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THE AMERICAN JOURNAL OF MANAGED CARE®

#1 IN CITATIONS & IMPACT FACTOR

Volume 19
Special Issue 2

Evidence-Based Diabetes Management

Healthcare Delivery

Diabetes and the Patient-Centered Medical Home

Teresa L. Pearson, MS, RN, CDE

Teresa L. Pearson, MS, RN, CDE, FAADE

"The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, union of forces is necessary."

William J. Mayo, MD, FACS

There have been efforts to overhaul the healthcare system for decades. At more than 7% of the GDP,[1] healthcare is big business. And, while healthcare spending has increased, diabetes is on the rise. With nearly 26 million people with diabetes and another 79 million with pre-diabetes, literally 1 in 3 people are impacted by the disease with

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Drug Optimization

Measuring the Value of Better Diabetes Management

Darius N. Lakdawalla, PhD; Michael R. Eber, BSE; Felicia M. Forma, BSc; Jeffrey Sullivan, MS; Pierre-Carl Michaud, PhD; Lily A. Bradley, MBA; and Dana P. Goldman, PhD

Darius N. Lakdawalla, PhD

The growing burden of type 2 diabetes mellitus has outpaced the modest progress in the efficacy of diabetes medications. However, it is unclear whether we are using our *existing* medications optimally. This article quantifies the value of addressing underuse of existing diabetes medications in the United States. Interventions—new technologies, public policies, or clinical approaches—that double the rate of initiation of insulin generate a value on average of more than $15,000 over the lifetime of a patient developing diabetes between ages 51 and 60 years, or $12.6 billion in the aggregate. Interventions that improve adherence would generate a value of more than $13,000 on average for the same patients, or $10.7 billion in the aggregate. The value of such interventions is on par with highly optimistic projections of technological progress in medication efficacy.

Type 2 diabetes mellitus (T2DM) continues to grow at a remarkable rate. Diabetes incidence in the United States rose by more than 45% from 2002 to 2010, and its substantial costs make this trend particularly troubling. Diabetes decreases quality of life, increases morbidity, reduces life expectancy by approximately 3 years in near-elderly cohorts, and imposes additional lifetime healthcare costs of roughly $200,000.[1]

Prevention is a natural response to the growing epidemic, and its social benefits appear to be quite large.[1] Yet the policy question of how to improve and extend the lives of the tens of millions of patients who already have or will soon develop the disease remains. Technological progress in treatment is one possibility. Indeed, the discovery of 8 new drug classes in the past 15 years has expanded the arsenal of

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VBID® Value-Based Insurance Design®

Managing Benefits for Diabetes: Changing Payer Strategies for Changing Times

Albert Tzeel, MD, MHSA, FACPE

Diabetes mellitus is a condition first recognized 3500 years ago in ancient Egypt and named 2000 years ago by a Greek, Aretaeus. It is characterized by hyperglycemia

Albert Tzeel, MD, MHSA, FACPE

resulting from the body's inability to appropriately metabolize glucose into energy.[1] In 2008, the Centers for Disease Control and Prevention estimated that 23.6 million Americans, or 7.8% of the population, had diabetes and another 57 million had prediabetes.[2] By 2010, that number had increased to 25.6 million Americans (8.3% of the population) with diabetes.[3] Those numbers represent increases of at least 50% in 42 states and 100% in 18 states.[4] And, the prevalence of diabetes will continue to get worse. Within the next 25 years, the number of individuals with diabetes is expected to increase to more than 44 million individuals and, as Huang et al[5] note, "without significant changes in public or private strategies, this population and cost growth are expected to add a significant strain to an overburdened healthcare system."

"Private strategies" employed by payers who either assume full risk or manage risk on behalf of government/

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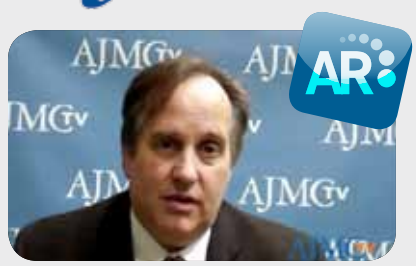

Michael Farkouh, MD, Talks About the Prevention of Diabetes Mellitus

Feng Zeng, PhD, Discusses Copayment Reduction in the Gap and Its Impact on Diabetes Medications

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April 2013 K02CAN13061A

Over the next 12 months, our healthcare system will undergo mass change as organizations in all sectors of the industry continue to implement various components of Obamacare. The hope is that all of the efforts involved will lead to more accessible and affordable healthcare. Diabetes patients and healthcare providers stand to gain significantly if such healthcare reform mandates bring better value and access to this patient population.

Despite cost controls being regularly available in many areas of medicine, there is an important and vulnerable link between pricing and innovation. For this very reason, there is increasing interest in value-based pricing that rewards and incentivizes the development of targeted treatments and programs that improve outcomes. However, the framework for balancing support for innovation, cost control, and continued evidence development is the subject of constant debate.

This inaugural issue of *Evidence-Based Diabetes Management* features several articles from thought leaders who are already laying the groundwork for more affordable diabetes care. Teresa L. Pearson, MS, RN, CDE, FAADE, documents the evolving role of the diabetes educator in the medical home and the many challenges and benefits to adopting the patient-centered medical home model. Albert Tzeel, MD, MHSA, FACPE, discusses specific strategies that payers are implementing when it comes to managing benefits for patients with diabetes. In addition, Darius Lakdawalla, PhD, et al discuss measuring the value of better diabetes management. Also, readers will find a comprehensive review on the Type 2 Diabetes pipeline, as well as coverage from Joselin Diabetes Center's first annual Diabetes Innovation.

Diabetes patients and healthcare providers stand to gain significantly if such healthcare reform mandates bring better value and access to this patient population.

An unprecedented era of healthcare delivery is under way. Federal regulations and increasing technological advancements are occurring at a rapid pace. Discussions to determine the best value for healthcare services and processes are becoming more important by the day, and our newly forged partnership with the *Center for Value Based Medicine*® promises to further that discussion. In addition, we are pleased to announce a diabetes-specific live meeting scheduled for June of this year that will focus on the future of patient-centered diabetes care and will feature a panel of the nation's premiere thought leaders. Please stay tuned for more details in the coming weeks.

We know that keeping up with all the issues related to diabetes care is more time consuming than ever, and we hope that *Evidence-Based Diabetes Management* will help you stay abreast of the latest news and research in diabetes so that you can spend less time searching for actionable information and more time applying it in your day-to-day activities. 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.

In This Issue...

THE AMERICAN JOURNAL OF MANAGED CARE

MH
Office Center at Princeton Meadows, Bldg. 300
Plainsboro, NJ 08536 • (609) 716-7777

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

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LANTUS®
insulin glargine [rDNA origin] injection

Proven 24-hour Coverage

Over 10 Years of Clinical Experience

Proven A1C Reductions

Established Safety Profile

Indications and Usage for Lantus® (insulin glargine [rDNA origin] injection)

Lantus® is a long-acting insulin analog indicated to improve glycemic control in adults and children (6 years and older) with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Lantus® should be administered once a day at the same time every day.

Important Limitations of Use: Lantus® is not recommended for the treatment of diabetic ketoacidosis. Use intravenous short-acting insulin instead.

Important Safety Information for Lantus® (insulin glargine [rDNA origin] injection)

Contraindications

Lantus® is contraindicated in patients hypersensitive to insulin glargine or one of its excipients.

Please see additional important safety information for Lantus® on the following page.

Please see brief summary of full prescribing information for Lantus® on the following pages.

Once-Daily 24-HOUR
LANTUS® SoloSTAR®
insulin glargine [rDNA origin] injection

Starring the #1-prescribed insulin[a]

[a]Based on TRx data from IMS Health, NPA™ Monthly database, time period from May 2003 to November 2011.

Please visit us at www.lantus.com.

SANOFI DIABETES

Indications and Usage for Lantus® (insulin glargine [rDNA origin] injection)

Lantus® is a long-acting insulin analog indicated to improve glycemic control in adults and children (6 years and older) with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Lantus® should be administered once a day at the same time every day.

Important Limitations of Use: Lantus® is not recommended for the treatment of diabetic ketoacidosis. Use intravenous short-acting insulin instead.

Important Safety Information for Lantus® (insulin glargine [rDNA origin] injection)

Contraindications

Lantus® is contraindicated in patients hypersensitive to insulin glargine or one of its excipients.

Warnings and Precautions

Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral antidiabetic treatment.

Do not dilute or mix Lantus® with any other insulin or solution. If mixed or diluted, the solution may become cloudy, and the onset of action/time to peak effect may be altered in an unpredictable manner.

Do not administer Lantus® via an insulin pump or intravenously because severe hypoglycemia can occur. Insulin devices and needles must not be shared between patients.

Hypoglycemia is the most common adverse reaction of insulin therapy, including Lantus®, and may be life-threatening.

Severe life-threatening, generalized allergy, including anaphylaxis, can occur.

A reduction in the Lantus® dose may be required in patients with renal or hepatic impairment.

Please see brief summary of full prescribing information for Lantus® on the following pages.

Drug Interactions

Certain drugs may affect glucose metabolism, requiring insulin dose adjustment and close monitoring of blood glucose. The signs of hypoglycemia may be reduced in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine).

Adverse Reactions

Other adverse reactions commonly associated with Lantus® are injection site reaction, lipodystrophy, pruritus, and rash.

In clinical studies in adult patients there was a higher incidence of treatment emergent injection-site pain (2.7% Lantus® vs. 0.7% NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy.

In elderly patients with diabetes, dosing should be conservative to avoid hypoglycemia. Hypoglycemia may be difficult to recognize in the elderly.

Important Safety Information for Lantus® SoloSTAR®

Lantus® SoloSTAR® is a disposable prefilled insulin pen. To help ensure an accurate dose each time, patients should follow all steps in the Instruction Leaflet accompanying the pen; otherwise they may not get the correct amount of insulin, which may affect their blood glucose.

Please visit us at www.lantus.com.

Once-Daily 24-HOUR
LANTUS® SoloSTAR®
insulin glargine [rDNA origin] injection

Starring the #1-prescribed insulin[a]

[a]Based on TRx data from IMS Health, NPA™ Monthly database, time period from May 2003 to November 2011.

SANOFI DIABETES

LANTUS® **Rx Only**
(insulin glargine [rDNA origin] injection) solution for subcutaneous injection

Brief Summary of Prescribing Information

1. INDICATIONS AND USAGE

LANTUS is indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

Important Limitations of Use:

- LANTUS is not recommended for the treatment of diabetic ketoacidosis. Intravenous short-acting insulin is the preferred treatment for this condition.

2. DOSAGE AND ADMINISTRATION

2.1 Dosing

LANTUS is a recombinant human insulin analog for once daily subcutaneous administration with potency that is approximately the same as the potency of human insulin. LANTUS exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

LANTUS may be administered at any time during the day. LANTUS should be administered subcutaneously once a day at the same time every day. The dose of LANTUS must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy.

Patients adjusting the amount or timing of dosing with LANTUS, should only do so under medical supervision with appropriate glucose monitoring *[see Warnings and Precautions (5.1)*.]

In patients with type 1 diabetes, LANTUS must be used in regimens with short-acting insulin.

The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue *[see Clinical pharmacology (12.2) in the full prescribing information]*. LANTUS should not be administered intravenously or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia *[see Warnings and Precautions (5.3)]*.

As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy *[See Adverse Reactions (6.1)]*.

In clinical studies, there was no clinically relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables, such as stress, intercurrent illness, or changes in co-administered drugs or meal patterns.

2.2 Initiation of LANTUS therapy

The recommended starting dose of LANTUS in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Short-acting, premeal insulin should be used to satisfy the remainder of the daily insulin requirements.

The recommended starting dose of LANTUS in patients with type 2 diabetes who are not currently treated with insulin is 10 units (or 0.2 Units/kg) once daily, which should subsequently be adjusted to the patient's needs.

The dose of LANTUS should be adjusted according to blood glucose measurements. The dosage of LANTUS should be individualized under the supervision of a healthcare provider in accordance with the needs of the patient.

2.3 Converting to LANTUS from other insulin therapies

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of shorter-acting insulins and doses of any oral anti-diabetic drugs may need to be adjusted.

- If transferring patients from once-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is the same as the dose of NPH that is being discontinued.
- If transferring patients from twice-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is 80% of the total NPH dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia [*see Warnings and Precautions (5.3)].*

4. CONTRAINDICATIONS

LANTUS is contraindicated in patients with hypersensitivity to LANTUS or one of its excipients.

5. WARNINGS AND PRECAUTIONS

5.1 Dosage adjustment and monitoring

Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision.

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral anti-diabetic treatment.

As with all insulin preparations, the time course of action for LANTUS may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.

5.2 Administration

Do not administer LANTUS intravenously or via an insulin pump. The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue

Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia *[see Warnings and Precautions (5.3)]*.

Do not dilute or mix LANTUS with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and the mixed insulin may be altered in an unpredictable manner. When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and a delayed time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs to humans is unknown.

Do not share disposable or reusable insulin devices or needles between patients, because doing so carries a risk for transmission of blood-borne pathogens.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin, including LANTUS. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with LANTUS.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia [*See Drug Interactions (7)*].

The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia. Patients being switched from twice daily NPH insulin to once-daily LANTUS should have their initial LANTUS dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia *[see Dosage and Administration (2.3)]*.

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

5.4 Hypersensitivity and allergic reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LANTUS.

5.5 Renal impairment

Due to its long duration of action, Lantus is not recommended during periods of rapidly declining renal function because of the risk for prolonged hypoglycemia.

Although studies have not been performed in patients with diabetes and renal impairment, a reduction in the LANTUS dose may be required in patients with renal impairment because of reduced insulin metabolism, similar to observations found with other insulins. *[See Clinical Pharmacology (12.3) in the full prescribing information].*

5.6 Hepatic impairment

Due to its long duration of action, Lantus is not recommended during periods of rapidly declining hepatic function because of the risk for prolonged hypoglycemia.

Although studies have not been performed in patients with diabetes and hepatic impairment, a reduction in the LANTUS dose may be required in patients with hepatic impairment because of reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. *[See Clinical Pharmacology (12.3) in the full prescribing information].*

5.7 Drug interactions

Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia *[See Drug Interactions (7)].*

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[See Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[See Warnings and Precautions (5.4)]*

6.1 Clinical trial experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of treatment-emergent adverse events during LANTUS clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment –emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=1257)	NPH, % (n=1070)
Upper respiratory tract infection	22.4	23.1
Infection *	9.4	10.3
Accidental injury	5.7	6.4
Headache	5.5	4.7

***Body System not Specified**

Table 2: Treatment –emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=849)	NPH, % (n=714)
Upper respiratory tract infection	11.4	13.3
Infection*	10.4	11.6
Retinal vascular disorder	5.8	7.4

***Body System not Specified**

Table 3: Treatment –emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency ≥ 10%)

	LANTUS, % (n=514)	NPH, % (n=503)
Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1
Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

Table 4: Treatment –emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency ≥ 5%)

	LANTUS, % (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

***Body System not Specified**

- *Severe Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS *[See Warnings and Precautions (5.3)]*. Tables 5 and 6 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The rates of severe symptomatic hypoglycemia in the LANTUS clinical trials (see Section 14 for a description of the study designs) were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes. (see Table 5) *[See Clinical Studies (14) in the full prescribing information]*.

Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	10.6 (31/292)	15.0 (44/293)	8.7 (23/264)	10.4 (28/270)	6.5 (20/310)	5.2 (16/309)	23.0 (40/174)	28.6 (50/175)

Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	1.7 (5/289)	1.1 (3/281)	0.4 (1/259)	2.3 (6/259)	7.8 (40/513)	11.9 (60/504)

- *Retinopathy*

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 7 for both the per-protocol and Intent-to-Treat populations, and indicate similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

Table 7. Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint

	Lantus (%)	NPH (%)	Difference*,† (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
Intent-to-Treat	63/502 (12.5%)	71/487 (14.6%)	- 2.1% (2.1%)	-6.3% to +2.1%

*Difference = Lantus – NPH

†using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function

- *Insulin initiation and intensification of glucose control*

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- *Lipodystrophy*

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. *[See Dosage and Administration (2.1)]*.

- *Weight gain*

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- *Peripheral Edema*

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- *Allergic Reactions*

Local Allergy

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

- *Antibody production*

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS *[See Patient Counseling Information (17) in the full prescribing information*]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

7. DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m^2. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m^2, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes *[see Clinical Studies (14) in the full prescribing information]*. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults *[see Dosage and Administration (2.3)* and *Clinical Studies (14) in the full prescribing information]*. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients.

Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly *[See Warnings and Precautions (5.3)]*.

10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

Rev. April 2010
sanofi-aventis U.S. LLC
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GLA-BPLR-SA-APR10

The Controversial Question of Metabolic Syndrome

Can Targeting This Symptom Complex Reduce the Burden of Diabetes and Cardiovascular Disease?

Marjorie P. Zimmerman, MS, BSPharm; and Stanton R. Mehr

The high prevalence of diabetes and cardiovascular disease (CVD) has tasked the medical community to not only treat but to better identify people at risk for these diseases. Risk factors for diabetes had been identified more than 90 years ago, and the term metabolic syndrome emerged in the late 1970s.[1,2] In the late 1980s, a potential link had been identified—insulin resistance, which itself has been strongly associated with obesity.[3] On the other hand, some believe that insulin resistance contributes to the development of the risk factors but is not the underlying cause.[4] Identifying a cluster of predictive risk factors would enable healthcare providers to identify and treat patients with metabolic syndrome, thus reducing the risk for a progression to diabetes, CVD, or both.

The Controversy: What Is Metabolic Syndrome, and Is It a Treatable Disorder?

Metabolic syndrome (sometimes referred to as "syndrome X" or "insulin-resistance syndrome") is defined as a grouping of several related risk factors,[4] including:

- Abdominal fat
- Dyslipidemia
- Hyperglycemia
- Hypertension

Merriam-Webster defines the term syndrome as "a group of signs and symptoms that occur together and characterize a particular abnormality."[5] What is truly more important to the final objective of preventing diabetes and CVD—identification of the underlying mechanism(s) for the syndrome, or identification of the risk factors that occur together and usually lead to diabetes and CVD?

