.2 mg (n=251), Victoza® 1.8 mg (n=246), or glimepiride 8 mg (n=248). The primary outcome was change in A1C after 52 weeks.

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The change begins at **VictozaPro.com**.

VICTOZA®
liraglutide (rDNA origin) injection

Indications and Usage

Victoza® (liraglutide [rDNA origin] injection) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Victoza® has not been studied in combination with prandial insulin.

Important Safety Information

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment.

Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) have been reported during postmarketing use of Victoza®. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza® and seek medical advice promptly.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, dyspepsia, constipation and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Victoza® has not been studied in type 2 diabetes patients below 18 years of age and is not recommended for use in pediatric patients.

There is limited data in patients with renal or hepatic impairment.

In a 52-week monotherapy study (n=745) with a 52-week extension, the adverse reactions reported in ≥ 5% of patients treated with Victoza® 1.8 mg, Victoza® 1.2 mg, or glimepiride were constipation (11.8%, 8.4%, and 4.8%), diarrhea (19.5%, 17.5%, and 9.3%), flatulence (5.3%, 1.6%, and 2.0%), nausea (30.5%, 28.7%, and 8.5%), vomiting (10.2%, 13.1%, and 4.0%), fatigue (5.3%, 3.2%, and 3.6%), bronchitis (3.7%, 6.0%, and 4.4%), influenza (11.0%, 9.2%, and 8.5%), nasopharyngitis (6.5%, 9.2%, and 7.3%), sinusitis (7.3%, 8.4%, and 7.3%), upper respiratory tract infection (13.4%, 14.3%, and 8.9%), urinary tract infection (6.1%, 10.4%, and 5.2%), arthralgia (2.4%, 4.4%, and 6.0%), back pain (7.3%, 7.2%, and 6.9%), pain in extremity (6.1%, 3.6%, and 3.2%), dizziness (7.7%, 5.2%, and 5.2%), headache (7.3%, 11.2%, and 9.3%), depression (5.7%, 3.2%, and 2.0%), cough (5.7%, 2.0%, and 4.4%), and hypertension (4.5%, 5.6%, and 6.9%).

Please see brief summary of Prescribing Information on adjacent page.

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Victoza® (liraglutide [rDNA origin] injection)
Rx Only
BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and prandial insulin has not been studied.

CONTRAINDICATIONS: Do not use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. In the clinical trials, there have been 6 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Five of the six Victoza®-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza® and one non-Victoza®-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis: Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza®. After initiation of Victoza®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Consider antidiabetic therapies other than Victoza® in patients with a history of pancreatitis.** In clinical trials of Victoza®, there have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Victoza® has been evaluated in 8 clinical trials: A double-blind 52-week monotherapy trial compared Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, and glimepiride 8 mg daily; A double-blind 26 week add-on to metformin trial compared Victoza® 0.6 mg once-daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily; A double-blind 26 week add-on to glimepiride trial compared Victoza® 0.6 mg daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily; A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza® 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily; A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily and placebo; An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza® 1.8 mg once-daily and exenatide 10 mcg twice-daily; An open-label 26-week add-on to metformin trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, and sitagliptin 100 mg once-daily; An open-label 26-week trial compared insulin detemir as add-on to Victoza® 1.8 mg + metformin to continued treatment with Victoza® + metformin alone. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five double-blind controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. In these five trials, the most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. *Common adverse reactions:* Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature. In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In the 26-week open-label trial comparing Victoza® to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza® and exenatide treatment groups (Table 3). In the 26-week open-label trial comparing Victoza® 1.2 mg, Victoza® 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza® than sitagliptin (Table 4). In the remaining 26-week trial, all patients received Victoza® 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza® 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

Table 1: Adverse reactions reported in ≥5% of Victoza®-treated patients in a 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Reaction	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Headache	9.1	9.3

Table 2: Adverse reactions reported in ≥5% of Victoza®-treated patients and occurring more frequently with Victoza® compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Reaction	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Reaction	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2
Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Reaction	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
Add-on to Metformin + Rosiglitazone			
	All Victoza® + Metformin + Rosiglitazone N = 355		Placebo + Metformin + Rosiglitazone N = 175
Adverse Reaction	(%)		(%)
Nausea	34.6		8.6
Diarrhea	14.1		6.3
Vomiting	12.4		2.9
Headache	8.2		4.6
Constipation	5.1		1.1

Table 3: Adverse Reactions reported in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Exenatide

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	**Exenatide 10 mcg twice daily + metformin and/or sulfonylurea** N = 232
Adverse Reaction	(%)	(%)
Nausea	25.5	28.0
Diarrhea	12.3	12.1
Headache	8.9	10.3
Dyspepsia	8.9	4.7
Vomiting	6.0	9.9
Constipation	5.1	2.6

Table 4: Adverse Reactions in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Sitagliptin

	All Victoza® + metformin N = 439	**Sitagliptin 100 mg/day + metformin** N = 219
Adverse Reaction	(%)	(%)
Nausea	23.9	4.6
Headache	10.3	10.0
Diarrhea	9.3	4.6
Vomiting	8.7	4.1

Immunogenicity: Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In the five double-blind clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five double-blind clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia* :In the eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza®-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza®-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza® as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza® monotherapy, the insulin treatment was the likely explanation for the hypoglycemia. In the 26-week open-label trial comparing Victoza® to sitagliptin, the incidence of hypoglycemic events defined as symptoms accompanied by a fingerstick glucose <56 mg/dL was comparable among the treatment groups (approximately 5%).

Table 5: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza® Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza®** (N = 497)	**Glimepiride** (N = 248)	**None**
Patient not able to self-treat	0	0	—
Patient able to self-treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
Add-on to Metformin	**Victoza® + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
Patient not able to self-treat	0.1 (0.001)	0	0
Patient able to self-treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
Add-on to Victoza® + Metformin	**Insulin detemir + Victoza® + Metformin** (N = 163)	**Continued Victoza® + Metformin alone** (N = 158*)	**None**
Patient not able to self-treat	0	0	—
Patient able to self-treat	9.2 (0.29)	1.3 (0.03)	—
Add-on to Glimepiride	**Victoza® + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
Patient not able to self-treat	0.1 (0.003)	0	0
Patient able to self-treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
Add-on to Metformin + Rosiglitazone	**Victoza® + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
Patient not able to self-treat	0	—	0
Patient able to self-treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
Add-on to Metformin + Glimepiride	**Victoza® + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
Patient not able to self-treat	2.2 (0.06)	0	0
Patient able to self-treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

*One patient is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Dehydration resulting from nausea, vomiting and diarrhea; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis; Angioedema and anaphylactic reactions; Allergic reactions: rash and pruritus; Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

OVERDOSAGE: Overdoses have been reported in clinical trials and post-marketing use of Victoza®. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.
For information about Victoza® contact: Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536, 1–877-484-2869
Date of Issue: April 16, 2013
Version: 6
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark
Victoza® is covered by US Patent Nos. 6,268,343, 6,458,924, 7,235,627, 8,114,833 and other patents pending.
Victoza® Pen is covered by US Patent Nos. 6,004,297, RE 43,834, RE 41,956 and other patents pending.
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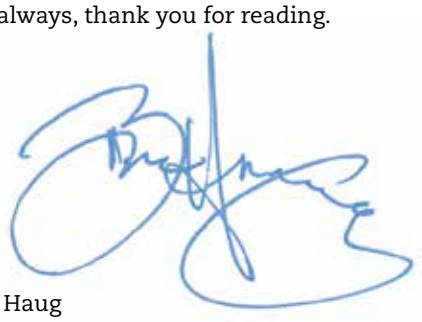
This edition of *Evidence-Based Diabetes Management* tells us both how far we have come in addressing this epidemic of 26 million Americans, and how far we have to go. Our coverage includes insights into preventing diabetes before it starts, articles on the most advanced ways to treat both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) when these diseases occur, and an exciting example of how the treatment *could be* the prevention for T1DM. Our review of the class of therapies known as SGLT-2s reveals the breadth of what is happening in research and the steps being taken to ensure patient safety. An interview with Robert Kritzler, MD, a pediatric endocrinologist and the deputy chief medical officer for Johns Hopkins Health Care LLC, discusses the challenges of transitioning young T1DM patients from childhood to their adolescent years, both in administering their own therapies and in taking steps to avoid health problems. His praise for recent efforts to combat obesity with the "Let's Move" campaign were borne out after his interview, through results we report in a series of stories on nutrition. Eating healthy food can be the first line of defense against T2DM, and this issue shows how important it is for ordinary citizens to take part in policy discussions like the 2015 update of the Dietary Guidelines for Americans. The good news? As we report, new data show the tide may be turning for our youngest Americans, as rates of obesity for children aged 2-5 years fell 43% in the past decade, according the Centers for Disease Control and Prevention. We also take a page from the new report of the US Surgeon General, on the 50th anniversary of the original call to arms against cigarette smoking, which is now listed as both a cause of diabetes and an aggravating factor for those already suffering. This issue includes key information for payers, from a discussion of how employers can aid the fight against diabetes and obesity, to a commentary about how to develop guidelines for diabetes therapies. An eye-opening story on what scientists are learning about what happens to some gastric bypass patients is a must-read. Finally, a first-person account of living with Medtronic's Minimed 530G, which captured attention with its advertised "artificial pancreas" technology, tells us customer service matters as much as the device itself, even when glycemic control is improved. There's much to appreciate in this edition, but what we appreciate most is your continued interest and feedback. Please visit www.ajmc.com, and let us know what you think.

Our review of the class of therapies known as SGLT-2s reveals the breadth of what is happening in research on the treatment of diabetes, as well as the steps being taken to ensure patient safety. We also cover what scientists are learning about what happens to some gastric bypass patients in their battle against obesity.

As always, thank you for reading.



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 care.

THE AMERICAN JOURNAL OF MANAGED CARE

New Orphan Drug in the T1DM Realm: Another Immunotherapy Success Story?

Surabhi Dangi-Garimella, PhD

In early January, the US Food and Drug Administration (FDA) granted an orphan drug status to the immunotherapy drug DV-0100, manufactured by the technology company DiaVacs.[1] This cell-based therapy to treat type 1 diabetes mellitus (T1DM), also known as juvenile diabetes, is the company's first product, based on a proprietary platform technology. The technology, according to the company website, is based on retraining a patient's dendritic cells (DCs) to prevent a T-cell stimulation-based autoimmune reaction.[2]

Orphan drug status is granted by the FDA for drugs treating rare diseases (<200,000 patients) and conditions for which adequate treatment options have not been developed. The sole purpose of this class of drugs is to incentivize research in an otherwise unprofitable field for drug developers. A number of large pharmaceutical companies (AbbVie, Bayer, Bristol-Myers Squibb, GlaxoSmithKline) have been investing in this field by focusing on biologics (like immunotherapy drugs), which make up 60% of the orphan drug market.[3] Other T1DM drugs granted orphan drug status include teplizumab (MGA031) in 2006, developed by Macrogenics and Eli Lilly and Company, which completed phase 3 trials in 2013, and TOL101 (Tolera Therapeutics Inc), which was granted the status in 2010 and recently concluded a phase 2 trial.[4] According to the Orphan Drug Act of 1983, the manufacturer of an orphan drug receives the following benefits to hasten the process of getting the drug to market:

- Tax credits for research expenses
- An annual grant to defray the costs of qualified clinical testing
- Assistance in clinical research study design
- Seven years of exclusive marketing post approval
- Waiver of Prescription Drug User Fee Act filing fees ($1 million per application for 2008).[3]

These benefits amount to significant cost savings to the manufacturing company, but the savings are not necessarily reflected in drug pricing. Although DV-0100 is in very early stages to predict efficacy in long-term clinical trials or to estimate its cost, 5 of the most recently approved orphan drugs, for various indications, were estimated at $150,000 per patient per year, and 3 of them were estimated to cost $300,000 or more annually. With the increasing number of orphan drugs being approved by the FDA (13 of the 39 drugs approved in 2012 were orphan drugs, >350 approved since 1983) that cover a wide spectrum of disease conditions such as AIDS, melanoma, ovarian and pancreatic cancer, and cystic fibrosis, payers are being more cautious.[5,6]

Gordon C. Weir, MD

Payer Perspective

The front-end cost of immunotherapy is expensive enough that at least 1 national payer said it's not a foregone conclusion that this treatment would be covered. Ed Pezalla, national medical director for pharmaceutical policy at Aetna, stated in an interview conducted last year that even with orphan drug expenditures increasing 20 to 25% (of healthcare spending per year) compared with 15% for other medications, managed care companies are not always allowed to drastically increase premiums. Pezalla added that the increase in orphan drug cost is much higher than increases in premiums, which would ultimately raise issues for patients to qualify for coverage.[5] A study published late last year evaluated the acceptance of cost-effectiveness analysis (CEA) by payers for orphan disease coverage.[6] The study included 7 health insurance companies, estimated to cover 75% of the US private insurance market and approximately 157 million individuals. Based on interviews and a survey, the study concluded that despite being concerned about the cost of orphan drugs, insurance companies have not directed efforts toward generating appropriate cost-assessment tools to regulate orphan drug cost. CEA is not considered useful due to a dearth of medicines for appropriate comparisons. Further, the Affordable Care Act (ACA) clarifies 2 points about orphan drug coverage:

- Medicare does not have any special coverage rules for orphan drugs; drugs are covered irrespective of whether they are reasonable and necessary
- Medicare and Medicaid cannot make coverage decisions for any drug solely based on its cost-effectiveness.[6]

Table. Annual and Lifetime Costs Generated by T1DM Patients[8]

Per Capita Costs	Total Yearly Costs (in billions)	Lifetime Costs (in billions)	
		Newly Diagnosed Patients	Current Patients
6288	6.9	3.3	133.7
7164	7.5	7.3	289.2

T1DM indicates type 1 diabetes mellitus.

A Look at the Numbers

According to the *2011 National Diabetes Fact Sheet* released by the Centers for Disease Control and Prevention (CDC), of the 25.8 million (8.3%) Americans who were estimated to have diabetes in 2010, only 18.8 million were diagnosed. Further, 215,000 (0.26%) of this diagnosed population was younger than 20 years, 15,600 of whom were newly diagnosed with T1DM between 2002 and 2005. Based on the statistics provided by JDRF (formerly the Juvenile Diabetes Research Foundation), the estimated total cost (direct and indirect such as loss of productivity and absenteeism) of diabetes in 2012 was $245 billion, with T1DM estimated at $14.9 billion; the average expenditure incurred by a diabetic patient was $11,700 per year in 2009.[7] A study published in early 2010 estimated that elimination of the disease by therapeutic intervention (the aim of the current immunotherapy approaches) in the current cohort of T1DM patients could yield projected savings of about $422.9 billion (lifetime cost, which includes disease maintenance with insulin, constant monitoring, and loss of productivity).[8] The study estimated the average annual medical expenditure of T1DM patients at about $10,000, compared with $3500 estimated for matched controls. A majority of T1DM patients fall in the 10-to-19-years age group, and they are expected to generate costs (medical and indirect) of about $10 billion.[8] Considering these high costs of disease treatment (**Table**), therapies that can help control or reduce the loss of beta cells could lead to significant cost savings. "We are an early-stage company, and the therapy is still in the early development stage. We have not yet discussed pricing with the payers," replied Hara Hartounian, PhD, CEO, of DiaVacs, in an e-mail.

The Disease Condition

T1DM, an autoimmune disease that may be regulated by family history, genetic and environmental factors, or viral infections, is associated with a varying preclinical period that results in autoimmune destruction of the insulin-secreting beta cells of the pancreatic islets and a subsequent upsurge in blood glucose levels. The disease remains preclinical until greater than 80% of the beta cell mass is destroyed, before clinical manifestation.[7] Typical disease symptoms include extreme fatigue, frequent urination, continued thirst, and severe hunger pangs. Pharmacologic immunosuppression for T1DM using agents such as cyclosporin A, although successful, is associated with unacceptable adverse events (AEs), while administration of insulin is associated with complications that can lead to morbidity and mortality.[7]

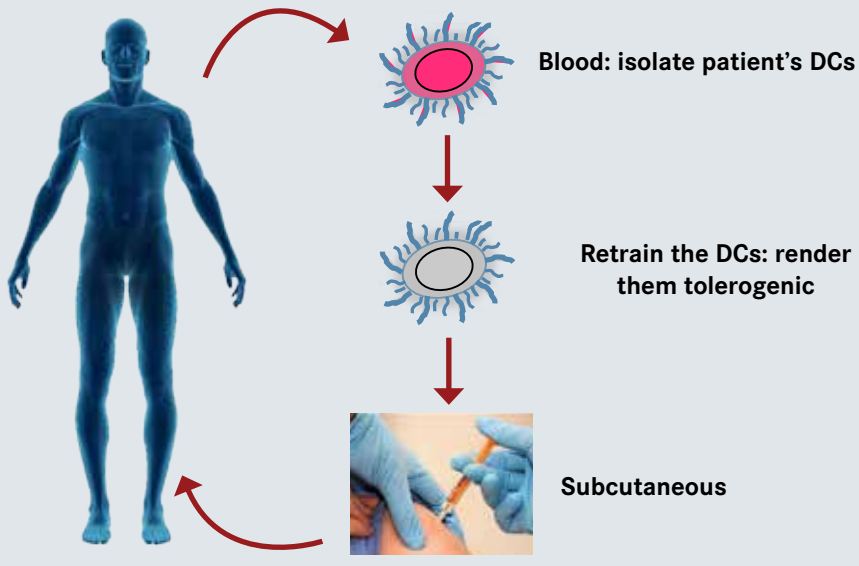
According to JDRF, none of the current therapies can prevent or cure T1DM. Insulin treatment is mandatory for these patients, and the lack of glucose homeostasis could lead to devastating conditions, including heart disease and kidney failure.[7] The preclinical period associated with T1DM could present a therapeutic window in which to slow down or inhibit the loss of pancreatic beta cells by targeting the immune system, which can result in an increase in cell mass.

Previous Immune Studies

Several clinical trials have explored immune cells as therapeutic targets or modified tools to treat T1DM patients.[9]

A collaborative phase 2 trial completed in 2008 by the University of Texas Health Science Center and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) evaluated the efficacy of oral interferon-alpha in slowing the immune attack on the islet cells of T1DM patients.[4] The trial reported that patients receiving 5000 units of human recombinant interferon alpha (hrIFN-α) maintained more beta-cell function at 1 year after enrollment compared with the placebo.[10] Antigen-based immunotherapy was another approach that was evaluated in both children and adults in a trial that was completed in 2011. Glutamic acid decarboxylase (GAD), a major target of the T1DM autoimmune response, was administered subcutaneously over 4 to 12 weeks, and the loss of insulin secretion was monitored over 1 year. However, the encouraging results obtained in animal models did not translate to humans: the loss of insulin production between the controls and the GAD-injected subjects was not different.[11] An ongoing phase I safety trial sponsored by the University of California, San Francisco, is investigating whether regulatory T cells (Tregs) can stabilize the beta cells from further destruction in T1DM.[4] The study, initiated in 2010, is estimated to be completed by 2016.

Figure 1. Protocol for Generating DV-0100



DC indicates dendritic cell.

DiaVacs' Vaccine Technology

The technology currently being utilized by DiaVacs is a result of the pioneering work by Nick Giannoukakis, PhD, associate professor of pathology and immunology at the University of Pittsburgh School of Medicine. In an interview published late last year in the journal *Immunotherapy*, Giannoukakis shared the story behind DV-0100. The extremely exciting findings with DC and T1DM by his research group were funded by venture capitalists, which led to the foundation of the biotechnology company DiaVacs. Giannoukakis, who actively serves on the Scientific Advisory Board of the company, believes that DC therapy can eventually help cure T1DM.[12]

According to Hartounian, "The granting of this orphan drug designation represents a key milestone for the company. We are excited by the promise that DV-0100 showed in our phase 1 *clinical* trial and look forward to assessing its therapeutic potential in the ongoing phase 2 clinical trial for this indication." The procedure involves acquiring DCs from the patient's own blood, modifying them using small interfering oligonucleotides, and vaccinating the patient by intradermal injection of the modified cells[13] (**Figure 1**). The most important hurdle that this technology has overcome is the generation of tolerogenic DCs, with a low T-cell stimulatory function in vitro, poor-allogenic T-cell proliferation in vitro, and the capacity to induce Foxp3+ Tregs in vitro, among others. To deal with concerns about DC maturation in vivo, resulting in a loss of tolerogenic properties and promotion of alloimmunity, maturation-resistant DCs have been generated[14] (**Figure 2**).

No safety issues were documented in the phase I trial, which was conducted in 10 generally healthy insulin-requiring T1DM patients between 18 and 60 years of age. The clinical trial results, published in the journal *Diabetes Care*, demonstrated no discernible AEs in any patient, except for a rise in B2 20_{+} CD11c– B-cell population.[15] If the promising results obtained in the animal model translate to the phase 2 trials initiated by DiaVacs, DV-0100 could revolutionize the treatment spectrum for T1DM patients.

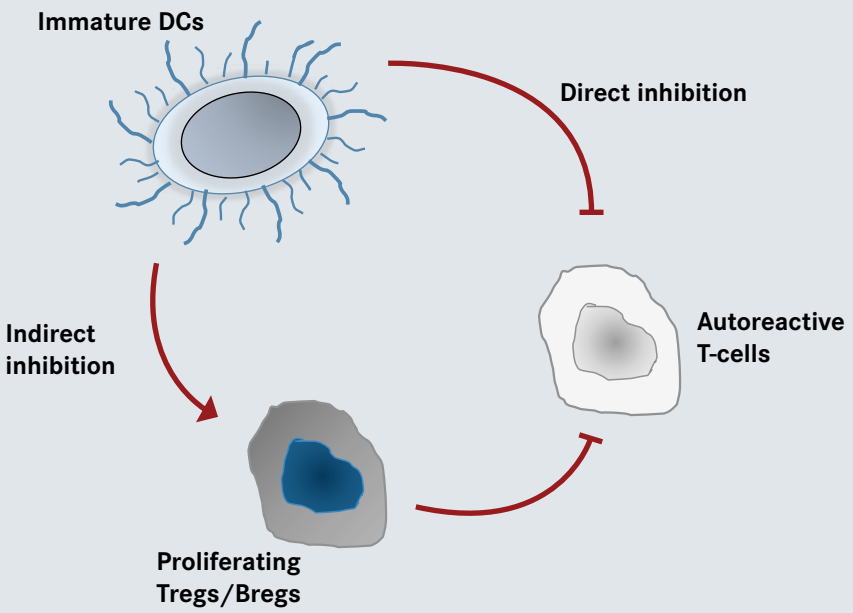
According to Gordon C. Weir, MD, chairman, Diabetes Research and Foundation, Joslin Diabetes Center, DC cells are a promising treatment approach for T1DM, but he believes the therapy, although safe, is in too early a stage to predict efficacy.

Alternate Vaccine Therapies

Encouraging results were obtained from a trial conducted in early 2013, led by researchers at the Stanford University School of Medicine. The trial evaluated the efficacy of a 12-week regimen of an intramuscular DNA vaccine (plasmid-encoded proinsulin) in 80 adult T1DM patients.[16] Blood insulin levels were monitored using C-peptide as a surrogate marker. The study was conducted on the hypothesis that by shutting off only a subset of immune cells (in this case the $CD8^{+}$T cells) instead of the entire immune spectrum, a much-controlled response could be achieved. This vaccine was designed to shut off an immune response, unlike conventional vaccines that turn on a specific immune response. The vaccine improved the C-peptide levels in the blood and specifically reduced proinsulin-reactive $CD8^{+}$T cells, without any serious AEs. However, the effects started declining after administration of the vaccine was stopped at 12 weeks. Large-scale studies over a longer duration are definitely called for to further these results.

The out-of-the-box immune-modulation approaches initiated by researchers could spare the patients a lifetime of dealing with insulin injections, pumps, counting carbohydrates, and associated health effects of the disease. A critical question that the ongoing phase 2 trial can answer is whether DV-0100 could eradicate the immune disorder in T1DM patients. Success of the trial would nullify all arguments on treatment coverage for orphan drugs, at least in the T1DM domain. **EBDM**

Figure 2. Mechanism of Action of Tolerogenic DCs



DC indicates dendritic cell.
Adapted from: *Immunotherapy*. 2012;4(10):1-12.

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Smoking and Diabetes

OSH Officials Discuss How 50th Anniversary Report Highlights Link Between Smoking, Diabetes

Mary K. Caffrey

Fifty years ago, when the original *Smoking and Health* report to the US Surgeon General[1] declared that cigarette smoking caused lung cancer in men and probably caused it in women, the news was alarming but easily understood. After all, the action of smoking involves inhaling.

With each successive Surgeon General's Report, evidence mounts about smoking's insidious path of destruction through the human body, not just for smokers but for all around them: their families, their unborn children, and, depending on where they travel, the hospitality workers who serve them. Statistics show that most of these bystanders will never pick up a cigarette themselves.[2]

Timothy McAfee, MD

Now, type 2 diabetes mellitus (T2DM) can be added to the roster of health ailments that, while not caused solely by cigarettes, can be caused by them. Diabetes is most certainly aggravated by smoking. A mountain of long-term evidence shows that smoking wreaks havoc with the body's ability to maintain insulin levels, but it's the research of the past decade that's even more troubling: nicotine's effects hit at the cellular level in the developing fetus, setting up the next generation to battle America's fastest-growing epidemic.

For payers, especially state Medicaid officials, the implications of these findings are daunting, as the evidence escalates of interwoven relationships among cigarette smoking, diabetes, and poverty (**Figure**).

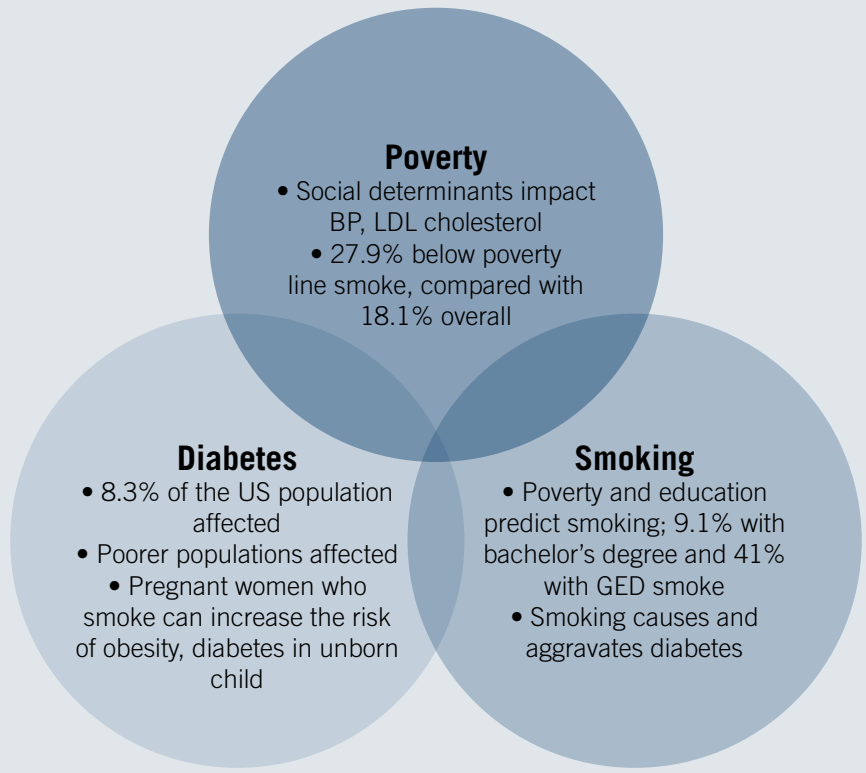
Diabetes was part of the evidence entered into history January 17, 2014, when Acting Surgeon General Rear Admiral Boris D. Lushniak, MD, MPH, Department of Human Services Secretary Kathleen Sebelius, and a host of others, including relatives of the pioneering Surgeon General Luther Terry, gathered to release *The Health Consequences of Smoking: 50 Years of Progress*.[3] While the 980-page report includes information on both T2DM and type 1 diabetes mellitus, most of discussion on the disease focuses on T2DM.

Two top officials with the Center for Disease Control and Prevention's Office of Smoking and Health—Director Timothy McAfee, MD, and Associate Director for Science Terry F. Pechacek, PhD—discussed the findings and implications of the report with *Evidence-Based Diabetes Management*.

The report made 3 chief conclusions about diabetes and smoking:

- The evidence is sufficient to infer that cigarette smoking is a cause of diabetes.
- The risk of developing diabetes is 30-40% higher for active smokers than nonsmokers.
- There is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.[3]

Figure. Understanding the Connections



BP indicates blood pressure; LDL, low-density lipoprotein; GED, General Educational Development.
Sources: Centers for Disease Control and Prevention, Office of Smoking and Health.

Biologic Connections

Some of the findings in the report are not brand new, Pechacek explained, but the report consolidates and draws a greater level of attention to studies released over the past decade that show how smoking and nicotine affect a diabetic's ability to control insulin levels, and how oxidative stress accelerates diabetes symptoms.[4-6]

Pechacek cited smoking's relationship to kidney damage, and to the studies referenced in the report over an extended period that show smoking's association with known markers associated with poor insulin control.[7-10] He also mentioned studies that cite impairment of the body's endothelial function.[11,12]

The report's long-term evidence is important for payers, especially as the Medicaid rolls expand nationwide under the Affordable Care Act: treating a smoker with diabetes costs more than treating a nonsmoker, because of research that shows the smoker will require more insulin to maintain glycemic control.[13] More recent findings, the report says, "indicate that people with diabetes may be particularly susceptible to the detrimental effects of smoking on insulin resistance."[14,15]

"All these things are not really new," Pechacek said. "We have not placed enough emphasis on the evidence that

was already out there. We're focusing more attention on the fact that smoking is one of the more dangerous aspects of the increasing diabetes incident prevalence."

The last portion of the biologic evidence summarizes evidence since 2005 on the effects of nicotine on beta cells in the pancreas, which takes on more meaning in light of McAfee's emphasis on the fact that smoking now affects as many women as men. This was not the case 50 years ago.

A study by Yoshikawa et al in 2005[16] showed the presence of nicotinic receptor in pancreatic islets and beta cells, and additional studies cited in the report have found connections between nicotine use by pregnant women and beta cell death in the fetus.[17-19] This can set in motion the process by which diabetes develops after the child is born.

Metanalysis on Smoking and Diabetes

Of great value is the epidemiologic evidence, which features a meta-analysis of 51 comparisons over 46 studies that overwhelmingly find a positive association between cigarette smoking and incident T2DM:

- 40 comparisons showed a significantly increased risk of diabetes among smokers
- 10 comparisons showed a nonsignificant association between smoking and risk of diabetes (in 8 studies, the risk ratio exceeded 1.0)
- One comparison showed a slightly increased association between not smoking and risk of diabetes[3]

The heterogeneity in the studies concerned the report's preparers; after further examination, they noted that those studies using measurements of blood glucose at baseline and endpoint were more likely to have strong associations between smoking and T2DM than those relying on patient reports and physician registries.[3]

A Public Health Response

What can be done?

McAfee said the most important response he has seen since the report's release has been the announcement by CVS Caremark that the retail pharmacy chain will remove tobacco products from its 7600 stores nationwide by October 1, 2014.[20]

"It's a very powerful statement that enough is enough," McAfee said, predicting that CVS' step will be "the beginning of a trend."

Pechacek said the evidence that smoking makes T2DM more difficult to treat makes it essential that insurers make smoking cessation services available. "Every diabetic smoker should be given access to the best available treatment services as quickly as possible," he said, putting such care on par with exercise, nutrition counseling and glycemic control.

Terry F. Pechancek, PhD

When asked what to tell a smoker who is afraid to quit because he or she will gain weight, Pechachek was adamant: Whatever risk is present from gaining weight is relatively small, he said, and it cannot compare with the risk presented by smoking.

Pechacek wasn't as blunt as the title of a 2013 study published too late to make the report: "It is better to be a fat ex-smoker than a thin smoker."[21]

Unfortunately, as the American Lung Association (ALA) reported in its 2014 "State of Tobacco Control," most states fall short in ensuring that those Americans who most need access to smoking cessation services get them, especially through Medicaid.[22]

ALA reports that only 2 states, Alaska and North Dakota, fund tobacco prevention programs at levels recommended by the Centers for Disease Control and Prevention (CDC). Only 2 states provide coverage to Medicaid enrollees for all 7 medications approved by the US Food and Drug Administration for smoking cessation, and all 3 forms of counseling,[22] despite evidence that multipronged approaches work best.[23] The ALA report singled out Alabama and Georgia—among the states with the highest diabetes and obesity rates—for offering "virtually no help" with smoking cessation for Medicaid recipients.[24]

Yet Medicaid, by design, is tied to poverty. And data show an undeniable nexus of poverty, diabetes, and cigarette smoking. Poverty is emerging as a powerful indicator for likelihood of diabetes; a review published just this month found social determinants have a strong impact on glycemic control, blood pressure, and LDL cholesterol.[25,26]

Similarly, CDC data show that the best predictors of smoking status are a person's education level and poverty status: while the overall smoking levels have fallen to 18.1%, they remain at 27.9% for those below the poverty line; only 9.1% of individuals with a bachelor's degree smoke, but 41% of those with only a GED do.[27]

Acting Surgeon General Lushniak took note of these disparities in presenting the report at the White House. "The burden of tobacco use is not shared equally by all of us. Our education, income, race; where we live, especially the Midwest and Southeast; our sexual orientation, and whether we have a mental illness—these factors affect whether we are harder hit by tobacco."

"The last century has taught us that public health leadership is essential to effectively deal with the aggressive tactics of the tobacco industry," he said. "Enough is enough." **EBDM**

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Employer's Perspective

The Continuing Evolution of Employer-Based Intervention in Diabetes Disease Management

Stanton R. Mehr

Employers have long had an interest in keeping employees healthy and productive. They have attempted many strategies toward this goal, with varying levels of success. High attrition rates, low employee engagement, and poor consensus on effectiveness hinder efforts by both employers and managed care to rein in diabetes and obesity.

For some employers, the difficulty starts with their own limitations. Large multisite firms with on-site clinics may be better positioned to implement health and wellness programs than smaller companies, which may have to rely on outsourced experts and vendors. Some companies have full-time corporate medical directors with expertise at designing and managing wellness programs. Others may hire nursing staff to run their programs.

Either way, these programs need to coordinate (and perhaps integrate) with a health plan partner to create seamless intervention in patient care. Yet a more basic problem remains: attracting employees to the program and keeping them engaged. There is also a lack of consensus about the effectiveness of financial incentives to help spur workers' participation and success in these programs.

Large Target Based on Costs

Corporate health programs have long targeted diabetes mellitus. The reasons are clear: In 2002, a landmark economic study established that the worker with diabetes costs an employer 5 times more than a worker without diabetes (**Figure 1**), and that half of the costs related to diabetes were indirect costs: disability payments, time away from work, and premature death.[1] Consider just absences for workers with diabetes: men accumulate 11 more days away from work each year than men without diabetes. Women with diabetes register nearly 9 more days absent from work than women without the disorder.[1]

The tools used by employers to address obesity and type 2 diabetes (T2DM) include disease management programs, counseling, call centers, gym memberships, and combinations of each. Many have used financial incentives. Value-based insurance designs (VBID) offer low or waived copays for medications used to treat T2DM, for example, because the drugs have been shown to reduce morbidity and mortality.[2] Others may offer lower health insurance premiums to those who actively participate in a disease management program. Some workers get discounts on gym memberships. In isolation, these programs may not provide the anticipated results—and savings—for the employer.

Beyond Health Fairs: What Comes Next?

Most midsize and large corporations actively promote on-site health fairs, offering an excellent opportunity to help identify patients with diabetes, prediabetes, or weight problems. The question then arises: what next? The employer and the managed care organization try to ensure individuals connect with their physicians. However, many corporations fail to take a comprehensive, public health approach. This may include offering only healthy snacks in the vending machines, not allowing sugared soda to be sold on premises, little toleration for smoking breaks, and promoting activity programs at lunch and after work. In other words, screening is only the start.

A Broad Attack Better Than a Precision Approach?

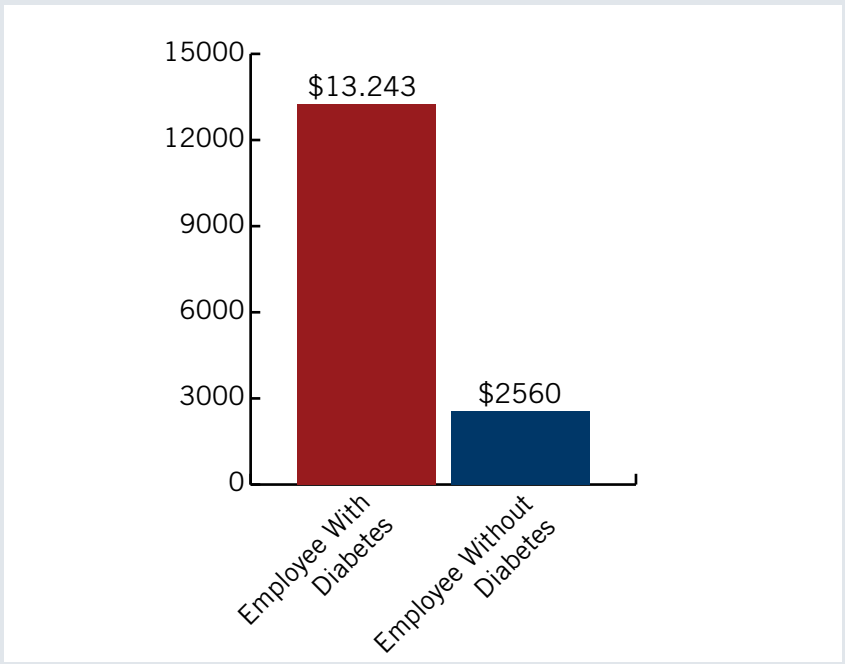
Perhaps the most effective, and the most logical, programs are wide ranging, and seek to influence patients not only while they are at work. Through a combination of health benefit design, health promotion on the job, worksite primary care clinics, disease management, and patient education, they seek to influence workers' decisions around the clock, on the job and at home. These programs may rely less on financial incentives (other than lower or waived copays) but more on better practices.