This question defines the debate within the healthcare community: Is metabolic syndrome a cluster of risk factors or a syndrome? Proponents for characterizing metabolic syndrome as a syndrome believe that the evidence linking the risk factors with the development of diabetes and CVD supports the view that it is a treatable entity. Detractors believe that metabolic syndrome is really just a clustering of risk factors, without any known underlying mechanism that associates the maladies. Confounding the discussion is whether metabolic syndrome is a pre-morbid condition—whether metabolic syndrome can only be recognized before a patient is given a diagnosis of diabetes or CVD, thus excluding the population with these highly prevalent chronic conditions. On the other hand, an actual diagnosis of diabetes or CVD does not affect the underlying mechanism (eg, insulin resistance or some other factor still exists).

Regardless of whether professional organizations are supporters or skeptical of metabolic syndrome, the medical community as a whole believes that additional research is needed to better understand its etiology.

In 2005, the American Diabetes Association and the European Association for the Study of Diabetes published a statement underscoring their concerns regarding metabolic syndrome.[6] Their concerns included the value of including diabetes in the definition, whether the criteria have accurate thresholds and are completely explanatory, and the omission of other cardiovascular disease risk factors. They worried that if the cardiovascular risk for metabolic syndrome is the same as the sum of the individual risk factors, treatment of the syndrome would be the same as the treatment for each of the respective risk factors. Furthermore, these professional societies were not convinced that insulin resistance is the unifying mechanism and whether there is overall value in diagnosing the syndrome.

Yet, 2 American professional organizations and several international societies generally agree on the risk factors that should be included in the definition of metabolic syndrome. Until this time, there were several different criteria discussed for metabolic syndrome, most notably from the World Health Organization, the National Cholesterol Education Program Adult Treatment Panel III, the International Diabetes Foundation, and the American Heart Association/National Heart, Lung, and Blood Institute. These organizations agreed on the risk factors that should be included in a definition of metabolic syndrome; however, they differed on the definition of the components and the number of risk factors that needed to be present to constitute the diagnosis. Members from these organizations came together in 2009 to meld together consistent criteria for metabolic syndrome.[4] Most disagreement involved whether body mass index or waist circumference should be used as the indicator for central obesity. They concluded that waist circumference was a useful screening tool and should correlate with specific country or population demographics, and that further research was required.

This coalition of professional societies did agree that having 3 of the abnormal findings from the cluster of 5 maladies would constitute a diagnosis of metabolic syndrome (Table 1). They also agreed that people with any of the identified risk factors usually also present with a prothrombotic and proinflammatory state.

Obesity and physical inactivity have been found to be important contributors to metabolic syndrome.[7] Other contributing factors include genetic and racial composition, aging, and the presence of other endocrine disorders. Patients with metabolic syndrome are usually susceptible to additional problems as well, some that may be associated with its individual component risk factors:

- Fatty liver
- Cholesterol gallstones
- Obstructive sleep apnea
- Gout
- Depression
- Musculoskeletal disease
- Polycystic ovarian syndrome[8]

The Prevalence of Metabolic Syndrome

Assuming one accepts the definition of metabolic syndrome, it is unsurprising that its prevalence has increased over time, perhaps reflecting the obesity epidemic and predictions of greater incidence of diabetes.[9] An analysis of the 2003 to 2006 National Health and Nutrition Examination Survey revealed that, based on a waist circumference threshold of ≥102 cm for men and ≥88 cm for women, the age-adjusted prevalence of metabolic syndrome in American adults was 34.3% (36.1% for men; 32.4% for women). This percentage increased to 38.5% for all adults when racial- or ethnic-specific criteria were used (41.9% for men; 35.0% for women). The prevalence increases with age, peaking in the 60- to 69-years group, which parallels a correlation with weight gain with increasing age. Caucasian and Mexican-American men had a higher prevalence of metabolic syndrome than African American men, whereas the prevalence for women was lower among Caucasian women than for African American or Mexican American women.[10]

Among the risk factors, abdominal obesity is observed in the majority (53.6% total [45.8% men; 61.2% women]) of the population with metabolic syndrome. The other risk factor components in the total population are, in descending order of prevalence, hyperglycemia, high triglyceride levels, elevated blood pressure, and low concentrations of high-density lipoprotein cholesterol.

Although each of the components of metabolic syndrome increases the risk for CVD, the combination of the risk factors appears to increase it substantially. The presence of metabolic syndrome is associated with a 2-fold increased risk for CVD (and a 5-fold greater risk for the development of type 2 diabetes).[8] Traditional risk algorithms for CVD, such as the Framingham Risk Score, may be more accurate in risk prediction.[11]

Table 1. Metabolic Syndrome Criteria: At Least 3 Risk Factors Must Be Present

Measure	Risk Factors
Blood pressure	Systolic BP ≥130 mm Hg and/or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension
Fasting plasma glucose	>100 mg/dL, or treatment of previously diagnosed type 2 diabetes
High-density lipoprotein (HDL) cholesterol	<40 mg/dL (men) <50 mg/dL (women), or treatment of previously diagnosed reduced HDL cholesterol levels
Triglycerides	≥150 mg/dL or treatment of previously diagnosed elevated triglyceride levels
Waist circumference	Population- and country-specific definitions for abdominal obesity (range) Men (85 cm to ≥102 cm) Women (80 cm to ≥90 cm)

BP indicates blood pressure.
Source: Adapted from Alberti et al. *Circulation*. 2009;120:1640-1645.[4]

The Cost Implications of Metabolic Disease for Payers

Unsurprisingly, patients diagnosed with metabolic disease can be expected to utilize more health resources than those individuals without it. A study of patients in 3 health plans confirmed this statement—members meeting at least 3 criteria for metabolic syndrome had 60% higher annual costs compared with patients without metabolic syndrome ($5732 vs $3581, respectively), and these costs increased incrementally by 24% when they met 4 or more risk factors.[12] When patients progressed to a diagnosis of diabetes, the healthcare costs were higher in patients with diabetes and metabolic syndrome than in those patients with diabetes without metabolic syndrome ($7896 vs $6038, respectively). Patients with diabetes do not necessarily meet all of the criteria required to be considered to have metabolic syndrome.[12]

Similar results were seen in a health plan that assessed the direct medical costs associated with patients who were overweight, obese, or met risk criteria for metabolic syndrome using a cost model.[13] Comparing patients who were overweight or obese with those who were not, direct costs were $4563 versus $4015, respectively. The highest annual costs (>$5000) were in the patients with risk factors meeting the requirements of metabolic syndrome. This cost was $2061 higher than in those without the risk factors for metabolic syndrome.[13]

Both of the above studies support the hypothesis that there are increased costs associated with patients meeting the risk factor criteria for metabolic syndrome.

However, another study of health plan members concluded that the higher costs were associated with the individual risk factors rather than with a clustering of the risk factors. In this analysis, 5 years of health data were evaluated for adults with metabolic syndrome risk factors and their impact on direct medical costs. They compared total annualized direct costs for all possible combinations of the metabolic syndrome risk components. Every risk factor except for impaired fasting glucose led to increased annual medical costs; however, the higher costs were independent of the other risk factors. The presence of each of the risk factors was associated with higher future medical costs, which were mostly attributable to the development of diabetes or the need for hospitalization due to cardiovascular disease.[14]

Current Approaches to Managing Metabolic Syndrome

Currently, there is no 1 specific treatment for treating patients meeting the criteria for metabolic syndrome. Rather, lifestyle modification and weight reduction, along with drug therapy for the respective risk factors (eg, hypertension, dyslipidemia, hyperglycemia, and weight reduction) are employed. Pharmaceutical companies have found it challenging to develop medications, as they would need to address multiple aspects of metabolic syndrome in order to be approved for the indication.[15] As a result, clinicians utilize available tools to address these risk factors (and usually, on an individual basis).

From the clinical and public health standpoint, however, the need for better tools to prevent and manage metabolic syndrome is urgent (Table 2).[8] Until an underlying mechanism is positively identified (or insulin resistance is finally recognized as the "smoking gun"), medications will be utilized that address the respective components of metabolic syndrome.

Patient Management and Metabolic Syndrome

The most important benefit of using the term metabolic syndrome appears to be that it focuses attention on an important clustering of health problems. Each of the criteria, as well as the clustering of the criteria, increase the risk for future disease. Lifestyle modifications can address each of the criteria for metabolic syndrome; however, each component requires separate, focused treatment.

Use of the term metabolic syndrome has been educational for both healthcare professionals and patients.[10] It has provided an easily understandable public health message, raised awareness of risk factor clustering as well as the need to identify additional risk factors among healthcare providers, and been an impetus for healthcare professionals to look beyond only diagnosed diabetes and cardiovascular disease to risk factors that progress to these diseases.[11]

Finally, additional research should be conducted to fully understand and appreciate the clustering of risk factors identified as metabolic syndrome. Further investigation will be required to better understand if there is underlying cause, such as a genetic defect. Finding an underlying mechanism would help settle the controversy as to whether the syndrome is a treatable entity or metabolic syndrome is just a clustering of risk factors. Until that time, educational endeavors need to continue to identify and reduce the modifiable risk factors for diabetes and CVD. Population-based strategies need to be further developed and implemented because of the importance of these diseases.

Conclusions

Professional organizations and government agencies are not currently in agreement about whether metabolic syndrome is clinically relevant in predicting the development of diabetes or CVD. Fundamentally, there is disagreement whether metabolic syndrome even fits the criteria of a treatable entity. We do know that the individual risk factors play an integral role in the development and advancement of these 2 important diseases. Until additional information is available regarding the potential underlying mechanism of this syndrome, healthcare professionals need to address the rising incidence of obesity and a sedentary lifestyle that are major contributors to the development of diabetes and heart disease. **EBDM**

Table 2. Therapy Targets for Metabolic Syndrome

Metabolic Syndrome Criteria	Treatment
All criteria	Lifestyle modification. No single specific agent is available at this time that addresses each criteria point
Blood pressure	Lifestyle modifications, increased exercise, dietary changes, and antihypertensive agents
Fasting plasma glucose	Lifestyle modifications, increased exercise, and hypoglycemic agents
High-density lipoprotein cholesterol	Lifestyle modifications, increased exercise, dietary changes, and antihyperlipidemic agents
Triglycerides	Lifestyle modifications, increased exercise, dietary changes, and antihyperlipidemic agents
Waist circumference	Weight reduction, increased exercise, anti-obesity drugs, and surgery
Prothrombotic state	No drugs are currently available that specifically target PAI-1 and fibrinogen. Low-dose aspirin is usually utilized
Pro-inflammatory state	Potentially agents that reduce C-reactive protein levels
Insulin resistance	Lifestyle modifications, weight reduction, and metformin and thiazolidinediones

Funding Source: None.

Author Disclosures: Mr Mehr reports receiving payment for involvement in the preparation of this article. Ms Zimmerman reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (SRM); acquisition of data (MPZ, SRM); analysis and interpretation of data (MPZ, SRM); drafting of the manuscript (MPZ, SRM); critical revision of the manuscript for important intellectual content (MPZ, SRM); and supervision (SRM).

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Payer Perspective

Interview With Ross M. Miller, MD, MPH

EBDM: **The term "metabolic syndrome" is fairly controversial. What's your view on whether this classification is practical as a disease or entity?**

Dr Miller: I believe it's a legitimate entity. The guidelines issued jointly from the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) in 2005[1] were a scientific, evidence-based approach to this multiple risk factor complex. It arises from a combination of insulin resistance, abdominal obesity (abnormal fat disposition), dyslipidemia (high triglycerides and low high-density lipoprotein cholesterol levels), and high blood pressure. The science definitely supports the connection of metabolic disease to coronary heart disease and type 2 diabetes mellitus. According to these guidelines, if you have at least 3 of the 5 risk factors, you're at greater risk for these clinical consequences,[1] and I totally buy into that.

I know it's controversial, but where there is some predictive value behind it, in terms of diabetes and cardiovascular events, I agree with it.

EBDM: **Would a highly publicized scoring system of risk factors, similar to the risk score profiles produced by the Framingham Heart Study for heart disease,[2] help bolster the case for recognizing and promoting metabolic syndrome within the healthcare community?**

Dr Miller: I would love that. It would be similar to the "know your number concept" we have for diabetes and cholesterol. If we could quantify a number based on the 5 risk factors, with some type of weighting of not only the risk factors themselves but within the 5 factors (ie, how far from the cut points one might be), where it can be calculated as a certain percentage risk over time, such as Framingham, or a certain numerical value that has been modeled with real-world data, this would be the Holy Grail. Then, all patients need to know is their number and they can work collaboratively with their provider to address their risks through stratified interventions.

EBDM: **Are disease management programs well equipped to address patients with metabolic syndrome?**

Dr Miller: Yes. Previously, if we had a patient with hypertension, they were enrolled in a hypertension disease management program. If they had dyslipidemia, they were enrolled in a dyslipidemia disease management program, and so on. If they had more than 1 condition—and so many of them do overlap—they should be in an integrated, coordinated multiple-condition management program. We have this capability today, mostly through use of interoperable technology. In metabolic syndrome, where multiple conditions overlap, a singular program is more appropriate in order to provide better care coordination, continuity of care, and management in an integrated model.

EBDM: **What is your perception of the proportion of patients already in diabetes disease management programs who would actually benefit from metabolic disease management programs?**

Dr Miller: I believe that most of the folks with metabolic syndrome are probably prediabetic anyway. However, patients with diagnosed diabetes may also meet some of the other 5 risk factors. Through diet and exercise, patients with type 2 diabetes can actually improve their glycemic levels and reduce the need for diabetes medications.[3]

EBDM: **Do you think a metabolic disease management program could be effective at preventing full-blown diabetes in those patients with insulin resistance?**

Dr Miller: A study by the Centers for Disease Control and Prevention found that approximately 34% of adult Americans may have metabolic syndrome.[4] It has somewhat paralleled the rise of the obesity epidemic in this country. The prevalence of metabolic syndrome is about double the rate for diabetes, so the idea is to prevent or reverse impaired glucose tolerance in these individuals by employing weight loss through diet and exercise.[5]

EBDM: **You probably remember, in the middle part of the past decade, when sanofi-aventis was trying to bring rimonabant to market with a metabolic syndrome indication. It was primarily a weight-loss agent. The US Food and Drug Administration (FDA) has still not approved any medication with a metabolic syndrome indication. Why do you think that is the case, based on the size of the potential market?**

Dr Miller: That's a difficult and complicated question. I believe that to obtain FDA approval, the manufacturer might have to show improvements to several of the outcome measures across the syndrome (eg, lower blood sugar levels, weight loss, lower blood pressure, improved lipid profiles). This would be extremely difficult to do in the context of a single, large clinical study. Today, pharmacologic management is related to treating the individual components of metabolic syndrome, such as statins for dyslipidemia or metformin for elevated blood glucose levels. Most interventions targeting the entire syndrome are focused on lifestyle modifications—changes in diet and exercise, for instance. Many experts believe that if you focus on weight loss (through diet and exercise), everything else follows—waist circumference goes down, impaired glucose tolerance improves, hypertension resolves.

I don't know if the 2 recently approved weight loss products are undergoing clinical studies (or subpopulation analyses) for their effects on these other components of the metabolic syndrome.

(Editor's Note: A review of the www.clinicaltrials.gov website revealed a total of 597 interventional clinical trials [phase II or III] for metabolic syndrome, testing everything from bloodletting and the use of walnuts to rosiglitazone and chloroquine, but not the new weight loss products lorcaserin or the phentermine/topiramate combination.)

EBDM: **Even if the use of the term metabolic syndrome has not been fully accepted, do you believe more physicians today are aware of the inter-relationships among the various risk factors and their management?**

Dr Miller: Absolutely. I'm not sure whether it's because of the coverage of obesity and diabetes epidemics in the lay press or because of the release of the AHA/NHLBI guidelines, but I definitely think there's increased awareness. I actually don't remember even hearing the term metabolic syndrome 15 or 20 years ago in primary care.

EBD: **From the standpoint of the Medicaid program in California, what types of public health education are emphasized with regard to the insulin resistance–cardiovascular–obesity axis of symptoms? Is Medi-Cal formally packaging this information?**

Dr Miller: Not that I am aware of as metabolic syndrome per se. A good deal of information has been disseminated on the individual components—there is tons of public education on obesity, including website information, posters geared to consumers, and fax blasts to providers. Some websites, such as WebMD and Mayo Clinic, which are frequently accessed by the public, provide educational materials on metabolic syndrome and its criteria, but I have not been involved in packaging it as such for Medicaid recipients and providers. Medicaid has patient messaging that says that if you are overweight and/or have other risk issues you may have a higher likelihood of developing diabetes. That is "packaging" the message to some respect, but maybe only "soft" packaging. Employer-sponsored wellness programs are also addressing this condition indirectly because health risk appraisals and biometric lab screenings commonly identify the components of metabolic syndrome.

Dr Miller is a medical director consultant and physician executive at Cerner Corporation in Los Angeles, CA.