Programs offering financial incentives to workers or patients have demonstrated mixed results. Some believe that financial incentives are not the way to go, that patients should not have to pay extra to do what's in their best interest.[3] A study by Cornell University investigators reaffirmed these results. The study found offering financial incentives in the form of fixed payments and forfeitable bonds did not produce desirable weight loss results in 2635 workers at 24 US worksites. Attrition rates were high and the improvements in body weight resulting from the financial incentives were described as "modest."[4]

It is probably not the best idea to focus on any one area, such as financial incentives. "What works best for companies is to have a coordinated strategy that ties in all the elements," said Margaret Rehayem, senior director of strategic initiatives and communications, Midwest Business Group on Health, Chicago. "This includes everything from promoting the program to engage their population to targeted follow-up and evaluation." She advised tying financial incentives, such as waived copays and paying for diabetes supplies and comorbidity drugs (i.e. cardiovascular and hyperlipidemia drugs), into the entire approach.

She cautioned, however, that some problems involving financial incentives can be avoided when designing the employer-based program: "Some employers make the incentive too hard to achieve by putting too many requirements in place or make people wait an extended period of time (such as once a year) to earn the incentive, and these

Figure 1. Average Annual Cost to the Employer of a Patient With or Without Diabetes Mellitus



Source: Ramsey et al, 2002.

can reduce a person's motivation to attain success," Rehayem said.

Another common, avoidable problem involves inaccurate alignment of the incentive. She commented, "We had one employer reduce copays for all drugs they covered whether you participated in the (diabetes management) program or not—this removed the need to participate in the program all together."

Further evidence that a singularly focused approach does meet expectations was published in 2012. In this study, employees who were overweight or obese were sent communications customized to each person, to try to influence behavior change.[5] The results of communication through this web-based program were analyzed in terms of their effect on employee weight, body mass index, blood pressure, cholesterol, and blood glucose levels. The researchers, from Johnson & Johnson's North American Global Health Services Division, studied the baseline and 2-year data from 101 employee-participants with 137 overweight or obese workers who did not receive the tailored communications. The researchers found significant mean differences in systolic blood pressure, high-density lipoprotein cholesterol, and glycemic levels, but "each in a clinically undesirable direction."[5]

Another approach that employers have adopted, in keeping with the broad targeting concept, is to try to address prediabetes or insulin resistance to delay or prevent the development of T2DM. As people with insulin resistance tend to be overweight,[6] this implies including obesity management and weight-loss programs in the mix.

Rehayem explained, "I've seen employer engagement become more focused regarding diabetes prevention/management. Many years ago, programs that targeted any chronic condition usually tried to only reach out to the sickest percentage of the population. Now employers have put together programs that target people across all levels of risk."

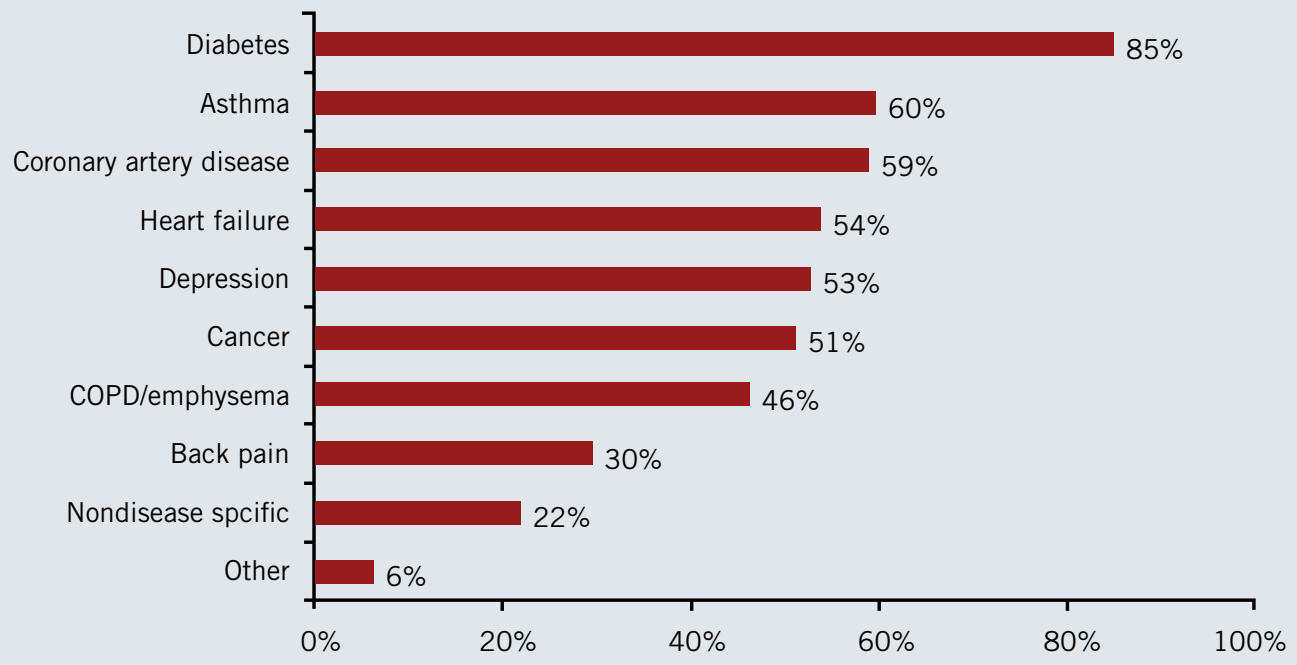
"There are new programs coming into the market that address those with prediabetes with the focus on preventing their condition from getting worse. Employers are also better at reaching out to their populations. For example, before they just relied on the health plan to reach out to people who are identified as at-risk; however, employers are now looking at follow-up from onsite health screenings to support their efforts to get people engaged," Rehayem said.

"To be fair, in the last few years, health plans have improved the quality of their outreach programs so that folks are identified quicker and can engage with either a program or even a qualified health coach."

Surveying Employer Wellness Programs

According to the 2012 RAND Employer Survey, approximately half of all employers surveyed (>50 workers) reported that they offer disease management programs to their employees. Of those, 85% offer diabetes disease management programs, far and away the most common chronic disease addressed (**Figure 2**). Obesity disease management did not make the list.

Figure 2. Approximately Half of Employers Offer Disease Management Programs, Percentage Offering Programs for Specific Chronic Conditions



COPD indicates chronic obstructive pulmonary disease. Source: RAND Employer Survey, 2012.

A More Holistic Concept

Over the past 15 years, as health costs climbed, "Many employers have shifted their focus away from managing costs for separate and distinct episodic health care encounters, and migrated to a broad holistic approach of managing an overall health profile, concentrating on underlying drivers and behaviors, as well as the price of specific health services," according to Ray Brusca, group vice president, human resources, Techtronic Industries Inc., Huntsville, Maryland. He told *Evidence-Based Diabetes Management* that this includes an emphasis on underlying lifestyle factors, such as smoking, excess weight gain, and sedentary activity levels, that are the drivers of high cost and long-term chronic disease states.

"This is particularly true with diabetes, where lifestyle factors are a major contributor to the onset of the disease," Brusca said. "By focusing on education, value-based benefit designs and incentive-driven programs, employers can slow down the advancement of disease. In some cases, we see health profiles reversed to levels previously thought unattainable."

David Groves, an independent industry consultant on health, wellness, and productivity management, shares this view. "Employers have moved away from the perspective of diabetes as a single disease," he said. "Over the years, companies (and, more importantly, health care providers) have begun to understand that managing this condition requires a complex, multifactored approach."

That means addressing not only the physical symptoms but "the behavioral aspects as well." Groves continued, "The high obesity and depression comorbid issues are only two of the many elements of managing diabetes. The engagement of the person with this condition and the ownership they take in managing their own choices is essential."

An Emphasis on Farming Needed

Over the years, the question of return on investment for diabetes disease management programs still remains unanswered.[7] The Midwestern Business Group on Health's diabetes management program, Taking Control of Your Health (TCOYH), is showing average annual cost savings of about $1000 to $1500 per year per participant. Rehayem cautioned that this is but one measurement: "We are looking at additional measures (ie, lowering level of risk over time) we can use to measure the success of this program, however, we don't have these figures yet."

Aggressively seeking return on investment is not really the point, according to Brusca. "From an employer's perspective, return on investment, while important, must be viewed in the same long-term window that resulted in the onset of diabetes and other chronic disease states," he pointed out. "These conditions did not develop in the short term. Having a positive impact will take patience and time, requiring a deep understanding that payback will come, but not right away."

The Better Target: Managing Patient Motivation

Groves still worries that corporate thinking in diabetes and obesity disease management has not yet moved past the mindset of "fix the problem" when it comes to employees with chronic disease. He told *Evidence-Based Disease Management*, "Disease/condition management programs have been a step in the right direction, but have not met expectations," he said. "They are still too 'medically' oriented and discuss too many things the patient is doing *wrong*

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and has to correct. That is not engagement."

This does not get to the essential aspect of "internal ownership/ intrinsic motivation" in daily decision making. Groves argues that using "strength-based" interventions rather than "deficits-based" interventions would enhance employees' engagement, ownership, and motivation to manage their daily decisions more positively."

He pointed out that "If one digs down with a client, very often the issue of low self-esteem, based on a negative self-concept and expectations of oneself are the root causes of not managing this complex diabetes condition." **EBDM**

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Research Report

Study on Protective Gene Mutations for T2DM Appears to Have Strong Implications for Drug Development

Mary K. Caffrey

It may be 10 years before the discovery of gene mutations that block type 2 diabetes mellitus (T2DM) leads to a therapy, but that did not diminish the enthusiasm of scientists who heralded the March 2, 2014, announcement as a "tour de force,"[1] and a potential game-changer in treatment of this worldwide epidemic.

An international group of scientists, led by the Broad Institute and Massachusetts General Hospital (MGH) and publishing in *Nature Genetics*,[2] announced that genetic tests on more than 150,000 people had uncovered the existence of mutations in a gene that can reduce the risk of developing T2DM, even among those who have risk factors like obesity or old age.[3] The results have huge therapeutic implications; if harnessed, they could shift the approach from treating symptoms and complications to prevention of the disease itself.

In the study, researchers sorted through the genetic analysis of a large group of patients who displayed rare mutations in a gene called SL30A8, whose protein had previously been shown to have a role in the insulin-secreting beta cells of the pancreas. Unlike an earlier variant of the gene that had increased risk of T2DM, the mutations identified by the team from Broad and MGH reduced the risk of the disease by 65%.[3]

If a therapy could be developed to mimic the behavior of the mutations, it could potentially allow physicians to prevent those at risk of diabetes from developing the disease. But much work remains, for scientists must now learn whether the presence of the mutation carries with it any harmful health effects.[1]

The discovery represents a triumph not only in studying human genetics but also for an international approach to studying diabetes. T2DM affects 300 million people of all ethnic groups across the globe, and one of the fruits of the study are findings that seem to hold up across ethnicities, which would bolster the aims of those seeking to translate the results into a therapy.

David Altschuler, MD, PhD

> *"This work underscores that human genetics… can also powerfully inform drug discovery."*
> —David Altshuler, MD, PhD

"This work underscores that human genetics is not just a tool for understanding biology; it can also powerfully inform drug discovery by addressing one of the most challenging and important questions—knowing which target to go after," said David Altshuler, MD, PhD, deputy director and chief academic officer at Broad, as well as professor at Harvard Medical School at MGH.[3]

According to a press release from the Broad Institute, work on the study stems from a 2009 research partnership among the Broad Institute, MGH, the Lund University Diabetes Centre in Sweden, and Pfizer Inc., which helped fund the study. Researchers took a different approach than what is normally done when using genetics to fight disease: instead of seeking out genetic mutations that revealed who was a greatest risk, the team sought out persons who had all the usual risk factors for T2DM but nonetheless did not have the disease and had normal blood sugar levels.

The team found a genetic mutation that appeared to block SLC30A8 function and was present in persons without diabetes in Sweden and Finland. Scientists were surprised by their findings because a similar mutation was known to cause diabetes in laboratory mice; for this reason, *The New York Times* reported, an early paper on the results was rejected.[1] But additional data became available when Amgen purchased a database from deCODE genetics, which revealed a second mutation of SLC30A8 that also blocked diabetes in a group of patients from Iceland. The team finally compared these findings to a database of multiple ethnicities created for the T2D-GENES Project, which is funded by the National Institutes of Health (NIH).

Pfizer's Tim Rolph, PhD, vice president and chief scientific officer of Cardiovascular, Metabolic & Endocrine Disease, praised the work of the partnership in identifying the mutations. "Such genetic associations provide important new insights into the pathogenesis of diabetes potentially leading to the discovery of drug targets, which may result in a novel medicine."

Besides Pfizer and NIH, major funding for the study also came from the Doris Duke Charitable Foundation.[3] **EBDM**

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A Big Step Forward in Treating Chronic Diabetic Foot Ulcers

Surabhi Dangi-Garimella, PhD

Diabetic patients, especially those with very high hyperglycemia, are at an increased risk of developing foot sores or ulcers.[1] The ulcers are often painless, which may be due to neuropathy or nerve damage, and can lessen the person's ability to feel pain, heat, and cold.[2] Subsequently, the ulcers may be neglected, resulting in infection and aggravation of the wound.

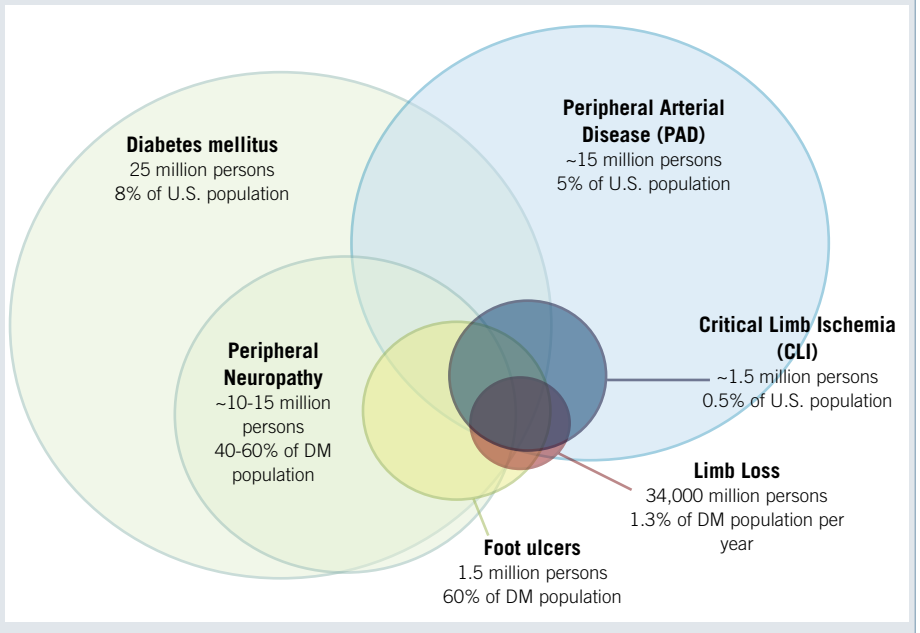
A study recently published in *The Journal of Clinical Endocrinology and Metabolism* by a group in Italy conducted a randomized, double-blind, placebo-controlled trial, wherein diabetic patients with hard-to-heal ulcers were randomized to receive placebo or polydeoxyribonucleotide (PDRN). The patients were treated with either the drug or the placebo 3 days a week for 8 weeks, intramuscularly and perilesionaly. The primary outcome of the trial was set at complete ulcer healing and the secondary outcomes were days needed for wound closure and reepithelialization of the wound surface. While 18.9% of patients on the placebo presented complete healing, 37.3% of PDRN-treated patients showed complete healing. Additionally, PDRN hastened the process of wound closure, with a median healing time of 30 days in PDRN-treated subjects versus 49 days in those treated with placebo.[3]

Foot ulcers, a common diabetic complication, can result in hospitalization and in extreme cases, lower limb amputation. Nearly 70,000 diabetic patients underwent a leg or foot amputation in 2008, and these procedures account for >60% of nontrauma related amputations according to the Centers for Disease Control and Prevention (CDC). The CDC data also identified an 8-fold increased risk of leg or foot amputation in diabetics.[4]

Primary Causes of Limb Loss in Diabetics

- Reduced blood flow, especially in the extremities, which decreases healing potential
- Neuropathy reduces pain, which can result in the patient neglecting the pain
- Neuropathy is aggravated in individuals who
  - Have very high blood sugar levels
  - Have high cholesterol
  - Have high blood pressure
  - Are overweight[4]

Figure. Risk Factors: Non-Traumatic Limb Loss in the United States



Source: *Diabetes Foot Ankle*. 2013,4:21847. http://dx.doi.org/10.3402/dfa.v4i0.21847.

Diabetic Foot Ulcers and Healthcare Costs

Costs associated with diabetic foot care (including amputations) have been identified as the single largest category of excess medical costs for diabetes, and are estimated at $11 billion for patients with neuropathy.[5]

A collaborative report presented at the 2013 annual meeting of the International Society for Pharmacoeconomics and Outcomes Research, by the Analysis Group, Inc, and Organogenesis Inc, assessed the annual burden of diabetic foot ulcers (DFU) on payers at $10-$15 billion, over and above work-loss and other indirect costs. This calculation was based on an estimation that 0.9 million patients suffer from DFU each year.[6] The report also estimated that private insurance companies bore twice the cost for DFU patients overall ($30,309 annually per patient) compared with matched non-DFU diabetic controls ($14,022). A similar trend was observed with Medicare ($27,040 annual cost per DFU patient compared with $15,743 for matched control). The authors emphasized the need for preventive measures to avoid the severity and cost of end-points like amputations among these patients.[6]

The following table provides a strategy that could help avoid DFU as well as successfully manage DFU to avoid limb loss.[5]

Table. Preventing Diabetic Foot Ulcers

Component		Priorities
Primary prevention	Avoid DFU occurrence	Identify moderate and high-risk patients
Secondary prevention	Identify DFUs and access care	Increase access to primary/specialist care
Tertiary prevention (DFU management)	Adequate DFU care to minimize risk of limb loss	Algorithms to ensure arterial perfusion to the foot, mechanical off-loading, local wound care.
Reducing recurrence	Avoiding DFU recurrence	Providing long-term options for off-loading at-risk area.

Current and Novel Treatment Options for Diabetic Foot Ulcers

Currently, the standard options for treatment of DFU include debridement of the wound, managing any associated infections, revascularization of the wound as needed, and off-loading of the ulcer.[7] Debridement, achieved surgically, enzymatically, biologically and through autolysis, removes surface debris and necrotic tissue. Off-loading helps heal the ulcers and also prevents recurrence.[7]

Growth factors such as platelet-derived growth factor-beta (PDGF-beta) are commonly used as a topical therapy for treating DFUs. Other options that have been evaluated include application of platelet-rich plasma, granulocyte colony-stimulating factor (G-CSF), other growth factors such as basic fibroblast growth factor (bFGF), and epidermal growth factor (EGF) locally to the wound. Matrix metalloproteinase modulators, bioengineered skin substitutes, and hyperbaric oxygen treatment are some of the newer and upcoming treatment options for DFU.[7]

According to Francesco Squadrito, MD, the lead author on the PDRN study, preventing ulcers can prevent up to 85% amputations.[8] So an effective treatment like PDRN could prove a tremendous advantage in DFU patients. The study researchers are planning a phase 4 study of PDRN and the manufacturer of the drug (Placentex) has filed for a patent.[8] **EBDM**

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Diabetes Patients More Susceptible to Flu Complications

Aimee Simone

A new study provides evidence that diabetes patients should receive the influenza vaccine, though its results are not as strong as those produced by previous studies.

New research finds that adults with diabetes are more likely to contract serious influenza-related illnesses, underscoring the importance of adhering to guidelines advising that all adults with diabetes receive the flu vaccine.

The new study, published online on January 24, 2014, in *Diabetologia*, analyzed the incidence and severity of flu-related sickness among adults with diabetes compared to those without diabetes in order to determine whether flu vaccination efforts should be targeted to working-age adults with diabetes. The cohort study used data collected from 2000 to 2008 in Manitoba, Canada. Adults aged 18 to 64 with diabetes were identified and matched to a control group of adults without diabetes. The rates of physician visits or hospitalizations for influenza-like illness, hospitalizations for pneumonia and influenza, and all-cause hospitalizations for patients in both groups were analyzed.

The study included 745,777 person-years of follow-up among 166,715 subjects with and without diabetes. Throughout the study, a total of 251,144 influenza-like illnesses, 1892 cases of pneumonia and influenza, and 36,955 all-cause hospitalizations were observed. Patients with diabetes were more likely to be vaccinated against influenza and pneumonia when compared with those without the condition. In diabetes patients, influenza was associated with a significantly increased incidence of all 3 outcomes, accounting for 13% of all influenza-like illnesses, 26% of influenza and pneumonia cases, and 6% of all hospitalizations occurring during flu season. In patients without diabetes, influenza season was only associated with an increased number of influenza-illness cases.

Influenza seemed to have a greater effect on pneumonia and influenza hospitalizations and all hospitalizations among diabetes patients when compared with controls. However, only the difference in all-cause hospitalizations was significant. When compared with adults without diabetes, patients with diabetes had a 6% greater increase in all-cause, translating to approximately 54 additional hospitalizations in the study cohort.

The results are similar to those of previous studies, which have also found diabetes to be a risk factor for flu-related hospitalizations. However, the effect of influenza observed in the current study was much smaller than that found in previous research. The authors of the study suggest that more research is needed to confirm the effectiveness of flu vaccine in adults with diabetes.

"Formal economic studies are also required, to ascertain the extent to which identifying diabetes as a high-risk indication for vaccination may mitigate the healthcare use and costs associated with influenza," they conclude. **EBDM**

Dietary Patterns, and Effect on Population Health, Get Attention from Advisory Panel

Mary K. Caffrey

Back in 1977, when a committee convened by then-US Senator George McGovern, D-SD, took the first official look at the American diet, the big concern was nutrient deficiency: In other words, what's missing that might make people sick?[1]

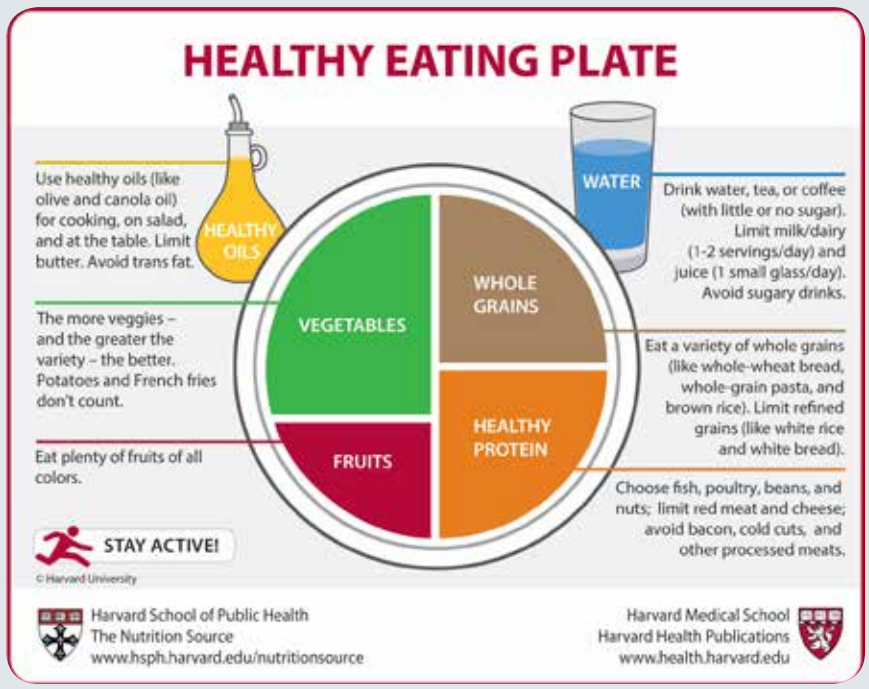
How times have changed.

On January 13-14, 2014, when the 2015 Dietary Guidelines Advisory Committee (DGAC) met in Bethesda, Maryland, the worries were generally not about too little but too much: Americans are making themselves sick alright, but most of the evidence concerns what we're *putting in* our diets, not what we're leaving out.

Rates of diabetes and obesity are soaring, especially in the Southeast, and at least part of this difference is attributed to the regional diet.[2] Institute of Medicine (IOM) Senior Scholar J. Michael McGinnis, MD, MA, MPP, opened the session with an historical overview of the Dietary Guidelines process, and noted that 500,000 Americans now die each year due to poor diet and exercise habits – more than die from smoking.[1,3]

But as McGinnis and DGAC Chairwoman Barbara E. Millen, DrPH, RD, made clear, the 2015 guidelines cycle is not happening in a vacuum: the process, which occurs every 5 years and rotates between the US Departments of Agriculture (USDA) and Health and Human Services (HHS), will unfold within HHS as the Affordable Care Act (ACA) takes hold across the country. And language heard throughout the 2 days of hearings was strikingly similar at times to that of healthcare reform itself.

Figure. Harvard's Healthy Eating Plate



Source: http://www.hsph.harvard.edu/nutritionsource/healthyeating-plate-vs-usda-myplate/.

Looking to Improve Population Health

McGinnis, when asked how the guidelines could engage primary healthcare providers, said he was encouraged with the creation of accountable care organizations, as envisioned in the ACA. McGinnis noted that the ACA not only calls for the improvement of population health but for primary and specialty care providers to "look beyond the clinic doors" and speak to a "broad set of factors" that affect the health of every American, and require primary care physicians to be engaged.

The next day, after public testimony had concluded, Millen opened reports of the subcommittees with a clear link to healthcare reform. The 2015 guidelines, she said, have the potential to affect "the implementation of the Affordable Care Act, the accountable care organizations," national prevention strategy, as well as grant funding within the National Institutes of Health and the Centers for Disease Control and Prevention. She then outlined what is good and bad about both the food and the healthcare systems.

The US population, she said, has the finest healthcare innovations in the world, including the best cancer care, but access to care is "variable." The nation needs to shift its attentions from a preoccupation with treatment to a system based on prevention. Despite what employers and families spend on healthcare, there are wide healthcare disparities, Millen said. "We have preventable disease morbidity and chronic disabilities, and they account for half of the nation's health burden."

Is there a link between these facts and what Americans eat? Millen seemed to suggest so.

"One in 6 households are food insecure, and two-thirds of the population is overweight or obese…we suffer from poor dietary patterns," she said. "Foodborne illnesses have reached 76 million annually, accounting for 325,000 hospitalizations and 5000 deaths each year."

Despite the many strengths of the agriculture and food distribution systems, Millen said, many experts believe that the committee must find solutions to these problems, and it must act aggressively to tackle diabetes and obesity, to do something about healthcare disparities among certain groups, to moderate alcohol use, and to lower metabolic risk factors. "These are the questions that are on the minds of the DGAC," Millen said.

A "Systems" Approach

Millen, DGAC Vice Chair Alice Lichtenstein, DSc, and the 2 returning members from 2010, Miriam Nelson, PhD, and Rafael Perez-Escamilla, PhD, have formed a science review subcommittee that is ensuring that the committee takes a "systems approach," and examines dietary patterns and best practices, rather than just go food by food, or ingredient by ingredient. In fact, the third presenter at the January 13 session, Susan Krebs-Smith, gave the panel an overview of how to evaluate diets based on different systems approaches. Millen called for looking at "what works" at *both* a population level and at an individual level. The 2015 committee will continue its predecessor's work in examining the effects of the places where people eat, cultural factors, and access to quality food, but it will dig deeper to examine the connection with health outcomes, Millen said.

This approach is more novel than it might seem. Past DGAC reviews have been criticized for being captive to corporate food groups; indeed, those interests gave it their best during the morning session of January 14. A literal smorgasbord of professionals paraded to the microphone, representing sugar, salt, potatoes, California walnuts, the American Meat Institute, nonalcoholic beverages, Ocean Spray cranberries, McDonald's, juice products, Dannon yogurt, food technologists, egg farmers, the Tea Council, the National Cattlemen's Beef Association, candy and gum, pistachio growers, and the United Fresh Produce Association, among others. Most interests came armed with a registered dietician, and everyone had studies to support giving their product a place at the table.

How food-specific the DGAC's recommendations will be remains to be seen. Anna Maria Siega-Riz, PhD, RD, who chairs the largest and most critical subcommittee on "Dietary Patterns, Foods and Nutrients, and Health Outcomes," explained in the afternoon session January 14 that her panel will first examine dietary patterns, and from those results will take its work into specific foods. She did not directly answer a question from Nelson on how the subcommittee would tackle thorny topics such as sugar-sweetened beverages, which has been the subject of important research since 2010, as well as high-profile public policy initiatives in New York City, Mexico, and the United Kingdom; and dairy, which dominated testimony in the public hearing January 14.

The Importance of Sustainability

Some topics of the January 13-14 meeting were anticipated: Given the public flap over a May IOM study that did not

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support sodium intake below 2300 mg per day, it was hardly surprising when a Salt Institute lobbyist asked the committee to take the "courageous step" of calling for more salt in American diets.[4]

Comments received in the fall from Johns Hopkins' Center for a Livable Future[5] presaged the presentation from its visiting scholar, Kate Clancy, PhD, who spoke January 13 about food sustainability and food security; essentially, the idea that it's best for the sources of food to be as close to the people that consume them as possible, to protect both population health and the environment.

> *"There is biodiversity available to people, but when we look at what people eat, the message is not getting through."*
>
> **—Kate Clancy, PhD**
>
> Johns Hopkins Center for a Livable Future

As the Hopkins center did last fall, Clancy addressed the beef industry's effects on the climate; she did not, however call for diets "bereft" of meat, but said "low-meat" diets produce many of the same benefits.

When it came to seafood, however, Clancy was clear: overfishing is a "wicked" problem, and the current dietary recommendations of 2 servings per week simply don't square with supplies of popular fish. The public needs better, more specific advice on what species to eat; the fish "conundrum," as Clancy called it, is part of a broader problem of food diversity. "There is biodiversity available to people, but when we look at what people eat, the message is not getting through," she said. "Just like anything else, a better diet would have more species in it."

Clancy said efforts to improve biodiversity and reduce portion size in school lunches in the largest districts and in college cafeterias have made some headway, but there's more to be done. The public has a huge role to play in food sustainability and food security through the choices it makes, she said.

Dueling Over Dairy

Opponents of meat and especially dairy were out in force January 14; 13 of 54 favored plant-based diets in some form,[6] and they ran the gamut: from the vegan mother who shared a typical daily menu, to the African-American doctor who showed up in scrubs after an overnight hospital shift, to the actress Marilu Henner. Mona Sigal, MD, the former emergency room chief at North Shore Medical Center in Massachusetts who today educates the public about healthy eating, used her 3 minutes to lambaste the USDA's publicly funded promotion of cheese, which left the audience laughing when the moderator announced that the next speaker was from the National Dairy Council. But Sigal's message was serious: like other speakers, she cited studies that link dairy consumption with cancer.

Milton Mills, MD

The African American physician, Martin Mills, MD, is a graduate of Stanford University School of Medicine and has led a suit by the Physicians' Committee for Responsible Medicine against the dairy industry, seeking warning labels on milk.[7] Mills did not mention those credentials; instead, he cited statistics that unlike Americans of Northern European origin, most ethnic minorities are naturally lactose intolerant, including 70% of African Americans, 90% of Asian Americans, and 55% of Mexican Americans.

Moreover, Mills said, connections between milk and cancer are emerging, and the troubling disparities of prostate cancer among African American men[8] demands that the committee, "stop holding Americans hostage to the marketing interests of the dairy industry."

While percentages in studies have varied, Mills' overall assertion that lactose intolerance is higher among minorities than persons of Northern European heritage is supported in the literature,[9-11] and his assertions about cancer links are supported as well.[12,13]

Thus, Mills likened the government's ongoing inclusion of recommended daily allowances of dairy in American diets to a form of "institutional government racism."

"Yes, I played the race card," he said.

Various dairy groups brought up past recommendations about "nutrients of concern," specifically calcium, potassium, and vitamin D, and cited studies showing that consuming dairy would contribute to meeting daily requirements.

Controversies over dairy recommendations are not new. The inclusion of a separate dairy cup to the side of the MyPlate graphic was a key criticism of the 2010 edition of Dietary Guidelines for Americans; Harvard's School of Public Health replaced the dairy cup with a glass of water in its "Healthy Plate" alternative, citing dairy links to prostate cancer as a reason.[14]

Next Steps

In opening the subcommittee sessions, Millen reminded the committee that its work is advisory in nature, and the final guidelines are set by the federal departments that oversee the group. Still, the committee has a significant role in shaping guidelines that Millen said shape massive federal programs and touch virtually "every American, every day."

The committee's work, she said, "must be thoughtful, it must be science driven, and it must be very careful."

Millen noted that the committee would consider online comments, in addition to those given in person at the hearing. The next committee meeting is set for March 14, 2014. **EBDM**

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New Studies Affirm Mediterranean Diet's Potential for Patient Self-Management, Prevention of T2DM

Surabhi Dangi-Garimella, PhD

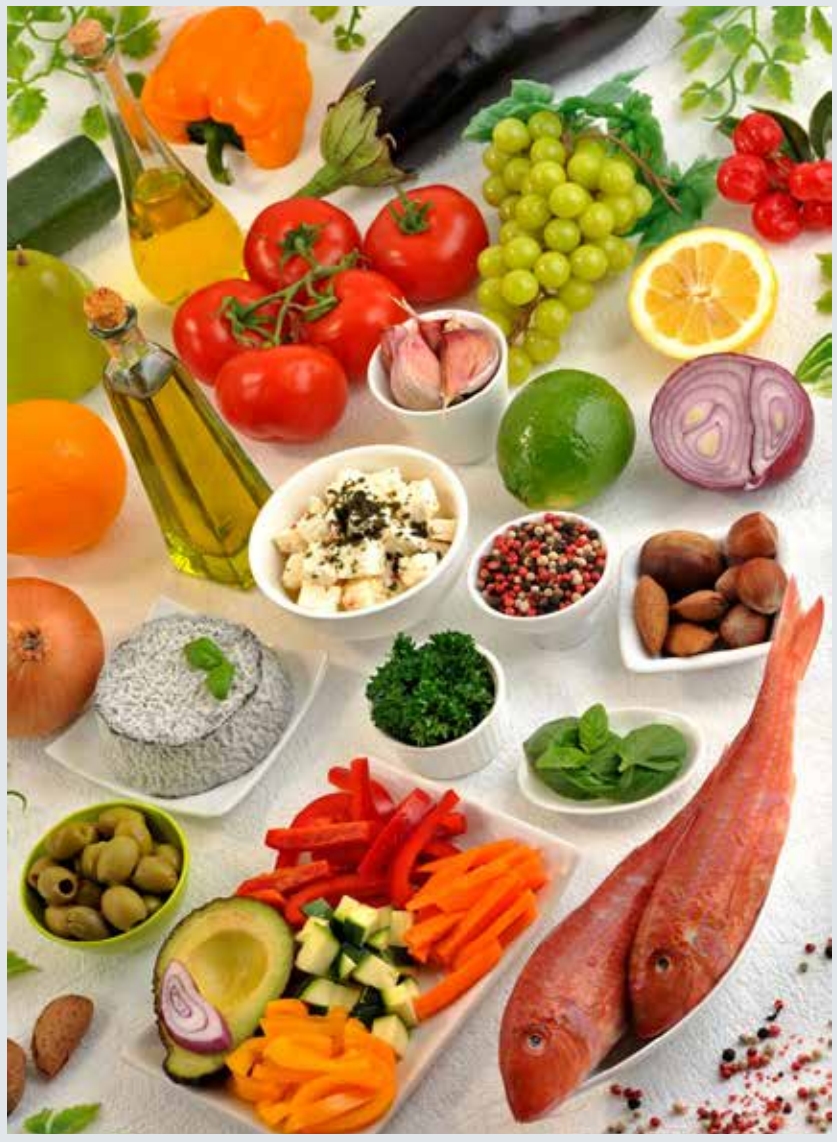
Diet control, over and above a healthy and active lifestyle, has always been recommended for hyperglycemic individuals. A diet rich in vegetables, whole grain, fruits, lean meats, fish, and low in high-fat, high-sugar, and processed foods could help prevent disease incidence and also help diabetics better manage their condition. The Mediterranean diet (followed by countries bordering the Mediterranean Sea) includes most of these listed food types and has been gaining increasing approval, especially following recent clinical trials that reaffirmed the benefits of this diet. In addition to being plant-based and low in dairy, the Mediterranean diet includes beans, nuts, and legumes and primarily uses olive oil (poor in saturated and trans fats) for cooking (**Figure**).[1] Additionally, the diet is low in saturated animal fats and provides for moderate fish intake, the source of polyunsaturated fats. This dietary pattern has been associated with benefits regarding cardiovascular risk factors such as obesity, hypertension, diabetes, and metabolic syndrome.[2]

The PLoS One study observed lower weight-gain, LDL-cholesterol, and metabolic syndrome and a higher HDL-cholesterol.

A subgroup analysis of a trial conducted in Spain among older adults (men and women) at high cardiovascular risk who were assigned to 1 of 3 dietary groups (control with reduced fat intake, Mediterranean diet supplemented with nuts, or Mediterranean diet supplemented with extra-virgin olive oil, or EVOO) found that supplementing with EVOO reduced the risk of diabetes after a 4-year follow-up. Fewer individuals in the Mediterranean diet groups developed type 2 diabetes mellitus (T2DM) than in the control groups. This trial primarily considered the implications of dietary modifications, without any intervention to increase physical activity or lose weight.[3]

A study published in the journal *PLoS One* evaluated the effect of dietary pattern in a non-Mediterranean and occupationally active young population, in this case a group of male firefighters. Unlike previous studies conducted primarily in older, Mediterranean cohorts, this study involved subjects in the United States who might not naturally choose a Mediterranean diet. In the absence of dietary intervention, the researchers developed a modified Mediterranean diet score (mMDS) to assess preexisting dietary habits. Obese subjects (high fast food and sweetened drinks intake) had lower mMDS scores and higher mMDS scores were found inversely correlated to risk of weight gain over a 5-year period. The study concluded that participants who adhered to the Mediterranean-style diet presented lower weight gain, LDL-cholesterol, and metabolic syndrome and a higher HDL-cholesterol. However, the authors recognized several deficits in their study, such as the absence of certain major dietary components (nuts, legumes, wine, and ocean fish); this limitation was a result of the population being examined. Based on the proven effectiveness of this diet, the authors are planning further intervention studies.[2]

Figure. Components of the Mediterranean Diet



Source: Getty Images.