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New Developments in the Treatment of Type 2 Diabetes Mellitus

Benefits May Outweigh Increase to Costs of Care

Brice Labruzzo Mohundro, PharmD, BCACP

Diabetes, a progressive disease of the endocrine system with a significant economic burden, is estimated to affect more than 371 million people worldwide and over 24 million Americans in 2012. In 2011, 4.6 million deaths could be attributed to diabetes, and diabetes healthcare expenditures, including costs to the healthcare system and the patient, were at least 465 billion US dollars, of which 11% of total healthcare expenditures were from adults aged 20 to 79 years, and 75% of that cost was spent on those aged 50 to 79 years.[1]

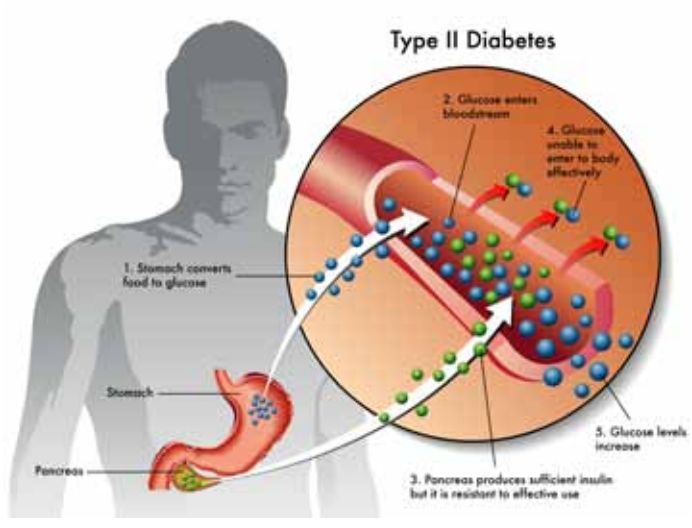
Current American Diabetes Association (ADA) Standards of Care recommend metformin for pharmacologic management of type 2 diabetes mellitus (T2DM), if no contraindications are present, at the time of diagnosis. If therapeutic goals are not met with monotherapy at maximal doses, a second oral agent, such as a glucagon-like peptide-1 (GLP-1) agonist or insulin, are recommended for addition. For patients who are newly diagnosed, markedly symptomatic upon diagnosis, and/or have markedly elevated blood glucose or glycated hemoglobin (A1C) levels, initial pharmacologic therapy with insulin should be considered, with or without the addition of other agents.[2]

The current classes of medications that are available to treat T2DM include biguanides, sulfonylureas, meglitinides, thiazolidinediones (TZDs), alpha glucosidase inhibitors, dipeptidyl peptidase-IV (DPP-4) inhibitors, GLP-1 agonists, bile acid sequestrants, dopamine-2 agonists, and insulin. Although these agents are effective initially, glucose-lowering effects are not typically sustained long term as beta cell dysfunction progresses. Therefore, newer agents that are able to lower glucose long term without causing hypoglycemia, delay decline in beta cell dysfunction, assist with weight loss, and have beneficial effects on cardiovascular disease need to be developed. It is important to acknowledge that, in addition to the aforementioned therapeutic effects, adverse effects must be minimized.[3] Several new classes of medications are currently in development, as well as a new long-acting insulin.

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2)

SGLT-2, a low-affinity but high-capacity transporter found in the brush border of the proximal tubule, is a mediator of glucose reabsorption in the kidneys. The kidneys contribute to glucose homeostasis via renal gluconeogenesis, glucose utilization, and reabsorption from glomerular filtration.[3,4] Data suggest that renal gluconeogenesis, renal glucose uptake, and renal glucose reabsorption are all increased in patients with T2DM due to the upregulation of SGLT-2.[5] In essence, SGLT-2 inhibitors exert their effects by causing the kidneys to excrete glucose into the urine. The effects are also independent of insulin secretion. These proposed mechanisms make SGLT-2 a viable target to help combat hyperglycemia in patients with T2DM. A review of the literature, conducted through a PubMed search of SGLT-2 inhibitors through April 2012, found that these agents decreased A1C anywhere from 0.5 to 1.5%, promoted weight loss, and demonstrated low incidences of hypoglycemia. Incidence of adverse effects with these agents has been low with no severe episodes of hypoglycemia documented. The most common adverse effects reported with these agents were urinary tract infections (UTIs) and/or genital tract infections.[6]

Dapagliflozin, a first-in-class SGLT-2 inhibitor, has been studied the most extensively. In a small study that evaluated 5 doses of dapagliflozin (2.5, 5, 10, 20, or 50 mg), extended-release metformin (titrated to 1500 mg), and placebo in drug-naïve patients with T2DM, dapagliflozin demonstrated statistically significant reductions in A1C of 0.55% to 0.9% over 12 weeks when compared with a decrease of 0.18% with placebo. A reduction of 0.73% was noted with patients taking metformin. Additionally, weight loss of 1.3 kg to 2 kg was observed in study participants.[7] Patients with T2DM who were inadequately controlled on metformin were evaluated in a phase 3, double-blind, placebo-controlled randomized controlled trial (RCT). Patients received metformin plus once-daily dapagliflozin 2.5, 5, or 10 mg, or matching placebo. Statistically significant decreases in mean A1C from baseline at 24 weeks were observed when dapagliflozin was compared with placebo (2.5 mg: –0.67%, 5 mg: –0.7%, 10 mg: –0.84%, placebo: –0.3%). Weight loss was also seen in the dapagliflozin groups. Dapagliflozin was well tolerated; however, more genital infections were seen in patients receiving dapagliflozin.[8] A more recently published study shared results of the effects of dapagliflozin in patients not controlled with the TZD pioglitazone. Patients were randomized to receive open-label pioglitazone plus either 5 mg or 10 mg of dapagliflozin for 48 weeks after a 10-week dose optimization phase with pioglitazone. Statistically significant reductions in A1C were seen after 24 weeks with both 5- and 10-mg strengths (5 mg: –0.82%, 10 mg: –0.97%, pioglitazone monotherapy: –0.48%), and these reductions were maintained through week 48. The decrease in A1C at 48 weeks was greater with each group: 0.95%, 1.21%, and 0.54%, respectively. Dapagliflozin also decreased the effect of pioglitazone-associated weight gain and edema. Overall, dapagliflozin was well tolerated; however, the incidence of genital infections was increased compared with placebo.[9] A total of 800 patients with T2DM who were inadequately controlled on 30 units or more of insulin were evaluated in a double-blind, placebo-controlled RCT that investigated the effects of 24 weeks of dapagliflozin or placebo on A1C. Patients may have been also taking up to 2 oral antidiabetic agents. Patients were randomized to receive 2.5, 5, or 10 mg of dapagliflozin or placebo in addition to their usual insulin dose and oral agents. At 24 weeks, patients receiving dapagliflozin experienced statistically significant decreases in A1C (2.5 mg: –0.79%, 5 mg: –0.89%, 10 mg: –0.96%) compared with placebo (–0.39%). A secondary outcome was to evaluate the change in A1C at week 48. Statistically significant decreases in A1C were maintained (2.5 mg: –0.79%, 5 mg: –0.96%, 10 mg: –1.01%). Over 48 weeks, increases in mean insulin doses increased with time in patients of the placebo group (10.54 units) but not with dapagliflozin therapy. Decreases in body weight were observed in patients taking dapagliflozin, but increased with the placebo. Rates of hypoglycemic episodes, genital infection, and UTIs were higher in patients taking dapagliflozin.[10] Despite the positive effects on A1C, dapagliflozin has not been approved by the US Food and Drug Administration (FDA) due to concerns of a potential link to breast and bladder cancers.[11] SGLT-2 is not thought to be expressed in either bladder or breast tissue, and therefore the mechanism of SGLT-2 inhibitors should not have a link to breast and bladder cancer risk; however, long-term surveillance is needed to exclude the association.[10] Proposed explanations for the increased incidence include the use of more urinalyses due to the increased incidence of UTIs, which may have led to earlier findings of hematuria or other abnormalities that are suggestive of bladder cancer. As far as the breast cancer incidences, breast masses may have been more easily identified after weight loss occurred in patients taking dapafliglozin.[6] The co-developers of dapagliflozin remain devoted to the development of the SGLT-2 inhibitor and will provide additional information as requested by the FDA.[11]



Canagliflozin is another SGLT-2 inhibitor currently in phase III development. A dose-ranging, double-blind RCT of canagliflozin added to metformin therapy demonstrated A1C reduction over a 12-week period. Canagliflozin therapy (50, 100, 200, or 300 mg once daily or 300 mg twice daily) was compared with the DPP-4 inhibitor, sitagliptin, which was used as an active reference treatment group, or placebo. A1C reduction with canagliflozin was noted with all doses investigated; however, the larg-

Date Updated	Company/Sponsor	Product	Mechanism of Action	Indication(s)	Stage(s)	Licensee/Partner(s)	PDUFA Date
11/23/2012	Bristol-Myers Squibb	Dapagliflozin (BMS-512148)	SGLT-2 inhibitor	T2DM	Phase II/III	AstraZeneca	01/28/2012
01/02/2013	Janssen Research & Development, LLC	Canagliflozin (JNJ-28431754)	SGLT-2 inhibitor	Renal insufficiency; T2DM	Phase II/III	Johnson & Johnson Pharmaceutical Research & Development, LLC	N/A
12/12/2012	Boehringer Ingelheim Pharmaceuticals	Empagliflozin (BI-10773)	SGLT-2 inhibitor	Hyperglycemia; T2DM	Phase II/III	Eli Lilly and Company	N/A
12/21/2012	Eli Lilly and Company	LY2605541	Long-acting basal insulin analogue	T2DM	Phase I/II/III	Boehringer Ingelheim Pharmaceuticals	N/A
03/13/2012	Incyte Corporation	INCB013739	11-β-HSD1 inhibitor	Obesity; T2DM	Phase II	N/A	N/A
11/29/2011	Eli Lilly and Company	LY2599506	Glucokinase activator 1	T2DM	Phase II	N/A	N/A
05/24/2012	Merck	MK-0893	Glucagon receptor antagonist	T2DM	Phase I/II	N/A	N/A
11/16/2012	Eli Lilly and Company	LY2409021	Glucagon receptor antagonist	T2DM	Phase I/II	N/A	N/A
N/A	Pfizer	CP-316819	Glycogen phosphorylase inhibitor	T2DM	Pre-Clinical	N/A	N/A
N/A	Astellas Pharma, Inc	AS1535907	GPR119 agonist	T2DM	Pre-Clinical	N/A	N/A
N/A	Metabolex	MBX-2982	GPR119 agonist	T2DM	Phase II	N/A	N/A
11/04/2010	Arena Pharmaceuticals, Inc	APD-597	GPR119 agonist	T2DM	Phase I	N/A	N/A
03/29/2012	GlaxoSmithKline	GSK1292263	GPR119 agonist	T2DM	Phase II	N/A	N/A

N/A indicates not available; PDUFA, Prescription Drug User Fee Act; T2DM, type 2 diabetes mellitus.

est reductions were seen with 300 mg daily (–0.92%) and 300 mg twice daily (–0.95%) versus with placebo (–0.22%). A weight loss of 2 kg to 2.9 kg was noted with canagliflozin compared with 0.8 kg with placebo and 0.4 kg with sitagliptin. Canagliflozin was well tolerated; however, females experienced an increased frequency of genital infections, including vulvovaginal mycotic infections and candidiasis, which responded to standard antifungal treatment and did not lead to patients discontinuing the study. It is thought that this increase in mycotic genital infections is due to the increased urinary excretion of glucose that occurs with SGLT-2 inhibitors, thus leading to increased colonization with *Candida*.[12]

A third SGLT-2 inhibitor in phase III development is empagliflozin. Empagliflozin demonstrated A1C lowering and improvements in glucose tolerance in animal studies, and had the highest selectivity of the SGLT-2 receptors compared with dapagliflozin, canagliflozin, and other SGLT-2 inhibitors.[13,14] Data from pooled phase IIb studies demonstrating that empagliflozin lowers A1C, weight, and systolic blood pressure were presented at the 48th European Association for the Study of Diabetes annual meeting.[15] A phase III clinical program is currently ongoing, which includes 10 phase III studies with a goal of enrolling over 14,500 patients. In addition to studies that are evaluating effects on glucose and weight, a large cardiovascular outcome trial will be included.[15]

Novel Long-Acting Basal Insulin

LY2605541 is a long-acting basal insulin analogue that is currently being evaluated in phase III studies in T2DM patients.[16] Insulin lispro is modified with a 20 kDa polyethylene glycol moiety that results in a molecule with large hydronamic size. The proposed effects of this larger molecule are a delay in insulin absorption and reduced clearance, thus leading to a longer duration of action.[17] Additionally, transport may be greater into the liver relative to muscle and fat tissues, which may result in more hepatic action.[17] The results of an RCT phase II study that compared LY2605541 with insulin glargine, an FDA-approved basal insulin, demonstrated that after 12 weeks of treatment, fasting blood glucose levels were similar. Investigators also noticed reduced weight loss and less nocturnal hypoglycemia with LY2605541. Three phase III trials are ongoing and are currently investigating T2DM patients using LY2605541. IMAGINE 2 compares the use of LY2605541 with insulin glargine over 52 weeks. This study, which is longer than previously published studies, will evaluate the changes in A1C from baseline to 52 weeks. Additionally, other secondary outcomes, which include nocturnal hypoglycemia events, weight, and liver transaminases, will be evaluated.[18] Another phase III study, IMAGINE 4, will compare the effects of LY2605541 with insulin glargine on A1C after 26 weeks in patients also receiving patient-specific preprandial and supplemental doses of the rapid-acting insulin analogue, insulin lispro.[19] The third actively recruiting study is IMAGINE 5, which may last up to 52 weeks. The primary objective of this study is to examine the changes in A1C over 26 weeks. LY2605541 compared with insulin glargine alone or in combination with up to 3 pre-study oral antihyperglycemia medications will be evaluated.[20]

11-β-hydroxysteroid dehydrogenase type 1 (11-β-HSD1)

The glucocorticoid, cortisol, serves several biological purposes which include the stimulation of gluconeogenesis in the liver and hindering insulin-mediated glucose uptake into adipose and muscle tissues.[21] Studies have demonstrated that 11-β-HSD1 is a catalyst capable of reactivating inert cortisone into cortisol within non-adrenal tissue, including adipose and liver tissues. Preclinical evidence indicates that 11-β-HSD1 has a function in both obesity and metabolic disease in rodents, which suggests that inhibiting this catalyst in liver and adipose tissues may lead to enhanced hepatic and peripheral insulin sensitivity, thus improving overall glucose levels and possibly decreasing overall macrovascular risk.[21] A 12-week, randomized, double-blind, placebo-controlled study evaluated the 11-β-HSD1 inhibitor, INCB13739, in patients with T2DM receiving a mean dose of 1.5 g per day of metformin. Investigators demonstrated a dose-dependent reduction in A1C, the primary objective, in patients receiving INCB13739 plus metformin versus metformin alone. A1C reduction was greatest among patients receiving 200 mg daily (the maximum dose in the study) and in those with a body mass index over 30 kg/m^2. INCB13739 was well tolerated with no drug-related serious adverse effects or hypoglycemic episodes occurring during the treatment phase.[22]

Glucokinase Activators

Glucokinase plays a role in glucose metabolism and adenosine triphosphate (ATP) production via glucose phosphorylation. The production of ATP has an effect on insulin secretion by closing potassium-ATP channels, thus triggering calcium ion channels to open, thereby activating calcium-dependent enzymes that control the release of insulin. The development of glucokinase activators has provided another pharmacologic mechanism to increase insulin secretion and decrease glucose secretion by enhancing the effects of glucokinase in beta cells. It is also thought that these agents have a secondary mechanism which decreases hepatic glucose metabolism, further decreasing glucose concentration. Unfortunately, these agents do have adverse effects. Incidences of increased triglyceride levels and hypoglycemia have been associated with the glucokinase activators.[3]

LY2599506, a glucokinase activator 1, was investigated in a phase II study; however, the study was terminated after enrolling 38 patients, due to non-clinical safety effects. The non-clinical safety effects were not identified.[23]

Glucagon Receptor Antagonist

Incretins are intestinal factors that are released in response to nutrients, contributing to blood glucose lowering. Incretin mimetics, such as exenatide and liraglutide, along with DPP-4 inhibitors, are currently available to treat patients with T2DM by addressing decreased concentrations of GLP-1. A less-well-known incretin is glucose-dependent insulinotropic peptide, or GIP. Currently in development, glucagon receptor antagonists (GRAs) belong to a new class of oral drugs that block the actions of GIP. In animal models, this blockade results in increasing energy

expenditure, as well as reduced fat deposition and lipotoxicity.[3] Investigators have identified MK-0893, a potent, selective, small-molecule GRA (which is a reversible and competitive agonist) with high binding affinity.[24] MK-0893 demonstrated 24-hour weighted mean glucose lowering effects similar to those seen with the combination of sitagliptin and metformin.[24-26] In this phase II study that evaluated MK-0893 with 2000 mg metformin daily, MK-0893 with sitagliptin 100 mg daily, or 100 mg sitagliptin plus 2000 mg metformin daily, MK-0893 plus sitagliptin was statistically less effective than the sitagliptin/metformin combination.[25] LY2409021, a potent and selective GRA, has been evaluated in phase I and II studies.[27] The results of a phase I, first-in-man study resulted in clinically significant glucose lowering without incidences of hypoglycemia or changes in laboratory tests, vital signs, or electrocardiograms.[28] Although both GRAs have been well tolerated, concerns about increased liver transaminases have arisen. A study evaluating the effects of LY2409021 on the liver is currently recruiting.[29]

Other Agents

Several other agents are being investigated for the management of T2DM. Glycogen phosphorylase is a catalyst for glycogenolysis, which increases glucose output from the liver. In a preclinical study, a glycogen phosphorylase inhibitor, CP-316819, prevented hyperglycemia after a glucagon challenge.[3] Protein tyrosine phosphatase 1B inhibitors enhance the effects of insulin by decreasing dephosphorylation of the β-subunit of insulin receptors, thus extending phosphorylation after insulin binding. In hyperglycemic animal models, protein tyrosine phosphatase 1B inhibitors reduce blood glucose levels, and may also improve weight loss and endothelial function.[3] In patients with T2DM, one consideration in postprandial hyperglycemia is the reduction of glucose-stimulated insulin secretion (GSIS). Activation of G protein–coupled receptor (GPR) 119, which is primarily expressed in pancreatic β-cells and intestinal L-cells, leads to insulin and GLP-1 release. A preclinical study demonstrated that AS1535907, a GPR119 agonist, stimulated the first phase of GSIS, resulting in an insulin release which was greater than that seen with the comparator sulfunoylurea.[30] Another study demonstrated that, in vitro, AS1535907 showed selective agonist activity for human GPR119 and could activate human insulin promoter. The study also demonstrated A1C-lowering effects in diabetic animal models.[31] GPR 119 agonists currently in development include MBX-2982 and GSK-1292263.[32]

Conclusion

Diabetes has profound effects on the economic burden of both patients and healthcare system. While new pipeline agents are currently in development, the cost-benefit analysis must be scrutinized in the presence of often less-expensive standards of care. Several novel agents have shown promise in the treatment of T2DM; however, it is too soon to determine their clinical and financial impacts. It is unclear if these agents will be used in combination with current therapies or primarily as first-line agents, but the ability of some of these drugs to mitigate weight gain suggests that they may have a role in both. Further, if ongoing studies validate the additive benefits seen with reducing macrovascular complications and blood pressure, there is a greater opportunity to influence current prescribing patterns. However, in the absence of long-term studies, caution should be exercised when considering a change from current therapies. Adverse effects of the new medication classes may limit their utility. That being said, when the costs of the drugs are known, these newer agents should be watched closely by benefit managers to evaluate the impact on total costs of care, as the benefit may outweigh the increased medication costs. Overall, the emphasis in the treatment of T2DM should still remain heavily on lifestyle modifications in conjunction with the use of evidence-based practice guidelines. **EBDM**

Author Affiliation: From the University of Louisiana at Monroe College of Pharmacy–Baton Rouge Campus, Baton Rouge, LA.