Disease Facts

Diabetes is defined as a fasting plasma glucose (FPG) ≥126 mg/dl, A1C ≥ 6.5%, and/or oral glucose tolerance test (OGTT) 2-h plasma glucose ≥200 mg/dl.[1] A metabolic disorder characterized by progressive hyperglycemia, declining beta-cell function, and reduced sensitivity to insulin, type 2 diabetes mellitus (T2DM), also known as insulin-dependent diabetes mellitus, is the most common form of diabetes. In patients suffering from T2DM, there is either a dearth of or resistance to insulin, subsequently resulting in increased blood glucose levels. As a consequence, the cells are energy-deprived and the long-term effects of this phenomenon may result in harmful effects to the heart, eyes, kidneys, or nerves.[1,4]

Disease symptoms include frequent urination, thirst, hunger despite eating, fatigue, slow-healing wounds, tingling or pain in the extremities. As of early 2011, 8.3% (25.8 million) of the US population was estimated to suffer from diabetes, of which 7 million were predicted to be undiagnosed, 25.6 million were predicted to be ≥20 years old and 10.9 million were over 65 years old. Among the 20 years and older population, no significant gender bias was noted.[1]

T2DM is associated with severe morbidity and mortality, with 71,382 deaths directly associated with the disease in 2007, and 160,022 deaths in which diabetes was a contributing factor. As noted earlier, the long-term effects of T2DM affects several different organs that can result in cardiovascular disease, stroke, high blood pressure, blindness, kidney disease, neuropathy, and amputations.[1]

Comorbidities and Treatment-Associated Risks

Two major issues with disease management include the increased cardiovascular morbidity and mortality associated with the disease and the lack of therapies with efficient glycemic control without long-term adverse effects.[4] Studies have shown a 2-fold increase in cardiovascular disease in the T2DM population and about 66% of patients have been shown to die following coronary heart disease or stroke, despite attempts at risk management with lifestyle changes (such as smoking cessation) and treatments.

Studies conducted to answer some of these questions found that exogenous insulin treatment was safe in newly di-

agnosed T2DM patients monitored for over 6 years, which allayed previously raised concerns about cardiovascular disease and cancer.[5] Another study concluded that intensive therapy with insulin and metformin or a triple oral therapy (metformin, pioglitazone, glyburide) after an initial treatment period with insulin can help preserve beta-cell function over 3 years.[6]

Economic Outcomes

For the year 2012, the total cost of treating diagnosed diabetes was projected at $245 billion ($176 billion direct medical costs and $69 billion indirect), with hospital inpatient care, prescription medicines, and physician visits being the major contributors to the direct costs. Indirect costs of the disease include absenteeism, reduced productivity at work, disability costs, etc.[1]

Lifestyle changes, such as changing or improving dietary patterns, could substantially influence disease outcome and slash the costs associated with disease management. However, food choices are primarily driven by financial restrictions, resulting in a greater intake of caloric- and energy-rich foods.

JOIN 4 ME (UHC, YMCA) has noted considerable success in weight reduction by emphasizing better food choices.

A study recently published by a research group in Italy reviewed published literature to analyze the cost-effectiveness of adherence to a Mediterranean diet and the prevention of degenerative pathologies by evaluating the economic performance of the diet.[7] Although most of the studies evaluated were conducted in the Mediterranean countries, a study conducted in a US population cohort concluded that although the diet recommends high-value food items such as vegetables, nuts, fruits, legumes, poultry, fish, and olive oil for cooking, the reduced dietary costs of red meat, desserts, sweets, and fast food could balance the equation. Overall, the various studies reached a consensus that the socioeconomic gradient drives dietary patterns, and economically challenged populations seem to suffer most from chronic conditions such as obesity, diabetes, and cardiovascular disease.[7] The authors who conducted the review called for conducting more studies that link food cost to diet adherence for various dietary patterns, the results of which could help frame policies to improve dietary adherence among prediabetics and diabetics.

A collaborative study between Lehigh University and the US Department of Agriculture's Economic Research Service, published back in 2010 in the *American Journal of Agricultural Economics*, evaluated the impact of low- and high-carbohydrate foods on the prevalence and medical costs of diabetes. The study proposed the use of subsidizing the cost of low-carbohydrate foods to improve the health of diabetics, which they concluded was more effective than taxing high-carbohydrate foods like soda. Additionally, insurer-initiated enrollment of patients with diabetes in disease management programs, which has already been introduced by payers, could serve as a means of subsidy interventions.[8]

Disease prevention would definitely prove more economical than disease management, as shown in the 2 trials discussed above. Preventing diabetes in adults 65 years and older would be a tremendous cost-saving for the society and the healthcare system. Several different studies have presented the cost-effectiveness of preventing diabetes and form the basis of the Preventing Diabetes in Medicare Act (2011), which has a provision for Medicare to provide medical nutritional therapists to prediabetics or patients at risk of diabetes, as well as for diabetics.[9]

Incentives to Improve Patient Self-Management of the Disease

Payers such as UnitedHealthcare recognize the need for the proactive involvement of patients in disease management, along with the providers and the payers. The company published a commentary last year in the journal *Health Affairs*, highlighting the need for a collaboration among providers, payers and patients to close treatment gaps. Patient engagement can lead to positive health outcomes and improve performance of the health system[10], and lifestyle modifications definitely play an important role in this scenario. In addition to *treatment decision support* and *informing care choices*, UnitedHealthcare is also collaborating with organizations like the YMCA to implement community-based weight management programs. JOIN 4 ME (initiated in 2010) has noted considerable clinical success in weight reduction by emphasizing better food choices and physical activity. Additionally, UnitedHealthcare provides financial incentives to its own employees and encourages other employers to do the same. Initiated in 2008, the Rewards for Health program provides participants the opportunity to gain points for specific health-related actions, such as screening, ultimately leading to health insurance premium reductions for the entire family in the subsequent year. Participation in coaching programs and achieving certain biometric targets are a means to win additional points. UnitedHealthcare noted a decrease in their employee healthcare costs over a 3-year period and a significant saving ($107 million) compared with industry averages.[10]

However, the American Diabetes Association, in collaboration with the American Heart Association and the American Cancer Society issued a joint brief with a word of caution about financial incentives being offered by policy makers for health management. The joint brief stated that although the associations support comprehensive wellness programs in the workplace, financial incentives should be closely monitored to avoid discrimination. Some of the concerns that were raised included:

- expensive premiums for the less healthy, which could restrict healthcare access for those most in need of it
- premium surcharges (associated with an individual's health status) might penalize the entire family
- privacy concerns with filling out the health risk assessment; employees are concerned that information on any health issues may keep them from being promoted
- the influence of financial incentives on long-term behavior change is still debatable

Rather, the brief encouraged companies to offer health promotion services such as fitness centers, weight loss programs and exercise classes on-site, along with healthy food options at the workplace.[11]

An operator of Blue Cross and Blue Shield, Health Care Service Corporation (HCSC), collaborated with a technology-driven healthcare company, WellDoc, to test the DiabetesManager platform among 156 HCSC employees with T2DM. Almost 90% of the participants were impressed by the beneficial effects of using the application for self-management of their chronic condition. With real-time feedback, coaching, and clinical decision support, based on blood-glucose readings and food choices through the mobile phone, DiabetesManager[12] might prove an extremely useful tool for patient engagement.

The emerging picture with T2DM points to overall disease management for healthy glycemic control. This would entail a balance between medication, a healthy diet, and an active lifestyle, supported by a proactive collaboration between the patient, the healthcare providers, and the payer. **EBDM**

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Evidence Shows Taking Part in School Nutrition Programs Helps Students Make Better Dietary Choices

Leah Schmidt, SNS

We all know teaching good nutrition at an early age is an important step toward preventing childhood obesity, but you might be surprised to hear how much work is being done to promote healthy diets in America's school cafeterias.

Leah Schmidt, SNS

In light of mounting scientific evidence linking good nutrition with student achievement, the Healthy, Hunger-Free Kids Act of 2010 set in motion a series of changes in our schools, designed to ensure that students have access to healthy, properly portioned school meals and snacks throughout the school day.

With approximately 100,000 schools nationwide serving more than 30 million students lunch and 13 million students breakfast, we have a tremendous opportunity to teach the next generation about making nutritious choices right in their school cafeterias.

It is important to recognize that many children have already formed their dietary preferences before the first day of school and still eat the majority of their meals at home or in restaurants, where right-sized portions can be a rarity.

The success of school food improvements hinges on efforts to entice students to try the nutritious options available to them, and to make smart choices like starting their school day with breakfast. Schools need to inform the healthcare community, parents, coaches, and the community about the healthy changes on campus. We all need to work together to teach kids the importance of a proper diet and the consequences of unhealthy choices.

From role modeling right-sized meals, to introducing kids to fruits and vegetables they'll find in their school cafeterias, we can all help nudge students toward the choices we want them to make when they walk through the lunch line or stop at the school vending machine.

Federal Standards Set the Bar

School nutrition professionals have revolutionized school meals in recent years. Even before the overhaul of federal nutrition standards occurred, research published in *Journal of the American Dietetic Association* revealed that "school lunch participants were significantly more likely than nonparticipants to consume milk, fruit, and vegetables, and significantly less likely to consume desserts, snack items, and beverages other than milk or 100% juice."[1]

Starting in July 2012,[2] the federal government raised the bar by requiring all schools participating in the National School Lunch and School Breakfast Programs to meet more stringent nutrition standards for school meals.

Under these rules, cafeterias must offer more whole grains, fruits and vegetables, including weekly servings of fiber-rich legumes, vitamin-packed dark leafy greens and red or orange vegetables. School milk is now fat-free or 1%, and meals meet new limits on calories, trans-fat, and sodium.

Even pizza has gotten a makeover. School pizza is now prepared with a whole grain crust, low-fat cheese, reduced sodium sauce, and it comes with a choice of fruit and vegetable sides.

Starting in July 2014, schools will also be required to meet similar nutrition standards for "competitive" foods and beverages—those items sold in school vending machines, snack bars and a la carte lines.

School nutrition professionals have been spicing up their recipes, working with chefs to mix up the menu and finding creative ways to promote these better-for-you choices to students.

Recognizing the power of a free sample, school cafeterias are hosting taste tests that allow students to sample and vote on their favorite fruits and vegetables. More schools are also fighting the fear of fresh produce by teaching kids where their food comes from and offering farm fresh produce on the menu. The US Department of Agriculture's recent Farm to School Census[3] found that 43% of schools surveyed are participating in farm to school activities.

We've also seen schools partner with the healthcare community. Beaver City School (Ohio) teamed up with a local hospital's wellness group to create free-standing mobile information kiosks that deliver nutrition education to middle and high school students right in the cafeteria. Hospital dietitians helped design the concept and content for the kiosks. Laptops allow students to explore everything from "the Facts of Fast Food," to healthy serving sizes and beverage choices. Dietetic interns dedicated time onsite to help familiarize students with kiosk operation and content.

Even with all these positive efforts, many school cafeterias have witnessed an increase in student plate waste since the new standards took effect. Many students simply don't recognize the fruits and vegetables they encounter in the cafeteria, and most kids are reluctant to try new foods.

Getting families to embrace healthy choices at home is just as important as teaching students about nutrition at school. Westside Community School in Nebraska recently hosted a community event that celebrated healthy eating and exercise. Families dined on a SuperPower veggie and fruit buffet, local celebrity chefs offered cooking demonstrations to teach parents how to prepare fresh and healthy meals at home, and members of the Westside freshman football team helped younger kids complete a Fuel Up to Play 60[4] fitness challenge. We need to see more of these unique partnerships nationwide.

It All Starts With Breakfast

Sometimes the greatest cafeteria challenge is getting students to eat anything at all—especially at breakfast. Hectic mornings, early bus schedules, and even the stigma that can be associated with receiving free or reduced price meals cause many students to miss out on the most important meal of the day.

There's no doubt that teaching students to start their day with a healthy breakfast could help improve everything from health to academic achieve-

CDC Reports Drop in Obesity Among Youngest Americans

Results announced February 25, 2014, by the Centers for Disease Control and Prevention (CDC), and published the next day in the *Journal of the American Medical Association* (*JAMA*) show a significant decline in obesity rates among children ages 2 to 5 years over the past decade, although overall obesity rates were unchanged.[1]

The latest CDC data show that obesity prevalence for the group aged 2 to 5 years fell from 14% in 2003-2004 to just over 8% in 2011-2012, a decline of 43%, based on CDC's National Health and Nutrition Examination Survey (NHANES).[2]

In a press release, the CDC noted that while the *JAMA* article does not specifically report a comparison of the 2009-2010 NHANES data with that from 2011-2012, the most significant drop of the decade occurred during this stretch of the decade, when obesity for the youngest children fell from 12% to the final mark of just over 8%.[1]

It is not a surprise that CDC would focus on that period, as that followed the implementation of the 2010 Dietary Guidelines for Americans. Resulting federal legislation overhauled school lunch programs, and the year 2009 also brought changes to the Special Nutrition Program for Women, Infants, and Children (WIC), a major federal nutrition program for persons in poverty.[2]

The *JAMA* study was based on 9120 participants in the 2011-2012 NHANES study. Overall, it found that 17% of youth in the United States are obese, although prevalence remained stable over the study period.[3]

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ment. A 2012 analysis by Share Our Strength's No Kid Hungry campaign and Deloitte revealed that on average, students who eat school breakfast have been shown to achieve 17.5% higher scores on standardized math tests and attend 1.5 more days of school per year.[5]

But of the 21 million students who receive free or reduced price school lunch, only half of those kids get school breakfast, even though they're eligible. Many children aren't getting meals at home either. Kellogg's recent Breakfast in America[6] survey polled over 14,500 people and discovered that 40% of moms report their child does not eat breakfast daily.

In recent years, schools have been stepping up to expand access to school breakfast, which offers lean protein options, whole grains, fruit or 100% fruit juice and low-fat milk. Innovative service options like grab-and-go breakfast choices, breakfast in the classroom programs, breakfast carts and kiosks around the school building are helping drive up breakfast participation. However, as with lunch, schools need the support of the broader community to educate students on why they should take advantage of school breakfast.

Good News on the Horizon

In late February, the Centers for Disease Control reported a 43% decline in the obesity rate among 2- to 5-year-old children over the past decade, an exciting sign that efforts to curb obesity are taking hold[7] (See page **SP113**).

School nutrition professionals will play a key role in nourishing those children by offering healthy food choices at school, but if we want kids to accept these better-for-you meals and develop healthy habits that last a lifetime, we all need to work together to educate kids on the importance of proper diets. Nutrition education—in school and at home—and community partnerships are key to continuing to move the needle on childhood obesity. **EBDM**

Schools are teaching kids where their food comes from and offering farm fresh produce.

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The Link Between a Common Type of Bariatric Surgery and Increased Alcohol Use

Stanton R. Mehr

Bariatric surgery is an expensive approach to weight loss, but it does seem to work. Major studies have verified up to 25% weight loss 2 years after surgery and the maintenance of at least 15% of weight loss 20 years after surgery.[1] In certain individuals, gastric bypass has been life changing, while resulting in vast alterations in body type and self-esteem.

Gastric bypass surgery, in its various forms, can be a valuable tool to combat obesity, having positive effects on mortality and comorbidities (including glycemic levels, insulin resistance, heart disease, and musculoskeletal stress).[1] For the most part, managed care organizations have recognized its value, and when making reimbursement decisions rely on guidelines of the major societies, like the American Society for Metabolic and Bariatric Surgery (ASMBS), to determine eligibility criteria for surgery (eg, body mass index > 40 m/kg^2 or 35–40 m/kg^2 with other risk factors).

As effective as it is, bariatric surgery does carry risks. These include not only perioperative mortality and infection, but other, less-obvious effects. An anecdotal finding that has received additional support recently may begin to concern managed care executives, for it highlights what we know and don't know about a 20-year-old procedure.

Popularity and Cost

The most recent figures on the popularity of gastric bypass in the United States are from the ASMBS: The group reported that the number of weight-loss surgeries of any type was about 220,000 per year in 2008, but fell to perhaps 160,000 per year 2010.[2] Still, the 15-year rise in utilization had been stunning: Only 16,000 surgeries were performed annually in the early 1990s.[2]

In a 2009 study by the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, of 4,779 patients followed, 71.4% had undergone Roux-en-Y gastric bypass (**Figure 1**), which is generally considered the most common procedure. In comparison, 25.1% underwent laparoscopic gastric banding, and 3.5% other procedures, including duodenal switch and gastric sleeve.[3]

Experts believe that patients undergoing the procedure, especially Rouxen-Y gastric bypass, have altered alcohol processing.

Cremieux and colleagues[4] published a study in 2008 outlining the economic impact of bariatric surgery. They found that the average cost for all bariatric surgery types was $24,500 ($26,000 for open surgery and $17,000 for laparoscopic surgery), which included costs incurred 1 month before and 2 months postsurgery. Laparoscopic band placement was at the low end of the range, and bypass surgery was at the high end. However, with the many benefits of significant weight loss resulting from the surgery, the investigators used modeling to calculate that health plans would still recoup their coverage investment within 2 to 4 years.[4]

A Link Between Surgery and Alcohol Abuse?

When determining the economic payback of bariatric surgery, Cremieux and associates[4] considered the principal known risks of surgery in 2008, including mortality and perioperative infection. The possibility of another significant complication that is associated with the most popular form of weight-loss surgery may well alter this estimate.

Until 2012, the link between bariatric surgery and alcohol abuse was only the subject of anecdotal reports.[5] In 2006, Oprah Winfrey hosted an episode of

her show which publicized the association (http://www.oprah.com/oprahshow/Gastric-Bypass-Surgery-and-Alcoholism-Video). Then the *Journal of the American Medical Association* published a study in 2012 that firmly demonstrated a connection between excessive alcohol use and bariatric surgery. Interestingly, the emergence of excess alcohol use in those undergoing weight-loss surgery is not immediate—it seems to occur only in the second year postsurgery.[6] As of now, only the association has been documented. This does not point to the possible cause of such a relationship, but a working hypothesis has the ring of truth to it.


Karen Saules, PhD

A 2010 study of patients entering a substance abuse program at one hospital yielded an important clue, that the number of patients who had undergone bariatric surgery was overrepresented—perhaps up to 6% of individuals entering the program had had gastric modification procedures.[7] A 2013 study of a separate, subsequent patient population at the same hospital confirmed the observation.[8]

Experts believe that patients undergoing the procedure, especially Roux-en-Y gastric bypass, have altered alcohol processing in the body. However, there is no consensus on the actual mechanism of this fault. Some suspect that alcohol reaches the small intestine more rapidly in patients who have undergone the procedure, where it is quickly absorbed, reaching the bloodstream more quickly than if it had to pass through the stomach. Researchers tested this hypothesis by studying alcohol absorption in patients before and after Roux-en-Y bypass.[9] After undergoing bariatric surgery, breath testing revealed that after 1 glass of wine, several patients exceeded the 0.08% legal limit for driving. This may not be the whole story though. Others have found through animal studies that the mechanism may be far more complicated.[10]

The Evidence Begins to Mount

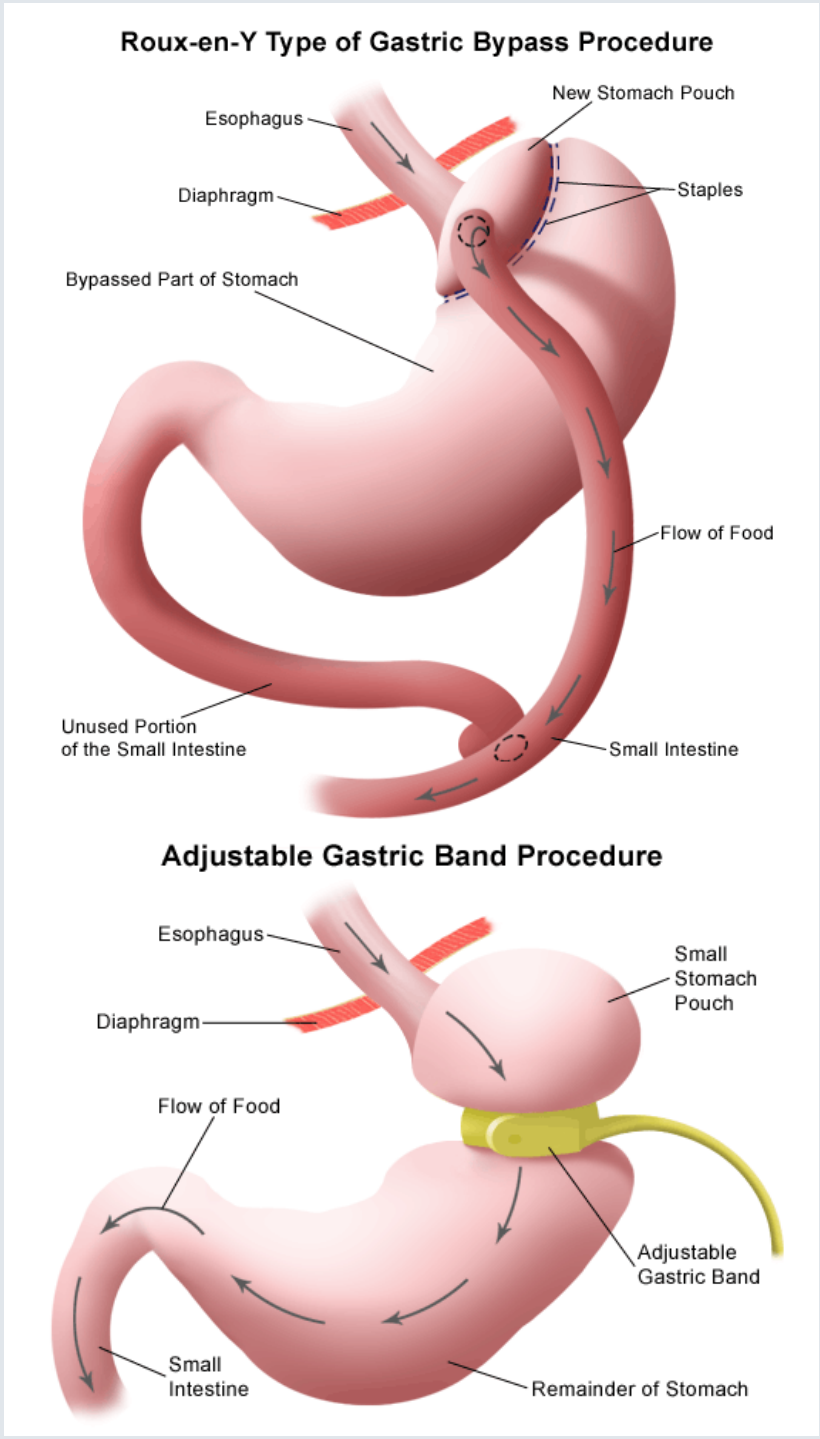
Most of the early, well-designed outcomes information on gastric bypass procedures comes from the LABS; their 2012 investigation put gastric bypass providers and the medical community on notice. Although the absolute incidence of excess alcohol use was still relatively low, the risk for heavier alcohol use (≥4 drinks per week) after the Roux-en-Y procedure was definitely higher than in patients undergoing gastric banding.

The researchers, from the LABS Data Coordinating Center at the University of Pittsburgh, prospectively studied all patients who underwent bariatric surgery at 10 American hospitals over a 5-year span, ending in 2011.[6] Nearly 2000 participants (median age, 47 years; median body mass index, 45.8 kg/m^2) completed assessments preoperatively, at 1 year, and 2 years postoperatively and were included in the study evaluation. The researchers observed that although alcohol use disorders were not different between the baseline and 1-year postoperative period, a significant difference was revealed by year 2. At that time, 9.6% of patients had excessive alcohol use compared after bariatric surgery compared with 7.6% of patients at baseline (P = .01). A previous history of regular alcohol consumption was associated with 6.3-fold increased odds of excessive alcohol use in year 2 (P <.001), but also a person receiving a Roux-en-Y procedure was estimated to have more than twice the risk of excessive alcohol intake compared with patients undergoing laparoscopic banding procedures (P <.001) (**Table**).[6] Significantly, half of these patients with alcohol problems did not have them before.[11]

And the addictive risks of bariatric surgery are not limited to alcohol use disorders, said Sameer Murali, MD, MHSH, a bariatrician from the Southern California Permanente Group, in Fontana, California. "After gastric bypass surgery, I've had patients who have been bankrupted from gambling, and another who racked up thousands of dollars in shopping bills." There appears to be something far more wide-ranging that is occurring in the addictive centers in the brain, according to Murali.

In 2013, researchers published the results of an investigation of 11,000 patients in Sweden.[12] They found that Roux-en-Y gastric bypass was associated with greater inpatient admission rates for alcohol dependence compared with banding surgery, which was not associated with an admission increase.[12] Over the mean follow-up for these patients of 8.6 years, the investigators observed a hazard ratio of 2.3 compared with baseline and twice the risk compared with gastric banding.

Figure. Schematic Illustrations of the Roux-en-Y Gastric Bypass and the Laparascopic Gastric Banding Procedure



Source: http://www.hopkinsmedicine.org/healthlibrary/test_procedures/gastroenterology/laparoscopic_adjustable_gastric_banding_135,63/.

A 2013 study from the New York Obesity Nutrition Research Center at St. Luke's–Roosevelt Hospital in New York revealed that the dependence may not be limited to alcohol intake but to other forms of substance use, like drugs and smoking.[13] They obtained preoperative assessments and evaluated the outcomes of 155 people who received either Roux-en-Y or gastric band surgery. Postoperative questionnaires were obtained at specific intervals until 24 months postsurgery (one-fourth of patients responded to the survey at year 2). They hypothesized that "patients who underwent weight-loss surgery would exhibit an increase in substance use (drug use, alcohol use, and cigarette smoking) following surgery to compensate for a marked decrease in food intake." Their findings confirmed a significant rise in alcohol use through 24 months after surgery in those receiving Roux-en-Y gastric bypass (P =.011) and overall greater substance use, starting at 1 month postsurgery (P ≤.002).[13]

Interestingly, participants who had undergone Roux-en-Y bypass surgery experienced an initial decrease in the frequency of alcohol use immediately

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Table. Surgical Procedures as Independent Risk Factors for Excessive Alcohol Use after Bariatric Operation

Procedure	N	Year 1	Year 2	Adjusted OR	*P*
Laparoscopic adjustable gastric band	485	5.4%	5.6%	1.0	—
Roux-en-Y bypass	1339	7.7%	9.1%	2.07	<.001
Banded gastric bypass	28	3.6%	0.0	0.26	.28[a]
Sleeve gastrectomy	46	2.2%	6.5%	0.80	.73[a]
Biliopancreatic diversion with switch	15	3%	3%	2.72	.15[a]

[a]Analysis is underpowered to detect a difference between this surgical procedure and the reference category. Adapted from: King WC, Chen J-Y, Mitchell JE, et al. Prevalence of alcohol use disorders before and after bariatric surgery. *JAMA*. 2012;307:2516-2525.

after the procedure, followed by the significant rise. Alexis Conason, PsyD, principal study author, told *Evidence-Based Diabetes Management*, "The overall effect was primarily driven by the use of alcohol in participants who underwent Roux-en-Y gastric bypass. We initially hypothesized a 'symptom substitution' theory, but the research has not yet clarified whether that is an underlying mechanism."

> *"Bariatric sugery breaks up the relation with food, with a suddenness that you cannot be prepared for."*
>
> **—Sameer Murali**
> MD, MHSH
> Southern California Permanente Group, Fontana, California

A further investigation into the reason behind the excess patients with substance use disorders (SUDs) after bariatric surgery was conducted by psychologists from Eastern Michigan University.[14] They assessed 141 patients who had gastric bypass at least 2 years previously through online surveys. Fourteen percent of the study participants reported misuse of substances in the postsurgical period. Karen Saules, PhD, and her colleagues found a connection between individuals' excess substance use behavior and presurgical food addiction and subjective hunger issues. However, Saules told *Evidence-Based Diabetes Management*, "About two-thirds of those who develop substance use disorders (SUDs) after bariatric surgery did not report having any substance use problems before surgery (ie, "new-onset" SUD). It might not be surprising that we found a 14% post-bariatric SUD rate in our study, but it is quite surprising that most of those cases were middle-aged women who developed SUDs out of thin air," she said.

Another common finding of the clinical research, Saules commented, is that "individuals who develop SUDs after bariatric surgery seem to be very likely to have a family history of SUD…but not one themselves."

Murali said, "The reward center in the brain is powered primarily by eating in those of us who struggle with our weight. Bariatric surgery breaks up this relationship with food, with a suddenness that you cannot be prepared for. Breaking up in any circumstance is pretty emotional," but this relationship must end. "When we end any relationship," Murali continued, "then something has to happen to that displaced emotion. It might be depression, it may be that you move on to a new relationship that is just as abusive as the one you left. Or you can go on to a new relationship that is beneficial to you, such as developing relationships with people instead," such as those in support groups, who have common challenges and have the patient's respect.

"As it turns out, this is a really complex issue that likely involves both psychological and physiological factors," Saules said. Animal models have shown that rats demonstrated increased alcohol uptake when it was administered orally after bariatric surgery.[10] These researchers followed up their earlier work by administering alcohol intravenously after bariatric surgery, finding that the uptake of alcohol administered in this way was increased after surgery as well. "If intake increases even with intravenous administration, this suggests the mechanism does not simply involve how alcohol is processed in the gut," said Saules.

The Unanswered Questions

Cremieux and colleagues'[4] research established that the return on investment in bariatric surgery for a health plan was relatively quick. The surgery's possible benefits include lower glycemic levels, lower stress on joints, and improved health status, all leading to lower costs over time. Thus, the risk–benefit for patients and plans seems to be positive for most individuals. The finding of an association (though not welldefined) between Roux-en-Y surgery and excessive alcohol use may begin to influence this equation for patients and health plans.

It is possible that stronger evidence to define this recently discovered relationship could shift future utilization of Roux-en-Y surgery to procedures like gastric banding, which do not appear to carry these risks. Health plans and insurers may consider adding assessments of possible SUD into their precertification criteria for Roux-en-Y bariatric surgery in an effort to better select patients who may not be subject to the increased risk.

However, additional research is needed to clearly define the interplay between physiologic factors, psychological components, and family and personal history of SUD before these actions can be supported. In the meantime, informed consent may be the only useful tool plan that providers have today to address this risk. And it is being discussed in the physician's office, when bariatric surgery is an option. Murali emphasized, "Even though it is a poorly defined risk factor, it is not necessarily rare, and I bring it up with patients considering bariatric surgery. It does come up as part of informed consent.

Although many health plans, like Kaiser Permanente, require health assessments and ask about addictive behaviors, it is still difficult to predict who may experience this problem. Even though a history of alcohol use or substance abuse disorder may be an identifier, "you can't really prohibit bariatric surgery because of this link," said Murali. "I do try to move these folks away from Roux-en-Y, but the addiction transfer problem still exists with other forms of bariatric surgery. If we identify patients who are high risk, we [at Kaiser] send them to our addiction specialists. In those patients, we actually ask for 1 year of sobriety before going into surgery. Even with those cases, because the effect size is so large, you cannot predict who is going to experience addiction transfer. Social support (of peers who are struggling with the same issues) may be a better predictor of success, of being able to weather these challenges." **EBDM**

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My Initial Impressions of Medtronic's New Pump

Brian Hegarty

With a great deal of hype, and a few delays from the US Food and Drug Administration (FDA), Medtronic in September 2013 released its newest combined pump and continuous glucose monitor (CGM), the Minimed 530G with Enlite. Medtronic is marketing this device in this country as the "world's first breakthrough in artificial pancreas technology," while putting in tiny print that the product is the first "approved by the FDA. Medtronic has a similar product already approved in Europe." [1]

After living for 30 years as a multiple daily injector (MDI), I finally considered making the change to pump/CGM use because of the major selling point the Minimed 530G offered: "Threshold Suspend" technology. With this, the pump, when measuring sensor sugar values below a certain predetermined level, will suspend delivery of insulin for up to 2 hours.

I anticipated a smooth transition, and even better glucose control. (Disclosure: My most recent A1C prior to starting on my pump was a 6.7. Prior to that I had 6.6, 6.4 and 6.5. Additional disclosure: CGM measures sensor glucose readings, which are taken from interstitial fluid. These readings are not as accurate as blood glucose readings, and can be up to 20%—or maybe more—off from blood glucose readings.) With 3 months in on my pump usage, here are some of my impressions about the Minimed 530G with Enlite.

Along with the pump and CGM transmitter, I was also sent a supply of CGM sensors, infusion sets, insulin reservoirs, inserters, and a new glucose meter whose readings can be read, via Bluetooth, by the pump. Purchase of the pump/CGM system comes with a subscription to Medtronic's CareLink diabetes management software.

The pump (530G) works exactly as expected, with an accuracy of basal and bolus doses up to 0.025 units. It provides a constant delivery of insulin, along with relative ease in programming, and a quick "Bolus Wizard" function that allows easy bolus programming with a few simple clicks.

CGM Is Great (Unless It's Lying)

The Enlite sensor is sometimes very inaccurate. It can also be very, very noisy.

I've been awakened several times by alarms alerting me that my sensor glucose readings have dipped below preset limits. Occasionally, I have been awakened by the alarm to find the sensor glucose reading at 59. Even after eating numerous glucose tablets and scaling basal rate back to 50%—or even suspending basal delivery altogether—alarms were still going off, with the readings stuck at 59. After testing my blood sugar and receiving readings over 120 (and even 180 on occasion), the CGM would continue to register readings at 59, triggering the alarms.

On contacting support, they informed me that the sensor should only be worn on the midsection (which it was), only works for 6 days before it needs to be changed (my incorrect readings usually came on the third or fourth day of usage), and the transmitter should be charged (which it was). Only once, while talking to a support team member, did I receive confirmation that the readings might just be wrong. (Or that I wasn't the only customer who's brought inaccurate readings to their attention.) I was recently told that, although the current sensors are a drastic improvement on the prior models in terms of comfort and accuracy, they do sometimes offer incorrect readings.

There are also issues with the pump and CGM communication, as "Lost Signal" errors occur when the pump is just a short distance away from the CGM transmitter. (Medtronic's official documentation says the devices should be within 3 feet of each other; I've experienced errors when the devices were almost directly next to each other.)

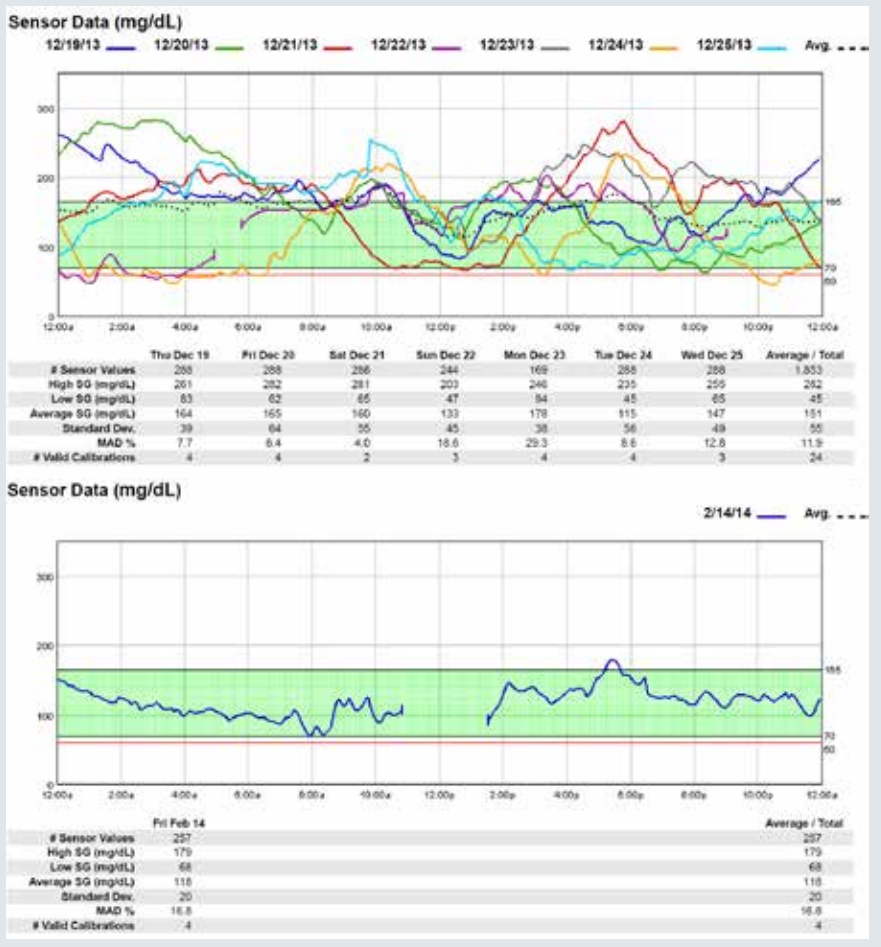
Alarms

Immediately upon starting CGM usage, I turned my alarms settings to "vibrate," to avoid interruptions during work or sleep. This seems only a polite suggestion, rather than a rule. If the vibrating alarm isn't acknowledged or turned off within a set amount of time, a persistent alarm sounds. Even after an exhaustive scrutiny of the settings, I could not disable this feature.

CareLink Software

Medtronic's CareLink software package is a key tool in keeping ahead of glucose trends. Working in conjunction with the pump/CGM, as well as the Bayer Contour NextLink blood glucose meter, I have been able to view statistical tables, overlays, and summaries over a period of time to be vigilant of any trends and to make adjustments to basal rates and carb ratios for tighter glucose control. The user interface could use an update, but the software itself is a pretty valuable resource.

Figure. Control, Before and After



Brian Hegarty's readings from Medtronic 530G with Enlite. Provided with permission from Brian Hegarty.

Customer Support

In a word: poor. I had my devices for 2 weeks when I realized no one had attempted to schedule device training. Several phone calls later, I received assurances that I would receive calls from my personal "Start Right" representative, only to have days and weeks go by without a word. In fact, during the first month as a customer, every conversation relating to my pump/CGM usage was initiated by me. A manager on the Start Right team, after pointing out again that I've received very little client support from my assigned representative, informed me recently that Medtronic has had considerable success selling their 530G with Enlite. They have actually been understaffed to handle the influx of new customers and manage all of the clients.

Summary

Despite this first step in artificial pancreas technology, there's still a long way to go until a true "closed loop" artificial pancreas system is developed. Like an "artificial pancreas," this device can control insulin production when the Enlite sensor detects that sensor glucose readings are too low.

Even with my complaints about the sometimes-inaccurate CGM readings, the customer service and support problems, and the issues with the device's alarms and errors, I feel my control has improved greatly, and I've been able to limit post-meal spikes and dips in blood sugar, while being aware of changes in my insulin consumption due to metabolic changes and other occurrences, such as the "dawn phenomenon."