Funding Source: None.

Author Disclosure: The author reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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Is There a Business Case for Diabetes Disease Management?

Stanton R. Mehr

Disease management programs, particularly for diabetes care, have been part of managed care benefit offerings for roughly 20 years. They are offered by nearly every health plan, whether commercial, Medicare, or Medicaid. Most experts would acknowledge that disease management programs can improve the health of patients with chronic disease. However, little reliable, reproducible information is available to answer the question of whether these programs are cost saving.

Back to the Beginning

With the evidence in hand that tight glycemic control can prevent long-term complications of diabetes mellitus[1,2] and the ability to measure and monitor a person's blood glucose levels at a moment's notice, a new medical concept and burgeoning industry spawned in just a few years. In 1991, the Boston Consulting Group characterized this as disease state management,[3] and described it as a new way for the pharmaceutical industry to prove (and enhance) the value of its medications. Soon after, pharmaceutical companies like Pfizer and Zeneca Labs began their own disease management programs,[3] shopping them to the health plans and insurers.

The health plans realized that the disease management process represented a workable way to improve clinical outcomes and health status over an entire population of patients and codified a way to broadly conduct and promote secondary prevention. Furthermore, disease management programs were acknowledged to be a type of quality improvement (QI) process, which helped managed care plans fulfill QI requirements for accreditation from the National Committee for Quality Assurance. However, they had a choice of whether to contract with these pharmaceutical company–sponsored providers, work with independent start-up disease management organizations (eg, Diabetes Treatment Centers of America [which later became Healthways] or Cardiac Solutions [which later became Healthways]), or start their own internal programs.[3]

Over time, pharmaceutical company programs became burdened with concerns regarding conflict of interest and were soon outpaced by independent vendors and health plan–sponsored programs. The concept, in any case, took off. By 2006, disease management programs were part of every managed care organization's portfolio of benefits: a survey by the Boston Consulting Group revealed that 96% of health plans had disease management programs.[4] In 2010, one source reported that 21% of patients with at least 1 chronic disease were in a disease management program.[5] Today, the domestic disease management market is $2.1 billion, but should grow significantly in 2014 (once health reform increases the size of the market for covered eligibles).[6]

The Poster Child of Disease Management

Although disease management can be applied to many chronic diseases, diabetes has been a prime target. Diabetes mellitus is highly prevalent, it results in tremendous costs (a significant portion of which are preventable), and it can be easily measured. The programs' interventions also were well suited for QI: patients can be tracked, their pharmacy claims can be assessed for adherence, and their outcomes can be quantified, in terms of glycated hemoglobin (A1C) levels, clinical events, and use of medical resources (including emergency department [ED] and hospitalization).

According to the Care Continuum Alliance (formerly the Disease Management Association of America), the principal components of disease management programs include[7]:

- A method of identifying populations requiring secondary prevention
- Standards of care according to evidence-based practice guidelines
- Collaborative practice models to include physician and ancillary healthcare providers, including case managers and nurses
- Patient education on how to self-manage their condition and change unhealthy behaviors
- A process for measuring outcomes, evaluating the effect of interventions, and managing the program
- Routine reporting and feedback loop to providers (which include communication with patients, physicians, health plan, and ancillary providers, and practice profiling)

Generally, patient interactions are through nurse call centers and are focused on health education and reminders.

Clear Economic Outcomes Are Elusive

These components were common to most first-generation disease management programs, and though they sounded like potent tools to contain costs and improve outcomes, their effect on outcomes was not generally impressive. Even when quality measures were demonstrated to improve, the savings did not necessarily follow.

A retrospective study of 2 years of claims data from an integrated healthcare system found that patients with diabetes enrolled in their disease management program had average claims of $394.62 per patient per month compared with $502.48 per patient per month for those with diabetes but not enrolled in the program.[8] According to the researchers, the system saw a return on investment (ROI) of 2.23:1 (that is, $2.23 of savings accrued for every $1.00 invested); others question this result based on the cost calculation.[9] Furthermore, this magnitude of savings could not be demonstrated by others. This was accompanied by modest—but statistically significant—reductions in hospital admissions and inpatient days.

In 2003, a study of HealthPartners' diabetes disease management program determined that accrued savings over 10 years in this program would amount to only $75 per patient with diabetes.[10] An analysis of Independence Health Association's diabetes disease management program showed that it cost more money than it saved.[10]

Linden[11] studied historical data of several chronic disease management programs. He performed an analysis (based on the number needed to decrease, as opposed to number needed to treat) to calculate the decrease in hospital visits (ED visits and hospital admissions) necessary to provide an ROI in the program. This analysis revealed that a decrease in admissions of 10% to 30% would be needed just to cover the costs of the program.[11]

It would seem then that the cost savings related to diabetes disease management programs are lower than expected, and the ROI is very much in question. A number of reasons for this may exist.[12]

Patients Identified Too Late. The use of predictive modeling programs that were available for use in first-generation programs did identify patients with type 2 diabetes who were at risk of increased expenditures and adverse health events, but that was because they had already occurred. As mentioned earlier, disease management programs were designed as *secondary prevention* programs, meaning that eligible patients were already subject to repeat ED visits or hospitalizations, and were already being treated (perhaps not optimally). As a result, these algorithms did not do a good job detecting patients who had high glycemic levels who had not yet incurred high costs (their primary, costly event, such as inpatient admission).

Comorbid Disease States. Patients with diabetes are at high risk for multiple comorbidities, including chronic kidney disease, hypertension, coronary heart disease, stroke, and others. A first-generation disease management program, which focused on the diabetic condition only, may improve some outcomes but not necessarily the comorbid clinical status. More recent disease management programs and population health models are patient-focused, rather than disease-focused, and are likelier to address the other related comorbidities.

Dependence on Call Center Management. The use of nurse call centers to deliver education and reminders to members is intuitively a positive aspect of disease management programs, but without other integral components, call center management has not been shown conclusively to significantly influence member education or to change members' behavior. Much educational information is already available on the web. Furthermore, the physical distance between the call center and the patient creates a barrier to familiarity, trust, and continuity of communication.

Member Behavioral Self-Change. The program's success depends on patients' long-term adherence to the medication and exercise regimens prescribed by their doctors. This often requires incentives of some type. In first-generation programs, health plans did not necessarily coordinate disease management activities with formulary access (eg, to improve patient access to appropriate medications through lower cost sharing). This is also not a universal feature of today's programs (coordination is particularly difficult in this respect with external program vendors).

Member Turnover. In addition to these factors, discontinuity in program participation may also pose a significant barrier. Related to annual turnover in health plans, the patient may be disenrolled in their previous plan's disease management program, having to enroll anew with their new plan's provider.

First- Versus Second-Generation Disease Management Programs

The greatest evolutionary differences in first-generation disease management with today's programs are (1) the move away from a single-disease focus to a patient focus, which could address multiple disease comorbidities in 1 program; (2) the improved use of data and access to information through the medical record; and (3) the addition of incentives to induce patients to adhere to the medical regimen and providers to offer quality care.

Diabetes is not truly separable from its related disorders; obesity often leads to insulin resistance, which damages pancreatic beta cells, and results in type 2 diabetes.[13] Patients with diabetes have high risks of hypertension, coronary disease, and cerebrovascular disease.[14] Therefore, disease management programs that account for these risk factors take a more holistic approach than first-generation programs that attempted to focus on improving glycemic levels only.

The quality, comprehensiveness, and interoperativity of electronic health records are considerably better today than in the mid-1990s. Today's information technology systems allow for better integration of pharmacy claims data, medical records, and laboratory data, which enables greater analysis and facilitates improved care coordination. This is critical to the concept of patient-centered medical homes and accountable care organizations.

The current generation of disease management programs have gone beyond a call-center focus, and have experimented with offering inducements to patients to adhere to their medical regimen. This can be found in value-based insurance design approaches,[15] which may include reduced copays for medications for those in disease management programs or discounts for gym memberships.

Health coaching is also a popular addition to disease management programs today, as is a multidisciplinary approach to care teams[16]—hence the broader scope of "care management" programs, which may rely on case managers in addition to physicians as central coordinating personnel.

The Business Case for Diabetes Disease Management

There is little doubt that following evidence-based diabetes management guidelines can demonstrate clinical benefits. The real question was whether those clinical benefits were great enough to translate into a strong economic argument. In a meta-analysis of randomized controlled trials of diabetes disease management programs, the authors found that disease management programs had the effect of improving A1C levels by 0.51% on average compared with usual care.[17] If one agrees with the findings of the United Kingdom Prospective Diabetes Study, which linked a 1.0 point reduction in A1C with a 37% reduction in the risk of microvascular complications,[3] the potential would seem to exist for significant cost savings years down the road.

From a societal viewpoint, this would make sense, if these efforts can be consistently applied over time. However, the high turnover rates at health plans alluded to earlier mean that a member with poorly controlled type 2 diabetes may move from one plan with extensive disease management program abilities to another with more modest abilities (if the patient is enrolled in the program at all).

Had the federal government decided that disease or care management programs were administrative costs for the purposes of calculating medical-loss ratios as part of health reform, this would have spurred a completely different business care argument (that is, can we even afford disease-management activities?).

From a health system standpoint, not only does the question of keeping patients in the program gnaw at medical executives and chief financial officers, but the very issue of ROI, which is one of the foundations of the business case for disease management, is not settled. Certainly, long-term savings associated with fewer complications in patients with superior care for diabetes would not be seen in the short term—a more likely scenario based on health plan turnover rates. However, some evidence does exist that short-term savings may result, not from lower complication rates, but from lower service utilization.

According to a study by RAND,[18] investigations of ROI for disease management programs vary greatly in their scientific rigor, and as a result, cost-effectiveness and ROI cannot be stated with any certainty.

In a review of the available evidence, Goetzel et al[19] stated, "For studies reporting costs and benefits, a $0.70 ROI was calculated (lower than a break even). On balance, these studies point to the potential for diabetes DM programs to break even, if treatment costs are well managed."

Regardless of the ROI, perhaps disease management is simply the "right thing to do." Clinically, it does appear to moderately improve glycemic levels, and it may spur patients with diabetes mellitus to think of their health in the wider terms of cardiovascular risk, kidney health, and obesity. A study from the University of Michigan found that a comprehensive diabetes disease management program not only obtained a 0.6 point reduction in A1C level, but also reduced mean systolic blood pressure by 3 mm Hg and low-density lipoprotein concentrations by 18 mg/dL.[20]

Does ROI Matter?

With more than 90% of health plans and insurers maintaining diabetes disease or care management programs as part of the benefit offerings, and with less-than-convincing evidence of ROI in these programs, it seems that something else is at work. Could it be that the competition for health plan members trumps any cost savings calculation for a program most implicitly believe is beneficial? With so many plans offering disease management benefits, and members and employers coming to expect them in their benefit packages, perhaps chief financial officers merely see disease management programming as a cost of doing business. **EBDM**

Funding Source: None.

Author Disclosures: Mr Mehr reports receiving payment for involvement in the preparation of this article.

Authorship Information: Concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

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Payer Perspective

Interview With Geoffrey Mwaungulu, MD

EBDM: **How long have you been personally involved in disease management programs?**
Dr Mwaungulu: That would be more than 10 years now, starting with my work at Health Alliance Plan.

EBDM: **Over that time, what has been your overall perception of disease management in the major chronic diseases (ie, diabetes, cardiovascular, asthma)?**
Dr Mwaungulu: Early on, our disease management programs were fairly "light touch," and they really weren't all that effective. We tended to just send educational items to the members we identified. We just weren't sophisticated in terms of our approach. And we often separated the diseases rather than aggregating them depending on the patient. We have also moved more toward managing the whole population in our messaging and interventions.

EBDM: **There might be a specific disease management program for diabetes, another for cardiovascular, and another for asthma?**
Dr Mwaungulu: Yes. More recently, our understanding of disease management and the sophistication of the approach to disease management improved. We now understand the importance of changing member behavior with regard to their chronic illnesses. As a result, the approach has included a bit more focused engagement with the member. For example, the case manager will do interviews using some standardized approaches that help members understand how they can change their "unhealthy" behaviors.

EBDM: **Does this mean more frequent contact with the patient?**
Dr Mwaungulu: More frequent and continuing contact with the patient. If the patient has 2 or more chronic conditions, they are addressed at the same time. This may involve, for example, managing the hypertension in the member with diabetes. We also understood along the way that we had to tier the members according to not just the chronicity of the condition but the severity of their illness. The interventions and the intensity of the interventions would reflect that.

EBDM: **You had mentioned that the case manager generally focuses on patient contact or engagement. How does this person interface with the patient's primary care physician (PCP)?**
Dr Mwaungulu: If the case manager, at the disease management level, finds issues that he or she believes should be brought to the attention of the PCP, the case manager has the option of reaching out directly to the physician, which they ordinarily wouldn't do unless an issue requires urgent attention. More commonly, the case manager will tell the member to talk to his or her PCP about this particular issue, and then follow up with the member. Beyond disease management–into episodic case management–the PCP must be involved more directly to closely monitor the patient's condition.

EBDM: **Does your health plan currently use an external disease management provider?**
Dr Mwaungulu: We have a layering of these things. Let me confine the discussion to the Medicare Advantage population first. We use an external vendor for the Medicare Advantage population for 4 target diseases: diabetes, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease. Diabetes represents the biggest population, by far. These days, in trying to engage the members to improve their health and outcomes, we meet with the vendor on a regular basis to try to close gaps in quality of care. In the case of diabetes, the vendor really has to know the patient's blood sugar levels, his or her hemoglobin A1C concentration, the cholesterol levels, whether the patient has had a kidney function test, whether the patient has had a follow-up eye exam, whether they have their blood pressure controlled, and whether they are on the right medication. They are responsible for doing a lot more today than in the past to improve the health outcomes of these members.

EBDM: **This must be quite a challenge in terms of information technology. If you're using an external provider, you must have some way to share the patient data.**
Dr Mwaungulu: We have started sharing claims data with the vendor, so they get an understanding about what types of services are being done. In a few instances, the vendor actually has a link to members' glucometers, in which glycemic concentration data can be uploaded by the vendor. They can communicate with the PCP if they see a problem.

EBDM: **I understand that for the Medicare population at your health plan, the plan identifies members at high risk for complications and gives the information to the disease management vendor. Is this also the case for the commercial population?**
Dr Mwaungulu: Yes, we identify which members are candidates and send the information on to our internal disease management staff.

We can't force members to participate in the disease management program. It's up to the vendor to engage as many of these patients as possible.

EBDM: **On the commercial side, do you link program participation with reduced copays or cost sharing?**
Dr Mwaungulu: I don't believe we offer any of these types of incentives to participate. I have seen other plans where copays have been reduced or waived. In those plans, if the member uses formulary-approved products, the copays can be reduced to generic levels. This encourages the member to be more adherent with the medication regimen.

EBDM: **What's your impression of any cost savings or return on investment with any disease management programs with which you've been involved?**
Dr Mwaungulu: The return on investment tends to be small with any disease management program. If you can get a 1:1 return, I believe you're still doing a great service for your membership. It is more than just saving the maximum amount of money–it is about improving outcomes. If you improve outcomes in general, you are probably going to see some savings. However, I don't believe that disease management has traditionally saved money.

EBDM: **For patients with diabetes, in particular, in what areas do you think disease management programs excel?**
Dr Mwaungulu: In terms of outcomes, I think we're seeing fewer people getting complications of diabetes, maybe less kidney disease over time. If you have regular eye checkups, there will be fewer cases of blindness. If you get your blood sugars controlled, you will probably see less peripheral vascular disease and more manageable coronary artery disease in the long run.

EBDM: **Yes, in the long run. In the face of high health plan turnover, how do we achieve these outcomes? From the health plan's perspective, what is the short-term benefit?**
Dr Mwaungulu: That has been one of the arguments against disease management. However, if the health plan works to optimize these outcomes today, they can receive some immediate financial benefits, in terms of improved HEDIS measures, which are part of the reimbursement formula for the Medicare Star program. For example, the Medicare Star program is interested in whether a patient with diabetes is taking their angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker. These are part of the quality metrics we report to Medicare–resulting in a short-term benefit for the health plan in diabetes disease management programs.

I also believe there is greater membership retention when they feel the health plan cares about them. In other words, the member turnover may be less than in the past.

EBDM: **What do you think the next generation of disease management programs (or care management programs) will look like? How will they differ from those today?**
Dr Mwaungulu: There will be more member engagement, showing them how to take better care of themselves. This will require even more case manager involvement with the member to emphasize educational approaches even more than in the past. There will also be more involvement by the members' physicians, especially as more of them become patient-centered medical home–accredited and more them join accountable care organizations. For the health plans, these newer ways of delivering care will allow for more population management.