My frustrations with my pump/CGM are far outweighed by the additional control I feel I have, and the freedom I've experienced from being able to live a life tethered to a small pump, instead of all the additional equipment being an MDI entailed. **EBDM**

Author Information

Brian Hegarty, a writer, editor, and content strategist who lives in Philadelphia, was diagnosed with T1DM in 1983. Follow him on Twitter at @brianhegarty, or on www.type1philly.com.

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SGLT-2s

(continued from cover)

The incretin mimetics overall are considered an incremental advance over the thiazolidinediones or TZDs. Although not associated with cardiovascular events, unlike rosiglitazone, glycemic control with the incretin mimetics is less efficient.

It has been a story of evolution, with health plans and insurers watching carefully for signs of superiority or at least filling an unmet need in T2DM.

A New Mechanism of Action, A New Wave of Products

The current cycle of new agents has introduced the sodium-glucose linked transporter-2 (SGLT-2) inhibitors, which work by blocking glucose reabsorption in the kidney. The first entrant, dapaglifozin by AstraZeneca and Bristol-Myers Squibb, suffered a setback in January 2012 when the US Food and Drug Administration (FDA) expressed concerns over higher incidences of breast/bladder cancer, genital/urinary tract infection, and hepatotoxicity associated with the product compared with placebo.

Janssen Therapeutics was poised to take advantage of the delay. Its new drug application (NDA) for canagliflozin was sent to the FDA in June 2012, and it was approved in March 2013 under the brand name Invokana. Dapagliflozin was approved in January 2014, while the FDA issued a complete response letter for empagliflozin on March 5, 2014. The FDA requires that certain deficiencies in the Boehringer plant (where the product will be manufactured) be addressed prior to product approval.[2] Astellas' ipragliflozin filed for approval in Japan in April 2013, but it is not clear when a US filing will occur.

Insulin dependence. The major advantage that SGLT-2 inhibitors offer is a new insulin-independent mechanism of action (**Figure 1**) in T2DM patients who are overweight or obese. The degree of glycemic lowering seems similar to that for other oral antidiabetic drugs (OADs), with average reductions in patients' glycated hemoglobin (A1C) levels of around 0.9 percentage points.[3] SGLT-2 inhibitors are indicated for use as add-on therapy with metformin. They also could be an option for patients with impaired glucose intolerance or prediabetes. Clinical trials with canagliflozin also found an average weight loss of 3.5 kg after 12 weeks of treatment.[3]

However, results published in January 2014 added some complexity to the discussion around the mechanism of action and glycemic benefit. As noted above, SGLT-2 inhibitors increase the excretion of glucose through the urinary tract. However, studies involving dapagliflozin and empagliflozin were paradoxically found to generate a compensatory *increase* in the endogenous production of glucose and glucagon. The researchers reported that the greater production of glucose offset about half of the total glucose excreted in urine through SGLT-2 inhibition.[4,5] At some point in the future, it could mean that combining SGLT-2 inhibitor treatment with a drug that inhibits glucagon production (eg, GLP-1s or DPP-4s) could produce substantially greater reductions in plasma glucose levels.[6] These recent results might not be unexpected, since SGLT-2 inhibitors were shown to have a diuretic effect in a 2010 study.[7]

Early Signs of Canagliflozin Utilization

The real question remains: Does the category fill an unmet need? Or do currently available OADs provide sufficient options, and what of the next cycle of diabetes medications due to go off patent?

The still unknown answer to the following questions may help define the

value and place of these new agents in the marketplace: Will SGLT-2s be found to preserve beta-cell function? On a related note, will SGLT-2s be found to delay progression to the need for insulin? The question of coverage is complicated by an issue that has dogged managed care executives in the recent past: Will payers take into account the fact that a medication produces a secondary, positive benefit of weight loss?

Early returns show some promise for coverage and utilization of canagliflozin. After its launch in early 2013, its uptake by endocrinologists and primary care physicians gave Janssen hope that it would catch on quickly in the provider community. According to data from IMS Health, a healthcare technology and information company, canagliflozin generated $90,864,000 in sales through November 2013, on the strength of 306,000 dispensed scripts (unpublished data, IMS Health, 2014).

In parallel, it has gained some early important formulary coverage wins, both in the commercial market and in Medicare (**Table 1**). A Janssen representative stated that "Invokana is available at a tier 2 or preferred status for over 105 million lives (48% of commercially insured lives and 11% of Medi-

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care Part D lives), and more than 80% of commercially insured patients can get Invokana without a prior authorization."

As the first SGLT-2 to market, this is not surprising; however, it could have implications for new market entrants. Following the fallout over rosiglitazone, the FDA now requires post marketing studies of canagliflozin to assess its cardiovascular risk. And now that BMS and AstraZeneca's dapagliflozin has been approved by the FDA, manufacturers will find out quickly what the managed care market will require in terms of clinical results, contracting offers, and pricing for subsequent formulary acceptance.

Table 2 illustrates, the current status of the SGLT-2 market (both newly ap proved and under clinical investigation).

Sorting Out the Differences in the Market

Dapagliflozin. In a long-term extension of a phase III placebo-controlled trial of dapagliflozin as add-on therapy to metformin, dapagliflozin 10 mg was found to sustain an average 0.78-point reduction in A1C levels from a mean baseline of 8.06% after 102 weeks.[8] This compared with a 0.02 percentage point increase in A1C in the group receiving metformin plus placebo (P <.0001). Body weight decreases averaged 1.10 to 1.74 kg after 102 weeks. The risk of hypoglycemia on

medication was low. The key side effect of mycotic genital infection, which is thought to be related to the flushing of excess glucose through the kidney and bladder, was up to 14.6% in patients receiving dapagliflozin, compared with 5.1% in those receiving placebo.

Other researchers revealed that in a study of 12 randomized controlled trials, the incidence of diagnosed infections associated with dapagliflozin was lower than anticipated, even though urinary glucose levels were found to be relatively high.[9] They found that the frequency of urinary infections did not increase with drug dose: 2.5 mg (3.6%), 5 mg (5.7%), and 10 mg (4.3%), versus placebo (3.7%).

A meta-analysis confirmed that dapagliflozin was associated with significantly greater weight loss than DPP-4 inhibitors (mean, –2.74 kg) and sulfonylureas (mean, –4.67 kg).[3]

In a phase III placebo-controlled study of dapagliflozin 5 mg or 10 mg as monotherapy in an Asian population not receiving previous diabetes treatment, investigators found a 1.04-point reduction in A1C level for the 5-mg dose and a 1.11-point reduction for the 10-mg dose.[10] The incidence of genital or urinary tract infection was low (< 5.5%) though higher than placebo. The risk of hypoglycemia (< 1% for both dos ages) was deemed small in this 24-week study.

Empagliflozin. Empagliflozin has been tested in a number of settings, including in combination with basal insulin.

Boehringer Ingelheim researchers collated the results of empagliflozin's phase III trials on nearly 2500 patients, employing either 10-mg or 25-mg daily dose given for 24 weeks as monotherapy, added to metformin therapy, combined with metformin and sulfonylurea, or added to pioglitazone plus metformin treatment.[11] They found that empagliflozin reduced A1C levels by 0.70 percentage points (10 mg) and 0.77 points (25 mg) compared with 0.08 points for placebo ($P < .001$). This was accompanied by a significant drop in fasting plasma glucose levels (as much as 23.2 mg/dL), greater than 2 kg reduction in body weight, and small but significant reductions in systolic and diastolic blood pressure, across all of these phase III trials.[11]

In their study of whether empagliflozin would improve glycemic control in patients who were inadequately controlled with a combination of metformin and sulfonylureas,[12] once-daily empagliflozin 10 mg or 25 mg was added to combination treatment of 225 and 216 patients, respectively, and the results were compared at 24 weeks against combination therapy plus placebo. Empagliflozin 10 mg lowered A1C by 0.82 percentage points and empagliflozin 25 mg reduced glycated hemoglobin levels by 0.77 points, compared with placebo (–0.17 points, $P <.001$). Urinary tract infections occurred in up to 10.3% of patients taking empagliflozin compared with 8.0% in the placebo group, but the incidence was higher in women (18.0% in the 10-mg group). Genital infections in those taking empagliflozin were not as common, but still slightly higher than placebo rates (2.7% for empagliflozin 10 mg and 2.3% for 25 mg, 0.9% for those receiving placebo).[12]

A Japanese phase II dose-extension study of empagliflozin monotherapy revealed patients' A1C levels decreased by a mean 0.86 percentage points with the 25-mg dose, and this was accompanied by an average 31.2 mg/dL decline in fasting plasma glucose level.[13] Body weight declined by more than 3 kg after 52 weeks of treatment. Hypoglycemia occurred in only 1 patient in each study group, and in none of these epi-

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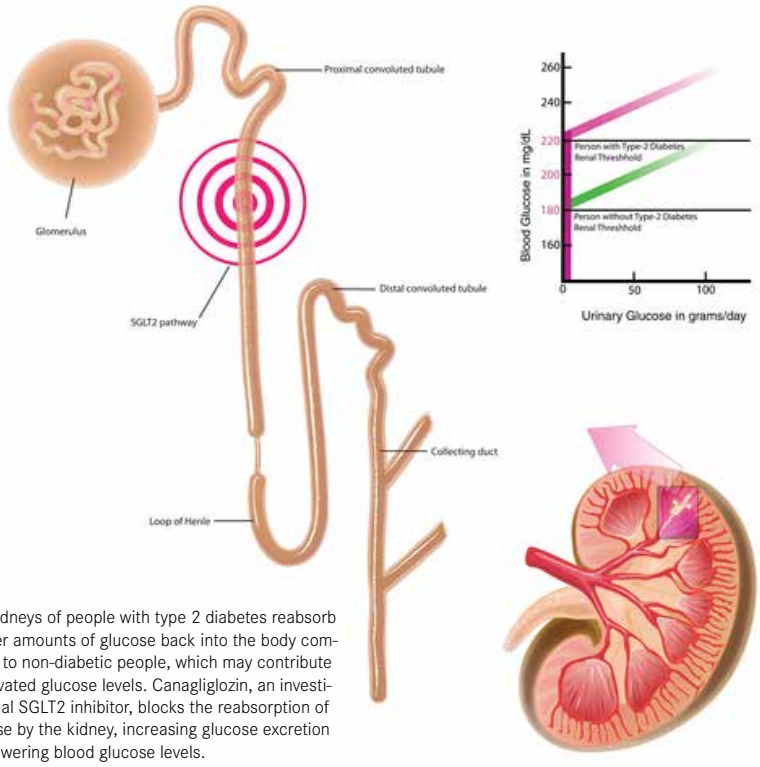
Figure 1. Site of Action of SGLT-2 Inhibitors in the Kidney



The kidneys of people with type 2 diabetes reabsorb greater amounts of glucose back into the body compared to non-diabetic people, which may contribute to elevated glucose levels. Canagliglozin, an investigational SGLT2 inhibitor, blocks the reabsorption of glucose by the kidney, increasing glucose excretion and lowering blood glucose levels.

Source: Janssen Research and Development, June 2012.

sodes did the patient require additional health care measures. The incidence of urinary tract infections and genital tract infections was low (no more than 2.6% and 3.0%, respectively, in each dosage group).

Interestingly, Rosenstock and colleagues[14] evaluated empagliflozin over 78 weeks in patients whose T2DM was inadequately controlled with basal insulin alone (baseline A1C, 8.2%). Patients were randomized to receive empagliflozin 10 mg (169 patients), 25 mg (155 patients), or placebo (170 patients) in addition to a constant dose of basal insulin for 18 weeks, after which insulin dose adjustments were made as needed. Significant reductions were observed in A1C levels at 18 weeks (0.57 points, 10-mg dose; 0.71 points, 25-mg dose; P <.001) and at 78 weeks (0.48 points, 10 mg-dose; 0.64 points, 25-mg dose; P <.001). Insulin doses were reduced (e.g., –1.21 IU/day for empagliflozin 10 mg, P <.01) at week 78 compared with baseline for both active treatment groups. Patients receiving empagliflozin lost approximately 2 kg of body weight at 78 weeks. The researchers again noted an increased incidence of urinary tract (15%) and genital infections (8%).

Ertugliflozin. Merck and Pfizer are copromoting another investigational SGLT-2 inhibitor, ertugliflozin.

Four phase III studies of ertugliflozin are currently recruiting patients, according to ClinicalTrials.gov. They cover monotherapy, a combination of metformin and glimipiride, metformin and sitigliptin, and in patients with chronic kidney disease.

Little information has been published regarding phase II trial results for ertugliflozin. One presentation at the 2011 European Association for Study of Diabetes reported on a phase II trial of 328 patients with T2DM placebo, ertugliflozin (1 mg, 5 mg, 10 mg, or 25 mg), or sitigliptin 100 mg for 12 weeks.[15] From a baseline A1C level of 8.1%, patients receiving ertugliflozin experienced up to 0.83-point reductions (dose dependent) compared with a 0.87-point reduction for those taking sitigliptin and a 0.11-point reduction in the placebo group. Fasting plasma glucose levels dropped by up to 31.5 mg/dL, compared with a 17.3 mg/dL reduction for sitigliptin and a 2.7 mg/dL increase in the placebo group. Body weight reduction approached 3 kg in the ertugliflozin group, although the placebo group also registered a mean loss of 0.75 kg. The incidence of genital fungal infections in the ertugliflozin groups was roughly twice that for the placebo groups, although both were relatively low (3.6% vs. 1.8%, respectively).

Ipragliflozin. In the third quarter of 2013, Astellas Pharma Inc and Merck announced that they would copromote Astellas' SGLT-2 inhibitor, ipragliflozin. Although Astellas has filed for product approval in Japan based on the strength of phase III trials in that country, it has been reported that Astellas is not intending to proceed with US trials and or an NDA, owing to increased competition in the area.[16] The phase II studies conducted to date indicate similar (or slightly less) effect on A1C levels, with a comparable safety profile to the other SGLT-2 inhibitors.

Tofogliflozin. This SGLT-2 inhibitor was originally developed by Chugai Pharmaceutical of Japan, who had entered into a development and marketing agreement with its majority stakeholder, Roche. In 2012, Roche returned the development and marketing rights back to Chugai, before the start of phase III trials. A new co-development partnership was formed, which included Sanofi-Aventis.[17] Information on its phase II trial program is also limited, but in a 12-week placebo-controlled dose-finding study, 398 patients were randomized to receive tofogliflozin 2.5 to 40 mg daily or placebo, with or without metformin.[18] Glycated hemoglobin reductions ranged up to 0.87 points for the highest dose of tofogliflozin compared with 0.27 points for placebo. Placebo-adjusted body weight loss was approximately 2 kg in the tofogliflozin group, and an increase in genitourinary infections were noted with the active drug.

LX4211. Phase II trials are underway for LX4211, a dual inhibitor of SGLT-1 and SGLT-2. Whereas SGLT-2 affects sodium excretion in the kidney, SGLT-1 mediates sodium absorption in the gut. A study of 299 patients demonstrated that LX4211 was associated with a significant, dose-dependent decrease in glycated hemoglobin levels, as well as small decreases in systolic blood pressure after 12 weeks of treatment.[19] However, in those with baseline systolic blood pressure of at least 130 mm Hg, placebo-adjusted reductions in those taking LX4211 400 mg were 14 mm Hg (P = .002). In comparison, only a 1 mm Hg decrease was seen in patients whose baseline systolic pressure was below 130 mm Hg.

Another phase II study showed that LX4211 was also associated with some mild genitourinary infections, none of which caused study discontinuation.[20]

Table 1. A Sampling of Managed Care Coverage of Canagliflozin

MCO	Coverage Status	Copayment Tier
Aetna (commercial and Medicare)	Not covered	
Anthem Blue Cross (California)	Not covered	
BCBS of Illinois	Not covered	
BCBS of North Carolina	Covered	Tier 4
BCBS of Texas	Not covered	
Blue Shield of California (closed formulary)	Not covered	
Blue Shield of California (standard gold)	Covered	Tier 3
Caremark CVS (Performance Drug List)	Covered	Tier 2
Catamaran (national)	Covered	Tier 3
CIGNA (commercial)	Covered	Tier 3
CIGNA (Medicare and HealthSpring)	Not covered	
Express Scripts (National Preferred Formulary)	Covered	Tier 2
Express Scripts (Medicare PDP)	Covered	Tier 2
Ford Motor Company	Not covered	
Health Net of California (commercial)	Covered	Tier 2
Health Net of California (Medicare)	Not covered	
General Motors (UAW)	Covered	Tier 2
Humana (Rx3)	Covered	Tier 3
Kaiser Permanente Northern and Southern California	Not covered	
Inter Valley Medicare Advantage	Not covered	
Molina (Marketplace Gold)	Not covered	
RegenceRx	Not covered	
SCAN Health Plan	Covered	Tier 4
UnitedHealth Care (OptumRx)	Not covered	
VA National Formulary	Covered	Tier 1

Source: Fingertip Formulary 2014 (http://www.fingertipformulary.com/drugs/Invokana/CA/). Accessed January 21, 2014.

Consistent Effects

It seems that the SGLT-2 inhibitors exert consistent plasma blood glucose and HbA1c effects in patients with T2DM,

Table 2. SGLT-2 Inhibitors in Development

Drug	Drug Designation	Company	Phase	Comments
FDA-Approved SGLT-2 Inhibitors				
Canagliflozin (Invokana)		Janssen	FDA approved March 29, 2013	
Dapagliflozin (Forxiga)		AZ	FDA approved January 8, 2014	• BMS sold rights to AZ in December 2013. • FDA denied approval in Jan 2012. • FDA approved January 8, 2014
In Development				
Empagliflozin	BI-10773	BI/Lilly	III	
Ertugliflozin	MK8835/ PF-04971729	Merck/Pfizer	III	
Ipragliflozin	ASP-1941	Astellas	III	Filed for approval in Japan, not proceeding with phase 3 program in the US
LX4211		Lexicon	II	• Dual SGLT-1 and SGLT-2 inhibitor • Phase III trials to be initiated soon
Luseogliflozin	TS-071	Taisho Pharm/ Novartis	III in Japan	
Remogliflozin etabonate	BHV091009/ GSK-189075	BHV Pharma/ GSK	II	• GSK does not list this product in its product pipeline. They discontinued trials in 2010 • BHV pharma is now developing the product • Ready for Phase III trials (completed 3-phase IIa & 2-phase IIb trials)
Tofogliflozin	CSG452	Chugai/Kowa/ Sanofi	III in Japan	• Chugai, Kowa and Sanofi entered into an agreement in October 2012 to develop the drug • Drug was being developed by Chugai and Roche (Roche owns majority stake in Chugai, and drug is still listed on Roche's [Genentech's] pipeline)
Discontinued While in Development				
	AVE2268	Sanofi	II	• No information has been updated on clinicaltrials.gov since Feb 2009 • Sanofi does not list this drug in their product pipeline even though stating in 2007 they would rapidly take the drug to phase III trials
	BI-44847	BI	II	
	R-7201	Roche/Chugai	II	
	YM-543	Astellas/ Kotobuki		
	TS-033	Taisho		
	T-1095	Tanabe		
Sergliflozin		GSK/Kissei		• Discontinued after phase II
Other				
	ISIS-SGLT2Rx/ ISIS-388626	ISIS	I	• Antisense oligonucleotide blocks expression of SGLT2 gene • Clinicaltrials.gov last updated Feb-2012 • ISIS does not list this product on its product pipeline listing

and the incidence of body weight reduction and adverse effects is characteristic across the drug class. This may make it more difficult for a new SGLT-2 inhibitor to differentiate itself from those already approved, and may spur considerable contracting/pricing competition among the products, as canagliflozin faces new market entrants. **EBDM**

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Evidence-Based Protocol
(continued from cover)

with little clinical differentiation, this approach allows organizations to focus on cost differences and comparative cost efficacy. It is also important to take rebates into consideration in these discussions for net cost comparisons. For example, in a medication class where there are 4 medications with the same mechanism of action and no clinical differentiation, a managed care organization can leverage rebates and market share to provide an overall cost savings to the health plan or employer group. It is not realistic that a payer should need to cover all the medications in this class. This is particularly important in the treatment of T2DM when there are more than 10 classes of medications available for the treatment of the disease. Therefore, approaches that a plan can apply include:

• **Comparative effectiveness research (CER)**: As defined by the Federal Coordinating Council for CER, this is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat, and monitor health conditions. The purpose of this research is to inform patients, providers, and decision makers, responding to their expressed needs, about which interventions are most cost-effective for which patients under specific circumstances.[2] This requires multiple data sources. Managed care is in the unique position of having data from clinical trials, administrative claims, laboratory draws, and access to all of the healthcare stakeholders involved in the delivery of care.