Dr Mwaungulu is medical director at Blue Cross Blue Shield of Michigan.

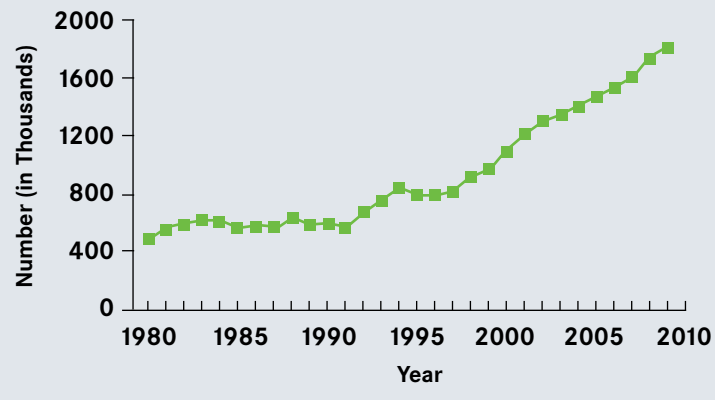
Targeting Insulin Resistance: The Ongoing Paradigm Shift in Diabetes Prevention

Tara Dall, MD; Dawn Thiselton, PhD; and Stephen Varvel, PhD

Tara Dall, MD

United Kingdom Prospective Diabetes Study have established beyond question that better blood glucose control can dramatically reduce these complications in diabetic patients.[4,5] However, the chronic vascular disease and inflammation that leads to such devastating complications begins years before the hyperglycemic threshold necessary for diabetes to be diagnosed. Here, the root of the damage lies in insulin resistance—often a result of obesity and inactivity—characterized by impaired tissue responsiveness to the metabolic effects of insulin in the liver, skeletal muscle, and adipose tissue. Insulin resistance can, for a while, be tolerated by increased production of insulin from the pancreas, while putting the pancreatic beta cells under considerable strain in the process. Insulin resistance alone, aside from predisposing to diabetes, is associated with early cardiovascular mortality, renal dysfunction, deterioration of the retina, and neuropathy.[6] In fact, the importance of obesity as a risk factor for heart disease is related to its promotion of the insulin-resistant state. Furthermore, people with MetS have a 2-fold increased risk of cardiovascular outcomes and a 1.5-fold increased risk of death.[7]

Figure. New Cases of Diagnosed Diabetes Among US Adults Aged 18 to 79 Years, 1980-2009



Source: Centers for Disease Control and Prevention website. www.cdc.gov/diabetes/statistics/incidence/fig1.htm. Accessed January 11, 2013.

The Cardiometabolic Epidemic

Prevalence of diabetes has reached epidemic proportions, affecting over 25 million people in the United States alone. In 2010, 8.3% of adult Americans had diagnosed diabetes, 3.5% had undiagnosed diabetes, and 38.2% had prediabetes.[1] What's more, the situation appears to be getting worse—with the annual rate of new cases more than tripling over the past 20 years (**Figure**), the Centers for Disease Control and Prevention estimates that as many as 1 in 3 individuals will develop diabetes by 2050 if current trends continue.[2] The dramatic increase in diabetes prevalence over time has paralleled the increase in prevalence of overweight and obesity.[1] On the basis of National Health and Nutrition Examination Survey 2003-2006 data, about one-third of men and women have metabolic syndrome (MetS), a cluster of major cardiovascular risk factors related to overweight/obesity and insulin resistance.[1]

Heart disease and stroke are serious complications of diabetes. Although death rates for heart attack and stroke have been decreasing, adults with diabetes are still twice as likely to die from these diseases as people who do not have diabetes.[2,3] Vascular complications are responsible for the bulk of the costs, and are the main cause of suffering and death, for patients with diabetes. Key studies such as the Diabetes Control and Complications Trial and the

Over the past decade, the cost of cardiovascular disease (including hypertension, heart failure, and stroke) has accounted for ~15% of increased medical spending and has increased at an average rate of 6% annually.

Prediabetes affects more than 87 million US adults (38%) aged 20 years or over, with a lifetime risk for conversion to diabetes of 30% to 50%.[1,8] By the time prediabetes has developed, untreated patients are at very high risk of developing full-blown diabetes, with even higher risk of cardiovascular events, complications, and death. Lastly, 20% to 30% of adults in the general population in Western countries have non-alcoholic fatty liver disease (NAFLD), a condition associated with insulin resistance that confers increased risk for fibrosis and cirrhosis of the liver, liver cancer, and heart disease, with prevalence as high as 70% to 90% of people who are obese or who have diabetes.[9,10]

The healthcare costs associated with diabetes are staggering: the American Diabetes Association (ADA) estimates that managing diabetes for just 1 year costs an average of $6649 per person, though costs can climb much higher when complications occur, and type 2 diabetes is projected to cost $500 billion a year by 2020.[11,12] Moreover, over the last decade, the cost of cardiovascular disease (including hypertension, heart failure, and stroke) has accounted for ~15% of increased medical spending and has increased at an average rate of 6% annually.[1] Individuals with MetS experience about $2000 greater healthcare expenditures annually and have higher utilization of inpatient, primary care, other outpatient, and pharmacy services than persons without MetS factors, even over the short time frame of 2 years.[13] Healthcare costs for patients with NAFLD have also been shown to be 26% higher, at 5-year follow-up, than costs for patients without the disease.[14]

Insulin Resistance as a Therapeutic Target

Part of the reason why our medical system has failed to stem this tide has been the fact that current approaches diagnose diabetes too late—by the time frank diabetes is evident, 80% of beta cell function has already been lost.[15,16] However, a paradigm shift is under way, changing the way we think of the disease. We now know that diabetes is the final stage of a long pathogenic process that starts with insulin resistance and increased strain on pancreatic beta cells, progressing to an impaired ability to control blood sugar (ie, prediabetes), and only develops into full-blown diabetes once pancreatic beta cell death has reached a point where natural insulin can no longer control fluctuations in blood glucose. At this point, extensive (and costly) efforts are directed toward managing the disease and minimizing occurrence of micro- and macrovascular complications. Just as the fight against heart disease has been revolutionized by recognizing that heart attacks and strokes are the end result of atherosclerotic disease that has progressed over many years (hence the logical necessity for early prevention of atherosclerosis with medical treatment and lifestyle changes), the battle against diabetes will only be won when we recognize that the disease we need to identify and ag-

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gressively treat is insulin resistance. Diabetes is the end stage to be prevented, not the jumping-on point for our medical system.

New Tools to Diagnose

The first step in preventing diabetes is identifying who is at greatest risk, and therefore most in need of aggressive lifestyle intervention and perhaps medical treatment. Several traditional risk factors such as age, sex, body mass index, blood pressure, and family history have long been understood to be related to diabetes risk. Validation of various risk models has shown that the predictive value can be enhanced with biochemical measures, most often fasting glucose or glycated hemoglobin (A1C).[17] However, traditional fasting blood measures alone will miss a substantial proportion of the prediabetic population who have become so due to a dysregulated ability to control spikes in blood glucose after a meal (impaired glucose tolerance). A significant step forward was made when the ADA specified diagnostic criteria for prediabetes that included impaired glucose tolerance (IGT), defined as a 2-hour post-load glucose level during an oral glucose tolerance test (OGTT) of 140 to 200 mg/dL, along with fasting glucose levels of 100 to 125 mg/dL (impaired fasting glucose) or A1C level of 5.7% to 6.4%.

Blood tests for fasting levels of A1C and glucose are easy, cheap, and often performed as point-of-care tests. Unfortunately, the OGTT is often impractical in the clinical setting and so, too often, IGT goes undiagnosed. Furthermore, these criteria only identify prediabetes once the underlying insulin resistance and beta cell strain have progressed to the point of being unable to adequately control blood glucose levels. Thus, there is a great need for simple diagnostic tests that can identify early signs of insulin resistance and IGT from fasting blood samples, while remaining sufficiently cost-effective to be employed in the large at-risk population.

Fortunately, as our understanding of the pathophysiology of cardiometabolic risk has advanced, a variety of biomarkers have been identified with potential clinical utility in detecting early signs of insulin resistance (eg, characteristic changes in lipoprotein metabolism).[18] Increases in total and small low-density lipoprotein (LDL) particles, large very low-density lipoprotein (VLDL) particles, and average VLDL size, along with decreases in average LDL particle size, high-density lipoprotein (HDL) particles, and average HDL size have been associated with glucose clearance in the "gold standard" measure of insulin resistance, the hyperinsulinemic clamp procedure, and also with incident diabetes in the Insulin Resistance Atherosclerosis Study.[19,20] Increases in fasting serum free fatty acid levels are known to be involved at an early stage of the disease process.[21,22] Importantly, indicators of adipose tissue dysfunction, such as increased release of leptin (which may indicate leptin resistance) or decreased release of adiponectin, have been shown to precede development of diabetes in many individuals.[23,24] Furthermore, novel biomarkers such as alpha-hydroxybutyrate and linoleoyl-glycerophosphocholine have recently been discovered via metabolic profiling to be independently associated with insulin resistance and predictive of progression from normal glycemia to prediabetes.[25,26] While additional trials are necessary to fully validate these and other novel markers, these tools are increasingly available now to clinicians who understand the importance of early detection.

New Approaches to Treatment

Alongside our growing understanding of how to identify early signs of insulin resistance has been development of new treatment options, and a burgeoning sophistication in how to direct optimal treatment and lifestyle advice at the personal level based on individual biomarker profile. Recent ADA treatment recommendations support this approach.[27] Lifestyle recommendations form the cornerstone of diabetes prevention efforts (eg, reduced intake of carbohydrates [especially refined ones] and increased daily activity). Several large trials have demonstrated that intensive lifestyle interventions consisting of programs directed at weight loss (7% reduction from baseline) and exercise (150 min/week) are remarkably effective in preventing diabetes in those at high risk, reducing 3-year diabetes incidence by over 50%.[28-32] Often, insulin sensitizers and weight loss through diet and exercise will improve key components of MetS.[33] NAFLD can also be reversed with changes in dietary habits aimed at modest weight loss (approximately 10% of initial weight) and blood pressure regulation, with a consequent decrease in insulin resistance.[34,35]

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To date, there are no medications with US Food and Drug Administration indication for use in prediabetes. There are, however, clinical trials showing safety and benefit of several classes of antidiabetic therapies in the setting of prediabetes and insulin resistance. Metformin has long been the frontline medical treatment for diabetes, and has been shown repeatedly to slow or prevent progression to diabetes in prediabetics by enhancing insulin sensitivity.[36,37] Quick-release bromocriptine, a newly approved antidiabetic therapy with unique mechanism of action (a dopamine agonist), may also be effective in the setting of insulin resistance and prediabetes, as it helps correct the dyslipidemia, postprandial hyperglycemia, elevated free fatty acids, and effects due to increase in sympathetic tone.[38,39] Thiazolidinediones (TZDs) have proved to be very effective insulin sensitizers, and several large trials have shown reductions in progression from prediabetes to diabetes of 62% to 72%.[40,41] Further, GLP-1 agonists, DPP-4 inhibitors, or quick-release bromocriptine may be indicated when signs of beta cell stain are present.[42,43] Importantly, these medications can be safely used in prediabetes, as they do not

cause hypoglycemia. While more randomized clinical trial data are needed before guidelines can be established, physicians are already using biomarker profiles to guide treatment approaches and are experiencing impressive success not only in preventing progression to diabetes but in actually reversing the underlying pathology. For example, a recent report described an approach that assigned patients in clinical practice to treatment with either metformin + pioglitazone or metformin + pioglitazone + exenatide based on indices of underlying insulin resistance and beta cell function. This approach successfully reverted more than 50% of prediabetics back to normal glycemic status.[44]

Return on Investment

Not only does a focus on detection and therapeutic correction of insulin resistance hold the promise of reducing diabetes incidence and the devastating impact this has on people's lives, but it could also have a huge impact on efforts to reduce overall health expenditures. A recent analysis of the potential for cost savings estimates that reducing diabetes and hypertension prevalence by just 5% would result in annual savings of approximately $9 billion in the short term and up to $25 billion in the medium term.[45] The ADA recommends that such diabetes prevention programs be covered by third-party payers due to the potential cost savings.[46]

...reducing diabetes and hypertension prevalence by just 5% would result in annual savings of approximately $9 billion in the short term and up to $25 billion in the medium term.

The largest diabetes prevention trial in the United States, the DPP, has shown that intensive lifestyle interventions or metformin treatment were cost-effective or cost saving during the 3-year intervention[47] and after 10 years of follow-up.[48] Further, economic modeling has suggested that when glycemic control is not achieved solely with lifestyle or metformin monotherapy, combination with a TZD is also cost-effective.[49,50] Cost analysis of individual A1C cutoffs suggests that the high-cost interventions used in the DPP should be cost-effective down to the current lower limit of prediabetes (A1C = 5.7%), and that intervening at even lower A1C values could also be cost-effective if the cost of the intervention were lowered.[51] By diagnosing the early signs of insulin resistance, those who are not yet technically prediabetic but would still benefit from intervention (ie, are most likely to progress to diabetes) can be identified and treated appropriately. As our interventions become more efficient and effective, the large population of high-risk patients currently being missed can be identified and treated cost-effectively.

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Conclusion

In order to achieve a better return on prevention efforts, 3 things must happen. First, patient screening must improve in order to better identify those at risk. Key to this is recognizing that the target is insulin resistance. Second, interventions must be more effective at not only slowing disease progression but in reversing disease itself—restoring normal insulin sensitivity and protecting against beta cell death. This will be achieved in part by recognizing that diabetes is a multifaceted disease and interventions should be tailored to the individual based on their particular underlying pathophysiology. Finally, only when a full cardiometabolic risk profile is evaluated on an individual basis can the most effective and efficient steps be taken to prevent diabetes and cardiovascular disease and promote future health in the population at large. **EBDM**

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Funding Source: None.

Author Disclosures: Dr Dall reports employment with HDL, Inc, and has received invitations from a commercial sponsor, Santaris, to lecture. Drs Thiselton and Varvel report employment with Health Diagnostic Laboratory, Inc, which performs diagnostic testing of diabetes risk factors.

Authorship Information: Concept and design (DT, SV); acquisition of data (TD); analysis and interpretation of data (TD); drafting of the manuscript (TD, DT, SV); critical revision of the manuscript for important intellectual content (TD, DT, SV); provision of study materials or patients (TD); and administrative, technical, or logistic support (DT).

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Diabetes and PCMH
(continued from cover)

an economic impact of approximately $174 billion in 2007.[2] All the while, people got fatter and more sedentary, and heart centers and dialysis centers have gone up like shopping malls. Clearly, something needed to be done differently.

In the 2001 Institute of Medicine report, entitled *Envisioning a National Healthcare Quality Report*,[3] a new phrase was coined—patient-centeredness. A collaboration among clinicians, patients, and their families (when appropriate) that takes into account the desires, needs, and preferences of the patient, in addition to providing patients with the knowledge and support they need to participate in their own care and make decisions about their care. The report emphasized meeting the patient's changing needs over the life cycle—needs about staying healthy, getting better, living with illness or disability, or coping with the end of life.[4]

Enter the patient-centered medical home (PCMH). In a PCMH, each participant has a care coordinator and a team that takes collective responsibility for providing and/or arranging for the patient's individual healthcare needs. Episodic care is replaced by coordinated care and a long-term healing relationship with a high level of accessibility. Communication among the patient, their family, clinicians, staff, and care providers such as a home care nurse, pharmacist, or mental health provider is timely and efficient. The latest information technology is used to prescribe, communicate, track test results, obtain clinical support information, and monitor performance (**Sidebar**).[5]

The idea is to reduce total cost of care by emphasizing prevention, improved practice efficiencies, reduced unnecessary testing and referrals, and reduced preventable emergency department (ED) visits and hospital admissions. Care teams are mobilized to better manage complex patients using the right provider at the right time in the right way with everyone working at the top of their licensure.

Efforts related to the implementation of the PCMH have been done all across the country in large and small settings since the '90s.[6] Yet, there is still a lot to learn about how to evaluate them. Improvements in diabetes care in glycated hemoglobin (A1C), blood pressure (BP), and low-density lipoprotein (LDL) or bundled scores have been reported (**Table 1**). Additionally, there has been documentation of improved patient/staff satisfaction and patient self-management.[6,7]

Out of these national projects grew other state efforts. In Minnesota, the development of the PCMH is part of the health reform legislation passed in 2008. As of the writing of this article, there are 214 PCMHs in Minnesota, most of which are in the Minneapolis-St. Paul metropolitan area, and most are parts of large integrated health networks.[8]

In 2010, to provide some support for smaller clinics to become certified, the Minnesota Department of Health posted a request for proposal for The Safety Net Primary Care Transformation Grant to provide expert support and facilitation for safety net clinics toward the implementation of the PCMH. Four sites were selected to participate and the author served as the consultant to provide the expert support to these 4 sites.

All of the 4 sites served the safety net population of their respective areas. Each had started toward becoming a PCMH, but there is still work to do. The process began with a gap analysis as the first step, allowing them to develop individualized work plans specific to their respective sites.

Three of 4 sites identified people with diabetes as their initial target population and the fourth site identified high utilizers, many of whom also have diabetes. Diabetes is a high-cost, high-risk, multi-factorial chronic condition, which requires a care team, and the PCMH is well suited to meet the needs of those patients who have the disease. The diabetes educator is often the designated care coordinator, and other members of the care team will participate in carrying out the care plan as appropriate.

Sidebar. NCQA: PCMH Recognition Program

To ensure consistency, the National Committee for Quality Assurance (NCQA) has a PCMH Recognition Program, which is based on specific elements in 6 standard categories.[5] Those categories are:

- ***Enhance Access and Continuity:*** Accommodate patients' needs with access and advice during and after hours, give patients and their families information about their medical home, and provide team-based care
- ***Identify and Manage Patient Populations:*** Collect and use data for population management
- ***Plan and Manage Care:*** Use evidence-based guidelines for preventive, acute, and chronic care management, including medication management
- ***Provide Self-Care Support and Community Resources:*** Assist patients and their families in self-care management with information, tools, and resources
- ***Track and Coordinate Care:*** Track and coordinate tests, referrals, and transitions of care
- ***Measure and Improve Performance:*** Use performance and patient experience data for continuous quality improvement

Recognition is becoming increasingly important because there can be an added payment for care coordination based on the complexity of the patient. Some states have their own certification/recognition processes based on similar concepts.

PCMH indicates patient-centered medical home.

Care Planning and Care Coordination

The care plan is established collaboratively with the patient, with goals appropriate for their needs at the time, and will change as needs change. Everyone on the team has access to the latest care plan and can update it based on their respective interaction with the patient. Once goals are reached, ongoing support is provided to maintain the progress and to prevent relapse. Additionally, the care coordinator connects the patient to community resources, such as diabetes support groups, online resources, or a walking group.

This ongoing tracking and monitoring is an essential component of the PCMH. Each PCMH has a registry or a list of all their participants in the PCMH generated from the electronic health records that can be stratified based on a predetermined set of parameters. For someone with diabetes, those parameters are most often A1C, LDL, BP, and/or body mass index, and may also include the date of the last clinic visit, date of last laboratory tests, date of last eye examination, smoking status, comorbidities, and any other relevant data points. This information is reviewed by the care coordinator along with the primary care physician (PCP) and the care team to determine the current status of the patient, update the care plan as needed, and track tests, referrals, and any transitions of care. This is often referred to as "working the list." If gaps in care are noted, the care coordinator will contact the patient to schedule an appointment with the appropriate care provider or make certain the patient follows up on a recommendation, such as visiting their eye doctor.

The complexity of care coordination increases as patient needs increase and always takes into consideration the "whole patient," addressing all preventive services and other health issues. This is the core of the PCMH.

Standardization of Work Flow

A key success factor is standardization of the clinic work flow. When a visit to the PCP is scheduled, the "pre-visit planning" begins. The care coordinator encourages the patient to come in a few days ahead of time for any laboratory tests that are due, and any other known issues that can be addressed ahead of time will be taken care of at that time. This will ensure that the PCP has the information needed to have a more meaningful conversation with the patient about their current status and any changes that will need to be made in their care plan. All too often, laboratory tests are done at the time of the visit and results are not available until days later, losing the opportunity for those teachable moments.

On the day of the visit, there is a similar set of tasks set in motion, often referred to as "during visit" care. Having a standardized process ensures that critical things are not missed. Once the clinic visit is done, an "after visit summary" may be given to the patient that reiterates any agreed-upon goals and recommendations.

After the visit, the care coordinator will follow up on any issues brought up during the visit. This is often referred to as ongoing support or "between visit" care. For example, if there have been any changes in medication,

Table 1. Improvements in Composite Scores

Healthcare System	Impact on Composite Scores (A1C, BP, and LDL)	
	Pre	Post
Geisinger Health System	2.4%	6.5%
WA Group Health of Puget Sound	51.0%	58.6%
HealthPartners Medical Group	4%	25%

A1C indicates glycated hemoglobin; BP, blood pressure; LDL, low-density lipoprotein.
Source: Data from Bojadzievski T, Gabbay R. *Diabetes Care*. 2011;34:1047-1053.[6]

Table 2. Cost Savings

Health System	Outcomes
WA Group Health of Puget Sound	Reduced ED visits by 29% Reduced in-patient admissions by 11%
HealthPartners Medical Group	Reduce ED visits by 39% Reduced in-patient admissions by 24% Reduced in-patient readmissions by 39%
Geisinger Health System	Reduced in-patient admissions by 20%

ED indicates emergency department.
Source: Data from Bojadzievski T, Gabbay R. *Diabetes Care*. 2011;34:1047-1053.[6]

the care coordinator/diabetes educator will continue to work with the patient to monitor blood glucose values and adjust medications according to a set of protocols.

Health Information Sharing and Quality Improvement

All of this is dependent upon a process whereby the health information follows the patient as they move through the system and is accessible to every care team member, including the patient. Although the PCP and the care coordinator are ultimately responsible for the overall care plan, different care team members may add to the plan. For example, a registered dietician uses the overall care plan as a base for an individualized meal plan created in collaboration with the patient. This meal plan is then added to the care plan so that all team members are aware of it.

Or consider this. If a participant in a PCMH enters an ED, imagine the PCMH and name of his care coordinator are in his record. The ED staff will care for him as appropriate, but they would also contact his care coordinator who would then follow up with him to ensure that he gets what he needs to ensure that any future preventable ED visits are avoided. If a patient is not part of a PCMH, with availability of his health information and in collaboration with the patient, the ED staff could connect him with a PCP before he leaves. The result is a reduction in total cost of care.

Sound impossible? All 3 of the care systems that experienced improvements in diabetes care using care coordination and care planning along with payment incentives for doing the work also experienced cost savings through significant reduction in ED visits and inpatient admissions (**Table 2**).[6,7]

While using the health information on an individual basis helps track progress of a specific patient, population-level data should be routinely reviewed to determine progress across the entire population. Diligence about using population-level data is critical in driving improvements in care. Examples of such population-level measures are A1C rate and levels, BP, LDL rates and levels, and patient satisfaction. The utilization rates of the ED, hospital admissions, and readmissions will be needed to determine any change in total cost of care.

Lessons Learned and Managing Change

However, none of this comes easily and without a lot of work. Things will happen. No matter how hard you try, there will be other things that will compete for time, and extenuating circumstances, such as budget constraints and staff turnover, that may cause a shift in corporate priorities. Time will always be an issue, especially when you want involvement of providers. Leadership support for the time to do the work is essential. And, it is critical to review the aim regularly to determine whether to stay the course. If leadership support wanes, it will be extremely difficult for the team to succeed.

But, even with leadership support and the time to do the work, there will still be some resistance to change. When given a choice, we all tend to fall back on what's familiar. The first step in the process of changing behavior is to "unfreeze" the existing situation. However, our openness to change is also affected by environmental influences, personal factors, and attributes of the behavior itself. Some say change is cyclical, taking relapses into account.[9] The team leader will need to assist the group through these relapses by facilitating a discussion about what they learned and what they could or would do differently. Thus, focusing on the change agent and the importance of this role cannot be underestimated.[10] Finding the right team leader and champion will be critical to your success.

And, having the confidence to make the change and operate in a new way is also an issue. Clearly, with changes in roles and responsibilities, many individuals at these sites needed to learn new skills. Often, the change looks good on paper, and makes rational sense, but the team does not have the skills to implement it. The team may get so excited about a change that they bypass the necessary training and preparation, finding themselves facing either resistance or little enthusiasm.[11] To avoid this potential problem, it is important to include those members of your team impacted in the change right from the start, so everyone has ownership in the process and the solution.

So Where Are They Now?

Two of the Minnesota sites are certified as PCMHs. One was given a variance on their care planning, which meant they needed to provide staff training, collaborative goal setting, and care planning. One site was busy opening a new clinic site and there was a strategic decision to delay PCMH certification until they were able to imbed the principles into all 4 of their clinics. They hope to submit their application within the year.

The fourth site is reexamining its vision without moving to certification as a PCMH at this point in time. Changes in strategic direction and loss of some key individuals caused it to halt the process toward certification for now. However, both of these sites did improve on all the processes considered core to becoming a PCMH.

Summary

Should you choose to adopt the PCMH, you need to recognize that there will be early adopters and there will be skeptics and it will most likely require a culture change for your organization. Starting small with a targeted population, such as diabetes, is helpful in allowing everyone an opportunity to test this change before implementing it with all patients.

You will likely struggle with IT and you can expect confusion as to how the PCMH and care coordination fit with the day-to-day work flow. And, everyone will struggle with staff turnover at some point. This will make it especially necessary to maintain organizational memory of the process.

In summary, the core concepts of the PCMH have demonstrated results. However, to get there, leadership support for not only the concept but also for the work is essential. Although the application and certification are important, the real results come from embedding the principles in your standard operating procedures. The PCMH becomes the way you do your work. **EBDM**

Author Affiliation: From Halleland Habicht Consulting, LLC, Minneapolis, MN.
Funding Source: None.
Author Disclosure: The author reports serving as a consultant for Lifescan and Novo Nordisk, employment with Halleland Habicht Consulting, LLC, receiving lecture fees from BD, Lifescan, and Novo Nordisk, and attending the American Association of Diabetes Educators and American Diabetes Association meetings.
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Value of Better Diabetes Management

(continued from cover)

medications for management of T2DM. Most of the benefits have accrued to patients who do not respond adequately or durably to older therapies (eg, metformin, sulfonylureas). As David Nathan observes, drug classes "that have been developed recently are generally no more potent, and often less effective in lowering glycemia, than the 3 oldest classes."[2] In other words, the newer drugs have benefited patients who are inappropriate for or unresponsive to established treatments by preventing longer-term macrovascular and microvascular complications.[3]

Since a substantial segment of patients have not enjoyed major benefits from new treatments, it is worth asking whether we are using existing therapies to the greatest benefit. In fact, evidence suggests underuse along at least 2 dimensions: 1) imperfect medication adherence[4,5] and 2) delays in or lack of insulin initiation.[6,7]

First, it is widely understood that patients with chronic illness do not always adhere to their providers' instructions. Patient adherence to oral blood glucose–lowering medication and insulin regimens generally ranges from 60 to 85 percent, with even lower adherence reported for certain populations, such as those covered by Medicaid.[5] A number of earlier researchers have documented the impact of poor adherence on diabetes-related outcomes.[8-10]

Pierre-Carl Michaud, PhD

Second, concerns arise about underuse of diabetes treatments. Many center on insulin because the injection regimen imposes inconvenience and other personal costs.[7] This is unfortunate because compared with prevailing standards, earlier use of insulin may be warranted, particularly in patients with poor glycemic control (ie, glycated hemoglobin [A1C] >9).[11,12] Clinicians may be reluctant to initiate patients on insulin because it is taken as a sign of "defeat."[13]

The healthcare delivery system also can delay insulin initiation because of the need for referral to an endocrinologist in complex cases.

In light of these issues, we study whether and how poor adherence to and lower uptake of insulin therapy quantitatively contribute to the costs of diabetes on patients and the healthcare system. Both the expansion of insulin use and the reduction of poor adherence are likely to require the investment of resources to develop new policies, clinical approaches, and technologies. We are interested in the potential return on such investments.

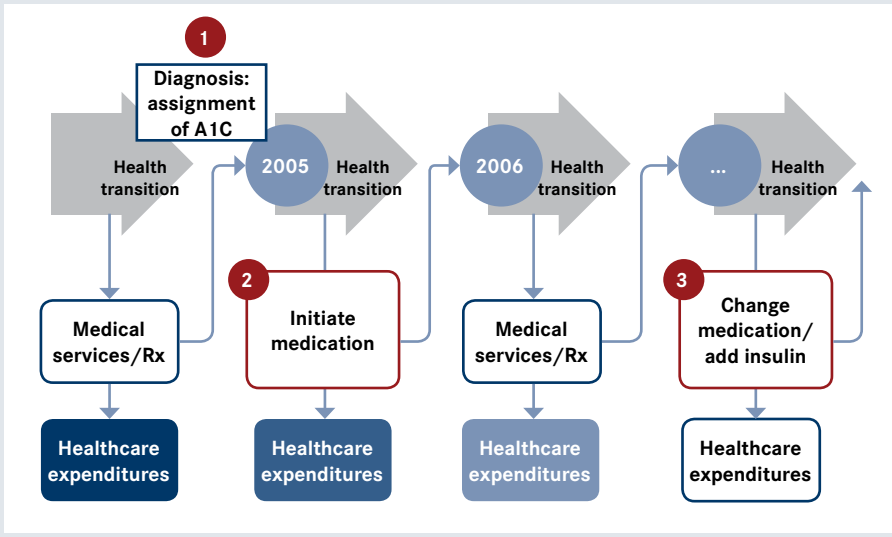
To investigate these questions, we calculate and compare the lifetime benefits to patients of scenarios that improve adherence and increase insulin use. We then compare these benefits with the value of a scenario generating further improvements in the efficacy of diabetes medicines. In particular, we calculate the future technological progress that would be required in this scenario to match the value of expanding insulin therapy.

For all such scenarios, we simulate outcomes for a cohort of newly diagnosed US diabetes patients who are aged 51 years in either 2003 or 2004 and who acquire diabetes between ages 51 and 60 years. We then examine the costs and benefits of each of the above scenarios, compared with current diabetes management.

Overview of the Model

We use a well-established dynamic microsimulation model, the Future Elderly Model (FEM),[14-17] to model the lifetime consequences of expanded insulin use, improved patient adherence, and future progress in the efficacy of diabetes medicines. The model simulates health status, health spending, and mortality experience of the US population with diabetes over the age of 50 years. The FEM is based on data from the Health and Retirement Study (HRS), a biennial survey of Americans 51 years and older that has been ongoing since 1992. We supplement the HRS with medical spending data from the Medicare Current Beneficiary Survey and Medical Expenditure Panel Study for persons who would not be eligible for Medicare. The FEM is well suited for this study, because it allows the simulation of alternative lifetimes for patients aged 51+ years in different treatment environments. Further detail on the mechanics and implementation of the model are provided in the **eAppendix** (available at **www.ajmc.com**).

Figure. Overview of the Diabetes Management Model



A1C indicates glycated hemoglobin.
Diagram is for illustrative purposes and does not reflect the progression of specific individuals in the model.

Treatment Options

Figure 1 gives a schematic view of how patients progress in the model. We model 3 steps in the management of diabetes. First, the model assigns an initial A1C level. Second, it assigns a first-line oral drug treatment regimen. Finally, the model predicts whether insulin therapy is initiated and whether oral drug therapy is modified.

Lily A. Bradley, MBA

Oral medications are categorized in 3 drug classes: metformin (biguanides), sulfonylureas, and thiazolidinediones (TZDs). They represent more than 90% of the oral diabetes medications taken by HRS respondents.

We allow for addition of insulin therapy as a second method of treatment starting in the second year of the simulation, because few T2DM patients are treated with insulin as a first-line agent. Upon initiating insulin, patients face a one-time decision whether to keep taking their oral medication or to depend solely on insulin.

Treatment Effects

For effects of drug treatment on health transitions, we focused on A1C, weight, and mortality, end points that were consistently reported in the literature and could be mapped to the health conditions in the model.

Table 1 presents estimates for clinical effects of oral diabetes medications used in the model by drug class and outcome. Since evidence on the effects of combination therapy is not universally available, we conservatively assumed that the effect of a combination therapy equals that of its most efficacious component therapy, relative to placebo.

For insulin therapy, clinical effects used in the model are summarized in Table 2. Because we focus on the effect of adding insulin to existing treatment regimens, we combined evidence of the effect of adding insulin treatment on A1C reduction with epidemiological evidence linking A1C to mortality, since the evidence on the direct effect of adding insulin is sparse.

In both cases, evidence of the effect of glycemic control from treatment on mortality is taken from the recent 10-year follow-up study of the United Kingdom Prospective Diabetes Study trial.[18]

Because poor adherence to diabetes medications decreases the effectiveness of treatment,[5] we include adherence measures in the model. We map adherence to effectiveness, using estimates from the literature (see eAppendix).

Monetizing Lifetime Consequences

Finally, it is necessary to monetize effects on life expectancy, in order to compare them with the financial costs

Table 1. Clinical Effects of Oral Drug Treatments

	Metformin	Sulfonylureas	TZDs
All-cause mortality after 10 years (relative risk)	0.73 (0.59-0.89)	0.87 (0.79-0.96)	0.87 (0.79-0.96)
Weight (kg)	0.3 (–0.3 to 0.9)	3.8 (3.6-4)	3 (1.7-4.2)
A1C (%)	–1.14 (–1.4 to –0.87)	–1.52 (–1.75 to –1.28)	–1.09 (–1.31 to –.86)

A1C indicates glycated hemoglobin; TZD, thiazolidinedione.
Reported effects are mean effects with 95% confidence intervals in parentheses. Estimates for the mortality benefit associated with TZD treatment were not available, and thus we used the lowest estimate of the mortality reduction associated with antihyperglycemic agents from the UKPDS 10-year follow-up study.
Source: Agency for Healthcare Research and Quality[3]; postinterventional 10-year follow-up of United Kingdom Prospective Diabetes Study (UKPDS).[18]

Table 2. Incremental Effects of Starting Insulin Therapy

	Insulin (Incremental Benefit)
All-cause mortality after 10 years (relative risk)	0.87 (0.79-0.96)
Weight (kg)	1.19 (0.61-1.76)
A1C (%)	–1 (–0.8 to –1.2)

A1C indicates glycated hemoglobin.
Reported effects are mean effects with 95% confidence intervals in parentheses. Clinical effects correspond to one-time incremental benefits over existing medication regimens.
Source: Postinterventional 10-year follow-up of United Kingdom Prospective Diabetes Study[18]; Type II Diabetes PORT Study.[12]

of increased treatment. The monetary value of longevity extensions is controversial. Viscusi and Aldy estimated based on a review of the literature that the value of a statistical life ranges primarily from $5 million to $12 million.[19] Assuming a 3% real rate of interest and a constant flow of value implies figures between $150,000 and $360,000 for each statistical life-year. We chose a value of statistical life-year of $200,000 for our calculations, which is inside but toward the lower end of this range. Note that we conservatively assume that the value of morbidity reductions, independent of mortality, is zero. Future benefits and costs were discounted at 3% to compare scenario outcomes.


Michael R. Eber, BSE

Scenario Implementation

For the improved medication adherence scenario, we simulated the effects of bringing all patients to full adherence with their diabetes treatment regimens. Within the model, better adherence increases the effectiveness of diabetes medications, according to estimated adherence effects in the literature.