• **Closed formularies**: These allow flexibility in driving prescribing to preferred agents while still allowing appropriate clinical choice.

• **Integrated care management:** The old model of traditional disease management has proved largely ineffective. Approaches like mailing letters and newsletters or utilizing automated voice messaging to remind patients to take medication, etc, do not have significant influence upon behavioral change. New approaches are needed that empower patients to become active participants in their healthcare.

• **Generic incentive**: The goal of a generic utilization improvement program is to conduct direct member outreach to curb inappropriate and wasteful spending among patients who are utilizing high-cost branded medications that have generic alternatives within their specific therapeutic class. By targeting nonadherent patients among this group, managed care organizations have an opportunity to improve quality outcome measures by positively impacting individuals who struggle to achieve their therapy goals due to an unknown understanding that equally effective lower-cost choices are readily available.

At VRx, after an evidence-based CER approach to pharmacy and therapeutics, and after applying a closed formulary benefit, a novel and innovative approach to collaborating with patients and providers has been incorporated—Veridicus Care Management (VCM).


Alexander C. Bitting, PharmD

VCM Case Report

Background:

VCM provides integrated care management using a team comprising clinical pharmacists, nurse case managers, and mental health specialists. Our VCM program utilizes population management tools and predictive modeling to identify high-risk populations based on various clinical triggers. These services are offered to provide quality improvement solutions to pharmacy benefit managers (PBMs), health plans, and employer groups. One of the clinical tracks focuses on patients with "gaps in care," such as diabetic patients who haven't had an A1C drawn, lack an office visit, are missing key medications (ie, ACE-I/ARB and statin therapy). These targeted "gaps in care" are defined based on the National Council of Quality Assurance Healthcare Effectiveness Data and Information Set measures that promote improved quality in the delivery of care.

Case Details:

The VCM team identified a diabetic patient who was flagged as having "gaps in care," who lacked treatment with an ACE-I/ARB and was noncompliant with his diabetic medications. The clinical pharmacist contacted the patient to address these issues and to provide comprehensive education regarding the patient's specific expectations and goals of therapy. Upon further discussion, it was determined that the patient was noncompliant with his DPP-4 inhibitor due to the significantly high cost burden. Additionally, the patient also reported taking metformin 500 mg daily without any prior dose titration. The most recent A1C was 8.7% and the patient's primary care provider had discussed initiating a new therapy with an SGLT2 inhibitor. The clinical pharmacist discussed the possibility of titrating the metformin to 2000 mg per day in divided doses, and replacing the DPP-4 inhibitor with generic pioglitazone. The case was then presented in the weekly VCM Clinical Coordination meeting, where additional insight was provided by the nurse case managers. The patient was then contacted by a nurse, who provided further diet and exercise education to supplement the recommended changes in medication therapy. All information related to the case was communicated to the patient's primary care provider.


Alan D. Pannier, PharmD, MBA

Upon follow-up with the clinical pharmacist, the patient reported successfully switching to a pioglitazone/metformin combination product with proper titration to 2000 mg per day. The clinical pharmacist assessed compliance and tolerability of the new medication regimen. At a 3-month follow-up, the patient demonstrated a 1.5% reduction in his A1C (to 7.2%).

Summary

New approaches are needed in the current healthcare environment, and more specifically, in the treatment of diabetes. Old methods of patient-outreach are largely ineffective. Models should include CER, closed formulary benefit design, and improved coordination of care. Integrated care management improves on the old model of disease management by involving all stakeholders in the treatment of diabetes. By using an integrated model, these stakeholders become empowered to collectively take responsibility for all clinical and financial outcomes. Healthcare is slowly shifting to an outcomes-oriented, collaborative team-based approach to patient management. An integrated care management model is a natural fit for managed care organizations to participate in the future of healthcare, which will consist of Patient-Centered Medical Homes and Accountable Care Organizations. **EBDM**

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Kritzler Interview
(continued from cover)

Our bigger concern right now is how we treat the many new young patients with type 2 diabetes, caused by the current epidemic of obesity in the community. We've seen a huge rise in the incidence of type 2 diabetes, particularly among teenagers. The obesity epidemic is throughout the United States, but it is hitting harder in the South, and Maryland's numbers are rising. To an extent, community efforts have resulted in some progress, if not awareness. Clearly, First Lady Michelle Obama's Let's Move program has helped to address physical fitness and obesity, as have several other community-based programs. Overall, we're still moving in the wrong direction with respect to type 2 diabetes.

EBDM: **What is the missing element from these efforts? Is it a matter of coordination? Is it a real motivation and commitment to participate in these efforts?**

Dr Kritzler: You hit the nail on the head. For type 2 diabetes, tied to the obesity epidemic, there have been fits and starts—not one concerted effort. The effort needs to work down to things like school lunches, convenience foods, and fast foods, and work at the main reasons our population as a whole is gaining weight.

It's seen by folks in the field, but not by the general public, as a public health emergency. I question whether all medical professionals consider it the public health emergency that it really is.

EBDM: **What might it take to raise that level of alarm?**

Dr Kritzler: It's hard to say. The data are already there. We see today the increased incidence of type 2 diabetes in teenagers and young adults. The data on the long-term costs of diabetes to the system are also there. Beyond that my crystal ball is as cloudy as everyone else's.

From my perspective as a managed care medical executive, we're trying to conquer the cost of medical care by weeding out unnecessary high-tech imaging and focusing on how much we pay for each individual service, but we don't pay enough attention to the major public health problem that's right in front of us.

EBDM: **You had mentioned the increased use of pumps and sensor devices for type 1 diabetes. What's your view on our progress toward the artificial pancreas?**

Dr Kritzler: It's interesting that you asked me that, because not a day goes by when I'm not asked by one of my patients whether the artificial pancreas is right around the corner. To some extent, the answer is no, although patients and their families desperately want this solution. Today, we have smart pumps that are hooked up to sensors. It even looks achievable with today's computer technology.

What people don't fully understand is that glucose regulation involves more than just injecting insulin. We have known for a very long time that glucose regulation involves many hormones beyond insulin. A true artificial pancreas would have to regulate, to some extent, many of those hormones. It's a more complicated construct than people think. Trials are under way, mostly in Europe, testing multi-channel pumps.

Today's smart insulin pumps connected with continuous glucose monitoring is a way station towards a more functional artificial pancreas. We're making progress, but a true artificial pancreas, enabling something approaching more rational glucose control, is further away. I believe this will occur before we see everyday islet cell transplants or that sort of thing. That's looking into my own crystal ball.

EBDM: **And a true synthetic pancreas, constructed through some type of regenerative tissue engineering? How far away are we, realistically, from that?**

Dr Kritzler: We're a long way from this. Some pretty good research is ongoing, but we're not anywhere near clinical utility.

EBDM: **Johns Hopkins is a major research institution. How involved is Hopkins in researching these types of new technologies?**

Dr Kritzler: Researchers from Johns Hopkins University and the University of Maryland are partners in the JHU-UMD Diabetes Research Center. It is headed by Dr Fredric Wondisford, an adult endocrinologist and metabolism physician. The Center is involved in a tremendous number of studies, probably way more than I know.

EBDM: **Let me ask you to put on your managed care hat. I'd like to talk about young patients with type 2 diabetes or prediabetes and how they transition from adolescents to teens and young adults.**

Dr Kritzler: Coordination is a challenge, not specifically for Hopkins, but in general. Patients with type 1 diabetes primarily receive their care through endocrinologists. Patients with type 2 disease receive their care through a combination of primary care doctors— pediatricians, family physicians, and adult internal medicine—and endocrinology consulting. Coordination can be a real issue. And at some point, teenagers have to transition from a pediatric care system to an adult care system. That's an issue, even for those with type 1 diabetes, and it's something the medical community doesn't do as well as we should.

As with any other hand-off in health care you're handing off between one provider to another or in some cases between one group of providers, primary care, endocrinologists, to a different group of providers. We all have different styles and different approaches. As a clinician, I tend to continue to see my patients with type 1 diabetes through their college years. These patients are undergoing life transitions at the same time. At some point, we have to transition these patients from pediatric to adult care. As with any other transition in medical care, it can be a challenge.

EBDM: **What is the most difficult part?**

Dr Kritzler: It really has very little to do with the medical care system itself. Part of the real challenge is the transition from being an adolescent to being an adult. They're undergoing numerous life transitions themselves, including from having a parent overseeing their care (particularly in type 1 disease), to having to oversee it themselves. They go to college, out into the workforce, and they move out of the parent's home. Suddenly they're adults, or at least the world calls them adults, and they have to take on more responsibility and accountability. For many of us in pediatric endocrinology, one of the things we try to do, particularly with our type 1 patients, is to be sure the transition to self-care begins well before the transition between pediatric medicine and adult medicine. I have many 11-, 12-, and 13-year olds who pretty much know how to run their own pumps and how to reprogram and how to change their basal levels, without a lot of input from their parents. But I also have 16-year-olds who can't. That becomes a problem.

With young type 2 patients, our first interventions are generally exercise and promotion of weight loss before we start medication therapy, and that's also a question of taking adult responsibility for themselves.

EBDM: **I can imagine this would be extremely challenging for a patient with type 1 disease who goes off to college. They're exposed to an entirely new environment, new stresses, the same risks that face other teenagers, including excessive drinking, and different eating habits and eating options…**

Dr Kritzler: Yes, everybody talks about the "freshmen 15"—new freshmen who gain 15 pounds on dormitory food. This is a bigger problem if you're already overweight and have prediabetes or diabetes: the freshman 15 can easily be the "freshmen 30."

EBDM: **Can you do any special preparation, other than reinforcement and education, to prepare these kids for major life change?**

Dr Kritzler: It is one of the challenges. That's why care for type 1 and type 2 diabetes is such a team effort. By team, I mean the physician, advanced practice nurse or other physician extender, clinical diabetes educator, nutrition educator, social worker, and psychologist.

By the time the patient is transitioned to an adult-care provider, we assume that he or she has already moved through these various changes. That's why I believe the pediatric care system, which is more family oriented, probably does a bit of a better job in facilitating those transitions.

EBDM: **In terms of treating younger patients with type 2 diabetes, you mentioned that it is not usually an endocrinologist but family physicians. They don't seem to be as comfortable treating these patients as children as they are as adults. Why does that seem to be the case?**

Dr Kritzler: Overall, I find that very few primary care physicians are comfortable treating type 1 diabetes, whether they're pediatricians or family physicians or internists. So those patients are left to the endocrinologist. As for type 2 diabetes, there are just too many people with type 2 disease for the number of specialists available. So our primary care colleagues have to treat them.

Family physicians need to have a much wider span of knowledge to treat so many disorders appropriately and in so many age groups. I know some family physicians who are very good with kids and teenagers, and I know some who certainly don't like to treat younger kids and are uncomfortable with teenagers. Then consider the specialty of adolescent medicine, in which youre primary training could be in any one of the pediatrics, family medicine, or internal medicine. This has become a larger subspecialty over the years, for the exact reason that adolescents are not children or adults. They are an entity unto themselves.

EBDM: **Well, if you have primarily family physicians treating these children with type 2 diabetes, at what point do you feel it's appropriate that they should be referred to**

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specialists? What becomes the tipping point?

Dr Kritzler: For type 2 diabetes in children, most family physicians and pediatricians are comfortable when they're just dealing with diet and exercise, and the glycemic levels are not widely abnormal. At that point, some are comfortable starting—certainly adult primary care physicians are—the first couple of oral antidiabetic drug steps for their patients. Pediatricians and family physicians may be less so in those younger than 18, because the higher incidence of type 2 diabetes in these patients is a pretty new phenomenon.

Robert Kritzler, MD

Many of the pediatricians are not trained in medical school in the use of these oral antidiabetes drugs. I was trained as a general pediatrician, and I was never trained in the use of oral antidiabetic medications. This has changed recently, because of the necessity of it.

I believe it can be helpful to refer to a specialist for one or two consultations, as glycemic levels demand, when beginning medications. Personally, I see a number of young patients with type 2 diabetes in order to start their medication therapy, because the general pediatrician or family practitioner is not as comfortable doing that. But they're comfortable enough managing the patient once the medication regimen is started and glucose levels are controlled. This may be different in an integrated system, where general pediatricians may be more comfortable dealing with diabetes, even type 1 to some extent. They usually have specialists more available for phone and E-consults.

EBDM: **Is this supported through your regular diabetes disease management programs?**

Dr Kritzler: At JHHC, we don't do disease management much anymore; instead, we focus on embedded, nonspecific case management. As a health plan, we're most interested in chronic disease.

EBDM: **If you could change one diabetes-related HEDIS measure, what would it be and how would you change it? (The Health Effectiveness Data and Information Set consists of 75 measures of healthcare quality and service.)**

Dr Kritzler: I think that most of the HEDIS measures on diabetes are directionally correct. I think one of the things that people forget about HEDIS measures are that they are population health measures, not individual patient measures.

Consider that there still is no consensus among the professional societies as to whether the goal A1C measure should be 7.0% or 6.5% (guidelines of the American Diabetes Association and the American Association of Clinical Endocrinologists, respectively). And diabetes blood pressure targets have just been changed, which would affect a large number of patients. The HEDIS measures are really just averages for what the population-wide target should be. Health care professionals can get caught up thinking, "I have patient Sally Smith in front of me, and she needs to meet all of these measures and all of these targets." That's not the intent of HEDIS.

I don't really have any beefs with any of the HEDIS diabetes measures as long as people remember the context in which they're meant to be used. For example, an elderly patient with type 2 diabetes who has had previous hypoglycemia should not have a target A1C of below 8.0%. An average A1C level of 7.5% among 5000 patients is very reasonable. I don't think there's a right answer.

EBDM: **On that same note, would you like to add a HEDIS measure for the future, one that might be helpful as an additional guide?**

Dr Kritzler: Keeping in mind that it's a population-wide measure, I think the existing HEDIS measures on diabetes are about right. I don't think there's much we need to add. Some people talk about measuring long-term outcomes in type 2 diabetes, such as amputations, renal failure, those types of things. But I wouldn't add anything right now to HEDIS with regard to diabetes care.

EBDM: **Let me ask you a question about current therapies. A new class of therapies has just been introduced—the SGLT-2 inhibitors for type 2 diabetes. As a medical director, you've probably been involved in some coverage decision making on these agents and the previous categories of drugs. What's your overall opinion not necessarily of just the SGLT-2 inhibitors but of the recent new oral diabetes therapies that have come along in the last 5 years?**

Dr Kritzler: It's an exciting area. For type 2 diabetes, exercise and weight loss are still the mainstays of treatment. Metformin is still the first medication choice, but there has been so much exciting research and many new medication choices, whether you're talking about the DPP-4s, GLP-1s, or the newest classes. And I'm sure that a year from now, we'll see yet another class.

From a managed care point of view, you're absolutely right. We look at a cost benefit in terms of where we'll place it on our formularies, what agents may have to be stepped through in order to cover the drug, and what we'll ask the patients to pay for them, assuming they are more expensive than the last class of treatments introduced. As each new class comes along or within a class, a medication may be introduced in a once-weekly injection instead of a once-daily injection, which can lead to better adherence. Each time something new comes out, we have to evaluate the gain versus the cost—the value.

The number of new options has resulted in the professional societies loosening their relatively rigid guidelines, recognizing what we in managed care are also recognizing, that one size doesn't fit every patient. There are a number of possible permutations and combinations, and we on the managed care side try to make those available within reason to our patients and to our clinicians.

That being said, I believe that insulin is not utilized as much as possible in patients with type 2 diabetes. Insulin's not new or sexy, but there are new formulations, there are new delivery systems, and there are pumps. Very few patients with type 2 disease are using insulin pumps, although we're starting to see an occasional request for them. Insulin is still an important therapy for type 2 diabetes, and it is underutilized.

EBDM: **For many years, needle phobia has been cited as a principal reason why the transition to insulin has been so difficult. Do you think there are certain things that are just so difficult to overcome; cultural, social, in terms of the insulin use that we're never really going to get that number where it needs to be in terms of equalization?**

Dr Kritzler: I've been practicing 30 years, give or take, and during that time, the insulin needles have become progressively smaller, to the point now that it's not the kind of needle phobia that existed when my grandmother took insulin in 1955. It's a little bit overrated as a barrier. You could point out that the many GLP-1s are given by injection, not as frequently administered as basal insulin, but you're still giving them with a needle.

There are clearly people who can't adjust to using needles, particularly some of the elderly. However, every one of my patients with type 1 diabetes use needles because they really have no choice—they're either on multiple injections a day or they're on a pump, which involves a needle. Everybody adjusts to a needle if they need to.

EBDM: **We alluded to the shortage of endocrinologists earlier. Do you see any action in payment reform that might someday attract more doctors to the endocrinology field?**

Dr Kritzler: Endocrinology in general is like most of the cognitive specialties; it is on the lower end of the pay scale. Of my medical school class in 1977, two-thirds went into primary care. Of last year's graduates, maybe 8% or 10% went into primary care. As a cognitive specialty, endocrinologists don't do many procedures other than thyroid biopsies. People just aren't attracted to it as a profession, because it carries pay that is relatively low. To the degree that we value endocrinologists, we'll see more people go into the specialty.

Let me make a related comment: There's a very nice set of programs out of the University of Connecticut where the provider is taking risk for diabetes care, especially type 1. The provider accepts global payments for care and then has to sort it out within their own system, taking some risk for performance. That sort of payment reform is very exciting to me, in terms of any chronic disease.

EBDM: **Is that program based on the patient-centered medical home concept?**

Dr Kritzler: I don't think they call it a patient-centered medical home, but rather a diabetes home. A patient-centered medical home for kids with type 1 diabetes pretty much describes the model. This and other similar experiments around the country will do little to attract more people to endocrinology, but what it will do is support the team care concept. On a fee-for-service basis, some of the non-physician team members don't always get reimbursed very well. If you think primary care physicians and endocrinologists are not reimbursed well, diabetic nurse educators and nutritionists are paid far less. A diabetic medical home allows caring for more patients with a multidisciplinary team, which I think in some ways may be as important as some of the technological advances, at least in the short run for type 1 diabetes care, anyway. **EBDM**

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Source: Centers for Disease Control and Prevention, National Diabetes Fact Sheet.

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