For the increased insulin initiation scenario, we doubled the rate of insulin initiation in the model, derived from predicted probabilities of insulin initiation based on HRS data. Effectively, current insulin users initiate therapy earlier, and the current nonusers who are predicted to be most likely to use insulin are "treated" with insulin by the simulation.

Finally, we estimated the increase in medication efficacy that would be required in order to match the value per patient of the insulin scenario. We measure efficacy as improvements in the relative risk of mortality and in A1C reductions. For simplicity, we considered a single uniform percentage improvement along both dimensions at once. The results of this scenario provide a benchmark to compare the value of increased insulin use with the value of technological innovation in treatment.

Results

Lifetime Costs and Benefits

In **Table 3,** we show life expectancy as well as discounted lifetime medical costs for each scenario for the average patient newly diagnosed with T2DM between ages 51 and 60 years. In the baseline scenario, remaining life expectancy at 51 is 30.2 years. On average, 27.2 years are spent with no limitations on activities of daily living (ADL), while 3 years (10% of remaining life expectancy) are spent with at least 1 ADL limitation.


Jeffrey Sullivan, MS

Both the increased insulin initiation and increased adherence scenarios provide an increase in life expectancy of 0.2 years, all of it disability free. Discounting the life expectancy gains and valuing a statistical life-year at $200,000, we obtain average individual benefits from life extension of $17,812 and $14,922 for the increased insulin initiation and improved adherence scenarios, respectively.

Both scenarios increase medical spending. The discounted average lifetime increase associated with the adherence scenario is $1529, and the increase associated with the insulin scenario is $3582, relative to baseline spending of $281,408. These increased expenditures are due to the additional cost of treatments for all conditions during patients' lifetimes, which are, on average, extended compared with the baseline scenario.


Dana P. Goldman, PhD

Computing the net value of each scenario as the difference between the longevity benefits and the increase in costs, we obtain a net value of $15,779 in 2004 dollars per newly diagnosed patient with diabetes for the increased insulin initiation scenario, and $13,394 for the increased adherence scenario.

Improvements in Medication Efficacy

We compared our scenarios with improvements in the efficacy of medicines through technological innovation. Specifically, we calculated the across-the-board improvement in the average efficacy of diabetes medicines that would match the net value per individual achieved by expanding the rate of insulin initiation. Efficacy would need to rise by about 6% to match the value of expanded insulin use, which is similar to the value of eliminating poor adherence. Below, we discuss how to interpret the magnitude of this effect and how to compare it with the values of reducing underuse.

Robustness of Estimates

The sensitivity analyses for both scenarios show varied but uniformly positive effects of intervention. Since our estimates of benefits are conservative (no impact on micro- or macrovascular outcomes), even if the efficacy of early glycemic control is at the lowest range supported by the evidence, increasing adherence or increasing insulin uptake should have positive real-world benefits. Further detail on sensitivity analyses is provided in the eAppendix, as well as a discussion of model limitations.

Discussion and Policy Implications

The underuse of diabetes medications is costly to patients. Interventions, policies, and new technologies that permit the expansion of insulin use when appropriate or the reduction of poor adherence would generate substantial value. Expanding insulin use among T2DM patients would generate net social value in excess of $15,000 to the average 51-year-old who will acquire diabetes in the next 9 years, a total value of $12.6 billion in the United States. Eliminating poor adherence to insulin and oral medicines would generate over $13,000 on average to each newly diagnosed patient or $10.7 billion in the aggregate. Underlying uncertainty about the clinical benefits of various diabetes medications leads to some uncertainty around these estimates, but alternative scenarios all showed at least some positive benefit from improving adherence, increasing insulin uptake, or improving non-insulin efficacy.

The value of adherence and underuse interventions is comparable to optimistic projections of technological progress in the efficacy of diabetes medications. We projected a 6% increase in the efficacy of non-insulin antidiabetic medications *for the average patient* that would be required to match the value of increasing insulin uptake. Historical experience suggests this would be an ambitious goal for the coming decades. For example, recently discovered classes of oral medicines have improved outcomes for particu-

Table 3. Benefits and Costs of Diabetes Management Scenarios

	Baseline	Adherence	Insulin
Life expectancy (years)	30.2	30.4	30.4
Disability-free life expectancy (years)	27.2	27.3	27.3
Lifetime medical spending (2004$)	277,573	279,102	279,607
Cost of diabetes treatment (2004$)	7866	7897	8539
Discounted value of life extension (2004$)		14,922	17,812
Discounted change in lifetime medical spending (2004$)		1529	2034
Net value per patient (2004$)		13,394	15,779
Aggregate net value		$10.7 b	$12.6 b

Results are average effects for cohort of type 2 diabetes mellitus patients aged 51 years in 2003-2004 and diagnosed between 51 and 60 years. The adherence scenario simulates the effects of bringing all patients to full adherence with their current (and future) diabetes drug regimens. The insulin scenario models the effects of doubling the rate of insulin initiation from current practice.

lar subgroups that failed on existing medications, but have not generated impacts large enough to impact outcomes for most patients. The Agency for Healthcare Research and Quality concluded that none of the major classes of new diabetes treatments (eg, TZDs, DPP-4 inhibitors, meglitinides, and alpha-glucosidase inhibitors) improved on earlier treatments for the average patient.[3] This finding appears consistent for monotherapies or dual combinations, where the newer agents were relatively similar to established alternatives for the average patient.[3] The value of newer agents lies in second- and later-line alternatives for patients who fail to respond to established therapies. They also may generate benefits not captured by the traditional end point of A1C, including reduced macrovascular and microvascular complications, lower risks of hypoglycemia, and weight loss.[3]

Our results, coupled with the challenge of sustaining continued growth in the efficacy of diabetes medications, suggest the need to expand the view of what constitutes "innovation" in the treatment of diabetes and possibly other chronic conditions. Traditionally, discussions of innovation have centered on the discovery of new therapies. Attention also must be paid to incentives for the discovery of new *approaches* to improve the use of existing medications. These include strategies to improve adherence and enhance the patient experience of inconvenient medication regimens such as injectable insulin.[8]

From a policy perspective, this suggests the need to strengthen incentives to invest and innovate in promoting adherence and improving patients' insulin experiences. In the current reimbursement environment, innovators cannot be confident of generous reimbursement for new approaches that focus primarily on improving the convenience and patient experience of therapy. The single-minded focus on efficacy of new treatments, as measured in randomized controlled trials, contributes to the problem. It is well understood that efficacy estimates from trials reflect an artificially adherent patient population. Therapies that are no more efficacious in trials but significantly enhance patient convenience may improve clinical outcomes in the real world. Our results suggest that this could be valuable to patients with diabetes and should be reimbursed accordingly.

This logic applies equally to nonpharmaceutical interventions. New approaches for monitoring poor adherence and encouraging compliance should be rewarded. Innovators—whether in pharmaceuticals, healthcare delivery, or insurance—will invest more resources in discovery when they expect greater rewards.[20] The most efficient mix of policies to encourage innovation is beyond the scope of this study, but it is notable that policy makers have a number of different levers to choose from.

Improving the use of existing diabetes medications will be just as challenging as discovering new ones. Yet, our study suggests that it might be just as rewarding. Long cycles of clinical research and development are necessary before new treatments come to market. Society may need to embrace an equally forward-thinking and long-term program of research on improving the use of existing diabetes medications. **EBDM**

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Funding Source: None.

Author Disclosures: Dr Lakdawalla is a partner with Precision Health Economics, which receives consultancies from life science firms. Mr Eber, Mr Sullivan, and Ms Bradley report employment with Precision Health Economics, which receives consultancies from life science firms. Ms Forma reports employment with sanofi-aventis US. Dr Michaud reports receiving payment from Precision Health Economics for involvement in the preparation of this manuscript. Dr Goldman reports receiving consultancies from sanofi, Bristol-Myers Squibb, and Pfizer.

Authorship Information: Concept and design (DNK, FMF, JS, P-CM, LAB, DPG); acquisition of data (DNK, JS, P-CM, DPG); analysis and interpretation of data (DNK, MRE, JS, P-CM); drafting of the manuscript (DNK, MRE); critical revision of the manuscript for important intellectual content (DNK, FMF, MRE, LAB, DPG); statistical analysis (DNK, MRE, JS, P-CM); provision of study materials or patients (LAB); obtaining funding (DNK, FMF, LAB, DPG); administrative, technical, or logistic support (MRE, LAB); and supervision (DNK, FMF, DPG).

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Table 3: Catheter Occlusions and Infusion Site Reactions

	HUMALOG (n=38)	Regular human insulin (n=39)
Catheter occlusions/month	0.09	0.10
Infusion site reactions	2.6% (1/38)	2.6% (1/39)

In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

Allergic Reactions

Local Allergy — As with any insulin therapy, patients taking HUMALOG may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of HUMALOG. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy — Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including HUMALOG. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular human insulin (n=2969) and 30 patients receiving HUMALOG (n=2944).

Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in HUMALOG *[see Contraindications]*.

Antibody Production

In large clinical trials with patients with type 1 (n=509) and type 2 (n=262) diabetes mellitus, anti-insulin antibody (insulin lispro-specific antibodies, insulin-specific antibodies, cross-reactive antibodies) formation was evaluated in patients receiving both regular human insulin and HUMALOG (including patients previously treated with human insulin and naive patients). As expected, the largest increase in the antibody levels occurred in patients new to insulin therapy. The antibody levels peaked by 12 months and declined over the remaining years of the study. These antibodies do not appear to cause deterioration in glycemic control or necessitate an increase in insulin dose. There was no statistically significant relationship between the change in the total daily insulin dose and the change in percent antibody binding for any of the antibody types.

Postmarketing Experience—The following additional adverse reactions have been identified during post-approval use of HUMALOG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors in which other insulins have been accidentally substituted for HUMALOG have been identified during postapproval use.

DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Following are some of the examples:

- **Drugs That May Increase the Blood-Glucose-Lowering Effect of HUMALOG and Susceptibility to Hypoglycemia:** Oral antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, pramlintide, disopyramide, fibrates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide).
- **Drugs That May Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones.
- **Drugs That May Increase or Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- **Drugs That May Reduce the Signs of Hypoglycemia:** beta-blockers, clonidine, guanethidine, and reserpine.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMALOG.

Although there are limited clinical studies of the use of HUMALOG in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

Nursing Mothers—It is unknown whether insulin lispro is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HUMALOG is administered to a nursing woman. Use of HUMALOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Pediatric Use—HUMALOG is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. HUMALOG has not been studied in pediatric patients younger than 3 years of age. HUMALOG has not been studied in pediatric patients with type 2 diabetes.

As in adults, the dosage of HUMALOG must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

Geriatric Use—Of the total number of subjects (n=2834) in eight clinical studies of HUMALOG, twelve percent (n=338) were 65 years of age or over. The majority of these had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of HUMALOG action have not been performed.

OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE AND ADMINISTRATION

Dosage Considerations—When given subcutaneously, HUMALOG has a more rapid onset of action and a shorter duration of action than regular human insulin.

The dosage of HUMALOG must be individualized. Blood glucose monitoring is essential in all patients receiving insulin therapy.

The total daily insulin requirement may vary and is usually between 0.5 to 1 unit/kg/day. Insulin requirements may be altered during stress, major illness, or with changes in exercise, meal patterns, or coadministered drugs.

Subcutaneous Administration—HUMALOG should be given within 15 minutes before a meal or immediately after a meal.

HUMALOG given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.

HUMALOG administered by subcutaneous injection should be given in the abdominal wall, thigh, upper arm, or buttocks. Injection sites should be rotated within the same region (abdomen, thigh, upper arm, or buttocks) from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions]*.

Continuous Subcutaneous Infusion (Insulin Pump)—HUMALOG may be administered by continuous subcutaneous infusion by an external insulin pump. Do not use diluted or mixed insulins in external insulin pumps. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy *[see Adverse Reactions]*. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant variability among patients, approximately 50% of the total dose is usually given as meal-related boluses of HUMALOG and the remainder is given as a basal infusion. HUMALOG is recommended for use in pump systems suitable for insulin infusion such as MiniMed, Disetronic, and other equivalent pumps.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HUMALOG 100 units per mL (U-100) is available as:

10 mL vials	NDC 0002-7510-01 (VL-7510)
3 mL vials	NDC 0002-7510-17 (VL-7533)
5 x 3 mL cartridges[1]	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled pen	NDC 0002-8725-59 (HP-8725)
5 x 3 mL Humalog KwikPen (prefilled)	NDC 0002-8799-59 (HP-8799)

Storage

Do not use after the expiration date.

Unopened HUMALOG should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use HUMALOG if it has been frozen. In-use HUMALOG vials, cartridges, pens, and HUMALOG KwikPen® should be stored at room temperature,

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below 86°F (30°C) and must be used within 28 days or be discarded, even if they still contain HUMALOG. Protect from direct heat and light. See table below:

	Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, (Below 86°F [30°C])
10 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL cartridge	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL prefilled pen	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, **Do not refrigerate.**

Use in an External Insulin Pump — Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days or after exposure to temperatures that exceed 98.6°F (37°C). A HUMALOG 3 mL cartridge used in the D-Tron® pumps should be discarded after 7 days, even if it still contains HUMALOG. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days.

Diluted HUMALOG for Subcutaneous Injection — Diluted HUMALOG may remain in patient use for 28 days when stored at 41°F (5°C) and for 14 days when stored at 86°F (30°C). Do not dilute HUMALOG contained in a cartridge or HUMALOG used in an external insulin pump.

Preparation and Handling

Diluted HUMALOG for Subcutaneous Injection — HUMALOG may be diluted with Sterile Diluent for HUMALOG for subcutaneous injection. Diluting one part HUMALOG to nine parts diluent will yield a concentration one-tenth that of HUMALOG (equivalent to U-10). Diluting one part HUMALOG to one part diluent will yield a concentration one-half that of HUMALOG (equivalent to U-50).

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling and Patient Counseling Information section of the Full Prescribing Information.

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[1] 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® Memoir™ and HumaPen® Luxura™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3-mL insulin delivery device and Disetronic D-TRON® and D-TRON® Plus pumps.

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Changing Payer Strategies
(continued from cover)

others certainly have and will continue to play a role in addressing the needs of the diabetic population when it comes to our "overburdened healthcare system." In fact, with the anticipated millions of newly insured achieving coverage through health insurance exchanges by January 1, 2014, payers will need to develop and promote changes in how they manage the diabetes benefit—the tactics of the past 2 decades will, by necessity and by practicality, yield to newer methods of cost control through promoting member health improvement. As the great Bob Dylan sang long ago, "For the times, they are a-changin'."

The Evolution of Payer Strategies for Diabetes

When it comes to addressing any benefit, let alone the benefits specific for members with diabetes, payers utilize multiple methods for "management." Each management method addresses a different stakeholder who is impacted by how the payer manages the diabetes benefit leading to a specific end product of said strategy. These payer strategies used to manage the needs of members with diabetes are not only applicable to other chronic conditions besides diabetes but are also currently in various states of flux as they evolve from where they are to where they need to be. The **Table** assists in showing the necessary evolution.

Managing the Patient/Member

When it comes to how payers manage the needs of members with diabetes, the current state leaves much to be desired. Typically, most payers, to analogize the Donabedian model of quality assessment, have set into place a structure whereby a simple process exists for the member with diabetes to obtain his or her medication—the physician writes a prescription for the requisite drug and the pharmacy charges that patient a portion of the medication cost as either a copayment or coinsurance. Despite the plethora of studies that have shown that there is benefit to the member's health when a so-called value-based benefit design (VBBD) is introduced, the great majority of payers have yet to fully embrace such a model in its complete incarnation—a recent survey showed that only 20% to 30% of large employers utilize some form of VBBD.[6] However, with payers adopting new philosophies with respect to improving the health of members with diabetes, VBBD may still have not maximized its full potential.

The basic premise for a VBBD program is to reduce member cost sharing for services, such as medications or preventive eye examinations, in which the affected outcome of said services (eg, promoting medication adherence or diagnosing diabetic retinopathy early) provide clinically relevant health benefits. Such benefits have accrued from limiting the costly implications for members seeking this care.[7] As payers promote VBBD programs for diabetes (or for other chronic conditions), their management of the condition in question evolves into one where, rather than focusing on mere process, the payers now focus on the outcomes of the process in question. Outcomes of care are where "the rubber meets the road," as it is this end product that determines member health and, as a consequence of member health, potential payer remuneration in the form of bonuses.[8] Given the number of members with diabetes and the dollars involved, it shouldn't be a big surprise that payer strategies for managing the diabetes benefit should include some form of VBBD.

Managing the Physician

An alternative method of managing a member's diabetes benefit, while less transparent to the member, is quite efficient. Payers manage the diabetes benefit through the physician caring for that member. Such management falls under the rubric of utilization management. For the physician caring for a patient with diabetes, this means managing of the member's utilization addresses 2 key factors—first, it ensures that the member receives the appropriate medication or other service needed to address the diabetes and, second, it discourages the wasting of dollars on unnecessary or inefficient care. Physicians are quite aware of this technique of "prior authorization" and, while they may not like it, they work within the prescribed parameters. Typically, a payer's prior authorization approvals follow and support clinical practice guidelines of key constituencies (eg, the American Diabetes Association or the American Academy of Clinical Endocrinologists). Physicians, even while tending to dislike these practices, still managed to increase their share of, for example, drug formulary use such that their use of specific medications became non-managed.[9] Changes to this area require payers to "manage the physician" less than they had been. This shift coincides well with payers' continuing evolution in diabetes benefit management. This shift also entails a change from a utilization management strategy toward one of quality management. For the purposes of benefit management, payers choose to focus more on improving the quality of care that physicians provide, and are doing so through incentives promoting good care. Examples that specifically address the diabetes realm include the creation of a patient-centered medical home for patients with diabetes as part of a pay for performance program in which objective improvements in a patient correlate with improved health.[10,11] Given that early returns from medical home initiatives show promise, this type of diabetes benefit management may be expected to increase or, better yet, to enlarge in scope through aligning a broader network of participants.

Managing an Organization

As payers align diabetes care management strategies for both patients, through VBBD, and physicians, through financial incentives, the next logical step is broadening the impact of diabetes management. Currently, payers manage their diabetic members' services at hospitals or other large entities contractually. Many payers look merely at the services provided, such as hospitalizations, bundle them together under a contractual diagnosis-related group payment, and adjudicate the claim. Payments of this type led to payer-provider negotiations where victory was "all about cost" and dollars. However, as payers develop newer strategies, as noted above, the next logical step aligns larger entities together. Following the recommendations of Fisher et al,[12] payers began to explore and have now contracted with accountable care organizations (ACOs). ACOs are accountable to payers for the overall cost and quality of care provided to, for our purposes, a population of individuals with diabetes. ACOs should not be viewed as a method for payers to manage the diabetes benefit per se, as their specific function involves redesigning healthcare delivery to result in more units of health, defined as total benefit, per unit of cost. In that way, ACOs are "all about value." For example, as more people with diabetes are better cared for and experience fewer readmissions, then the ACO physician members would share in the savings accrued from this endeavor. ACOs become a natural and logical extension of paying for outcomes on a grand scale.

Managing the Community

As discussed earlier in this article, diabetes is and will continue to be a national problem. However, this national problem trickles down to a community level. In that respect, as they address the full ramifications of diabetes with their individual members, their contracted physicians, and with ACOs, payers are also changing how they are working with the communities in which they operate. More recently, payers defined their community contributions through their public relations departments—a payer's effectiveness resulted from their CAHPS (Consumer Assessment of Healthcare Providers and Systems) results or if they had fewer complaints filed against them with the Department of Insurance. Payers looked at their claims data historically and descriptively. But this, too, is changing. Following the proposals of Sinek,[13] payers are also moving away from explaining what they do to promoting why they do it. Payers know that addressing the diabetes epidemic requires engaging more than their individual members and the physicians or organizations providing care for them—making a difference in diabetes requires community engagement and community engagement requires data mining and predictive analytics. Payers already know who their members with diabetes are; now they need to identify which of these members will experience a myocardial infarction or a stroke or who is less likely to comply with a given medication regimen. The ability to leverage "big data" from the claims they have allows payers to promote healthier communities in concert with how they are managing the diabetes benefit in other ways. These changes are already evident, with one national payer defining itself through its "expertise in health benefits solutions and health information technology,"[14] whereas another one defines itself as committed to "improving the health and well-being of our members, our associates, the communities we serve, and our planet."[15]

Summary

Just as there are many ways to treat a condition such as diabetes, there are also many ways for payers to manage the diabetes benefit. Although none of these methods is specifically right or wrong, they are grounded in a payer's philosophy and created in response to the needs of the time. Yet, just as in any other business, new ideas and, for diabetes, new scientific discoveries will surely mandate new strategies to achieve goals. As payers find themselves adapting to new political realities and new partnerships, one cannot be sure if their new strategies will succeed or not. But, in actuality, this becomes moot as the 1 point we can be sure of is that benefit management will continue to evolve. **EBDM**

Author Affiliation: From HumanaOne & KMG, Waukesha, WI.
Funding Source: None.
Author Disclosure: Dr Tzeel reports employment with Humana Inc, as well as stock ownership. He also reports receiving consulting fees from Amylin Phar-

maceuticals.

Authorship Information: Concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and administrative, technical, or logistic support.

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Table. A Continuing Evolution of Diabetes Benefit Management

Stakeholder	Current Benefit Management Example	Due to Current End Product of	Evolving to	Future End Product of	Future Benefit Management Example
Patient/ Member	Copayment/ Coinsurance	Process	—>	Outcomes	Value-Based Benefit Design
Physician	Prior Authorization	Utilization Management	—>	Quality Management	P4P PCMH
Organization	Contract (bundling)	"All About Cost"	—>	"All About Value"	ACOs
Community	Public Relations (start with what)	Explaining What They Do	—>	Promoting Why They Do What They Do	Healthy Communities (start with why)

ACOs indicates Accountable Care Organizations; P4P, pay for performance; PCMH; patient-centered medical home.

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Examining Models of Care and Reimbursement, Including Patient Management Fees, ACOs, and PCMHs: A Panel Discussion

A panel discussion on healthcare reimbursement and payment fees at Diabetes Innovation 2012 that included leaders from diverse backgrounds in the healthcare industry was moderated by Susan Dentzer, editor-in-chief of Health Affairs *and publisher of Project HOPE. Panelists included James (Larry) Holly, MD, chief executive officer of Southeast Texas Medical Associates (SETMA), LLP; Keith Shealy, MD, president of Mackey Family Practice; Laura Long, MD, MPH, vice president of clinical innovation for BlueCross BlueShield of South Carolina; and Sam Ho, MD, chief medical officer and executive vice president at UnitedHealthcare.*

Moderator: **How does the new way diabetes is managed compare with the older way?**

Dr James Holly of SETMA stated that the biggest change is that providers now have a concept of accountability and that there is a renewed sense of responsibility to improve healthcare and lower costs. Dr Holly discussed quality metrics as a major determinant of medical care and compared quality metrics with a GPS system. A GPS system only works if you know where you are. "Can you imagine a GPS system that told you where Dallas was but wouldn't tell you where you are and gave you no signposts along the way?" asked Dr Holly. A medical treatment plan is the same: you cannot have a system in which you only know what the end goal is. Constant and continuous quality metrics are needed so that adjustments can be made as the treatment proceeds. Those metrics need to be universal so that the pharmacist, the doctor, the patient, and the provider can all look at the metrics to understand how the treatment is proceeding. Dr Holly noted that if the patient knows where they are in the overall treatment plan, they will be more compliant and more involved in the treatment. Dr Holly also stated that the patient-centered health model can change how clinicians perform. If the patient has a public forum to report on a clinician's or provider's performance, that performance will improve. These changes may be challenging for some populations to adjust to, but adjustment will occur over time.

Dr Keith Shealy of Mackey Family Practice agreed with what was said by Dr Holly, adding that an open system is good for competition. "Doctors are competitive, very competitive," said Dr Shealy. Doctors who are low on a public rating system will strive to do better, meaning better care for patients.

Dr Laura Long of BlueCross BlueShield, South Carolina, noted that traditionally, BlueCross BlueShield had a care management model in which coaches reached out to patients. During that period "We worked primarily with our members and we tried to coach them as best we could and we would periodically reach out to the physician but we weren't necessarily collaborating," said Dr Long, adding, "Historically, we were working in our traditional silos." That has changed. Today, the patient-centered medical home model is more open. Dr Long added, "What we are doing in the patient-centered medical home is we are sharing information." Claims information is shared with clinicians and case managers. Case managers can access the electronic medical records and add electronic "sticky notes" that clinicians can see and use to adjust treatment if necessary.

Another important change is that in addition to paying physicians for traditional services, BlueCross BlueShield is also paying physicians for outcomes in 2 new ways. First, clinicians can get reimbursed for additional services, including pharmacy visits, education visits, and home visits. Second, if clinicians are doing a better job at controlling certain clinical parameters (eg, blood pressure) they will get paid more. Such measures lead to fewer emergency department and hospital visits and therefore are cost-effective for the provider.

> *"In a patient-centered medical home, we have not done our job unless we can give patients access to care that we have prescribed."*
>
> **—James (Larry) Holly, MD**
> Chief Executive Officer
> Southeast Texas Medical Associates

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Robert Galvin, MD, says there are many challenges to ensuring the success and longevity of a patient-centered medical home (PCMH). For example, the lack of time for physicians to spend with patients, a large enough staff, and expensive IT systems are all issues that the PCMH faces (http://bit.ly/XeS9Ly).

Dr Sam Ho from UnitedHealthcare agreed with the other panelists on how significantly the healthcare system has changed in the last few years toward a more patient-centered system.

Dr Ho stated that the changes encompassed 5 levels:

1. Healthcare needs to be more patient centric instead of disease focused.
2. There needs to be a transformation of the records delivery system that allows all members of the team to be informed. For example, if a patient is in the emergency department and the primary care physician does not know that, the system is failing.
3. The payment system should be value based instead of volume based.
4. Transparency should be universal and encompass the consumers, the doctors, and the hospitals, and include data on how they are performing in relationship to standard guidelines.
5. The program should reward those who adhere to the treatment plan. If a patient is improving and adhering to the treatment, then premiums, copays, and out-of-pocket expenses should be reduced.

"He was angry, hostile, bitter, and mean."

Dr Holly provided an example of patient-centered healthcare from his own practice. "I saw a man in the hospital; he was a patient of one of my partners, a new patient. He was angry, hostile, bitter, and mean. The nurses said, 'You don't want to go in there,'" explained Dr Holly. He took the time to talk with this man and he discovered that the patient had several problems: he couldn't afford his medications, he was going blind due to his uncontrolled diabetes, he was incapacitated and could not work, he could not afford the gas to see the doctor or attend diabetes educational programs, he could not afford the copays for the educational programs, and he could not afford to go see an ophthalmologist to save his eyes. Dr Holly told the audience that he and his team used funds available for these patients and worked to get the patient gas cards, reduced copays, and an appointment with an ophthalmologist. As Dr Holly noted, "In a patient-centered medical home, we have not done our job unless we can give patients access to care that we have prescribed." Dr Holly concluded the story by stating that he saw the patient 6 weeks later and "[the patient] had something I could not prescribe….He had hope, for the first time in years."

Moderator: **The emotional and social needs that often accompany a medical need have not always been addressed or covered by more conventional health insurers. How is your organization addressing those non-medical needs?**

Dr Long noted that their organization recognizes that the social needs of a patient are often greater than the true medical needs and that social needs have a significant impact on medical care. Issues such as the person having financial or transportation problems, or other comorbidities, for example, depression, can have a major effect on treatment adherence. Dr Long also said many providers have programs in place to help patients. However, those programs are not effective if implemented in isolation from the physician. "The thing that has me excited about patient-centered medical homes is that they are now being integrated with the physician," stated Dr Long. Also, the physicians are being incentivized in this new model for better outcomes instead of for the volume of patients they see. That means that a physician will be rewarded for taking the time to address some of the behavioral, financial, or emotional issues that can impede treatment. In return, the patient is rewarded with better care.

Dr Shealy stated that they screen all of their patients for mental and emotional

issues. They are well aware that patients with depression cost more money, so an integrated behavioral health curriculum is part of their practice.

Moderator: **What about physicians who don't have their own private foundation? Who pays for that physician to develop a patient-centered model?**
Dr Ho answered this question by admitting that it is a challenge. Developing a network of pharmacists, certified diabetes educators, social workers, nurse practitioners, and other providers can be done; however, much work is required. As more insurers and granting agencies accept the patient-centered approach to healthcare, such networks will likely become easier to establish.

Moderator: **Is the patient-centered home model the basis of the care within accountable care organizations (ACOs) or will something else evolve?**
Dr Long said, "I see the patient-centered model as the foundation for accountable care organizations." According to Dr Long, the primary care physician is the basic provider of management services for patients with chronic conditions. From that foundation, specialists and other health professionals may be added; however, patients need to be able to return to their primary care physicians as the ACOs continue to expand and evolve.

Moderator: **Will the patient-centered model work better for preventing diabetes or treating it?**
Dr Long answered that the model is best designed to prevent diabetes. Historically, the medical community treats patients after they get sick: it is a reactive model. The patient-centered model is proactive: it provides rewards when patients do not get sick. Dr Long said doctors are aware of individuals in their patient populations who are at risk for a medical condition (diabetes, hypertension, etc) and they can develop algorithms and teaching programs for those patients before they get sick. Under the patient-centered model, doctors will be properly compensated for this care. "We know that prediabetes is a huge problem, especially in South Carolina, where the diabetes rate is very high. The way you can address that problem is [that] you can screen your patients at high risk for prediabetes, you can put in place weight management programs, you can be aggressive with metformin, etc. And you can get reimbursed for that," said Dr Long.

One thing that the patient-centered model is well suited for is preventive care. At the core of the model are the patient and the primary care physician. If the model allows the physician to take their time before medical problems develop and the doctor is properly compensated, the patient is healthier and the provider has lower healthcare expenditures. Everyone wins. **EBDM**

Reprinted from A Special Report on Diabetes Innovation 2012. *Am J Manag Care*. 2012;18:10-12.

Real-World Examples of Patient-Centered Healthcare

Many healthcare communities have implemented programs to help patients with the plethora of issues that arise during the course of their medical care. Craig Brammer, a member of the Senior Leadership Team at the Office of the National Coordinator for Health Information Technology in Washington, DC, moderated a session at Diabetes Innovation 2012 entitled "State Based Solutions and Beacon Communities," which provided examples of how different healthcare communities have helped their patients with diabetes.

Montana Cardiovascular Disease and Diabetes Prevention faThe roots of the Montana Cardiovascular Disease and Diabetes Prevention Program began in 2007, when Montana's legislature authorized the use of state funds to evaluate whether or not it was feasible to provide Montana with a diabetes prevention service consistent with the evidence-based Diabetes Prevention Program (DPP), according to Steve Helgerson, MD, state medical officer and Medicaid medical director of the Montana Department of Public Health and Human Services. The feasibility of this initiative has been demonstrated in Montana. Starting in 2008, Montana has continued to increase the number of diabetes and cardiovascular disease prevention sites across its state each year. Some sites have associated telehealth sites, which are especially important for delivering services to Montana's geographically large but sparsely populated state.

The 16-week DPP program focuses on diet, exercise, and behavior change to work toward the goals of 7% weight loss and 150 minutes per week of physical activity.

At present there are 15 locations for the preventive program. The program lasts 16 weeks and is administered by trained healthcare professionals. The participants are selected only after meeting specific criteria. The key criterion is that the patient has to want to change their current lifestyle. Also, the program is limited to those recommended by their primary care physician to be at risk for developing diabetes.

The program itself is similar to the DPP developed by the National Institutes of Health, which reported a 58% reduction in the incidence of diabetes among participants.[1] The 16-week DPP program focuses on diet, exercise, and behavior change to work toward the goals of 7% weight loss and 150 minutes per week of physical activity. The Montana program also includes 6 monthly follow-up classes.

Table. Areas of Improvement in the Hawaii Island Beacon Community

• Group Problem Solving and Performance Improvement
– Practice redesign strengthening leadership
– Hospitals collaborating on standardized discharge process and hand-off to care coordinators
– Care coordination–developed common registry of complex patients
– Health information exchange supporting care transitions
– Complex patients learning self-management with help of fun, interactive technology
• Health Plans
– Significant rewards for performance
• Community Organizations
– Promoting culturally appropriate healthy lifestyle programs

The results of the program in Montana have been very impressive. Dorothy Gohdes, MD, a consultant for the Montana Chronic Disease Program, said that the latest statistics on the program (2008-2011) show that over 2700 participants completed the 16-week program and lost an average of 12 pounds. Furthermore, 34% of the participants met the program's weight loss goal (loss of 7% of their starting weight) and 54% met the physical activity goal. Improvements have also been observed in blood glucose, blood pressure, low-density lipoprotein cholesterol (LDL-C), triglycerides, and total cholesterol. More information about this program can be found at http://www.dphhs.mt.gov/publichealth/diabetes/prevention.shtml.

The challenges facing the state of Montana in trying to start (and maintain) this type of program are similar to those facing other public and private institutions, and they include securing reimbursement and training program leaders. Moving forward, Dr Gohdes is optimistic that this program will continue to be successful in teaching participants how to lead healthier lifestyles. Dr Gohdes also hopes the program will have a ripple effect in getting family members to adopt the program as well. To learn more about Montana's Cardiovascular Disease and Diabetes Prevention Program, visit www.mtprevention.org.

Beacon Communities
Healthcare providers generally have the same 3 aims: 1) to provide better healthcare, 2) to help patients achieve better health, and 3) to do that at a re-

duced cost. According to Craig Brammer, a member of the Senior Leadership Team at the Office of the National Coordinator for Health Information Technology, a key component to achieving these 3 goals is the use of information technology (IT). Beacon Communities are leading the way in using IT to provide better healthcare at a reduced cost to improve the health of their participants. The Beacon Community Cooperative Agreement Program demonstrates how health IT investments and meaningful use of electronic health records (EHRs) can advance the vision of patient-centered care. At present, there are 17 Beacon Communities in the United States and the National Coordinator for Health IT is providing $250 million over 3 years to develop secure, private, and accurate systems for EHR adoption and health information exchange (HIE). For more information on how the federal government is helping to advance health IT integration and about the Beacon Communities, visit www.healthit.gov.

Described below are 2 Beacon Communities that use IT in unique ways to help patients with diabetes.

Hawaii Island Beacon Community

The Hawaii Island Beacon Community (HIBC) is a federally funded collaborative project administered through the College of Pharmacy at the University of Hawaii at Hilo. The collaboration brings together healthcare professionals, hospitals, community organizations, and residents to eliminate barriers to quality healthcare on Hawaii Island. The main goal of HIBC is to empower residents to take control of their health and wellness. Part of that process is allowing patients to have easy access to their EHRs. HIBC is working with healthcare providers and clinicians to assist them in integrating health IT into their practices.

Since communication is local, the HIBC adapted a program that is uniquely Hawaiian. Its concept, according to Susan Hunt, chief executive officer of the HIBC, drew on the traditional Hawaiian land divisions, or ahupua'a: wedge-shaped areas running from the mountains to the sea, following natural watershed boundaries.

Ms Hunt noted that the key to their success has been recruiting participants to embrace EHRs. That began with the primary care providers. At the start of the program, approximately one-half of their 184 primary care providers were using EHRs at a "meaningfully useful" level. One year later, 86% had adopted the use of EHRs.

Equally important, patients have joined the program in record numbers and the registry for diabetes and cardiovascular disease has grown steadily since the beginning of the year. That increase coincides with improvements in various diabetic and cardiovascular outcomes.

To create HIBC, leaders in the public and private sector joined together, including federal, state, and private hospitals, the Native Hawaiian Health Care System, the Hawaii Island Care Coordination Services, the National Kidney Foundation of Hawaii, and the state's largest health plans (eg, AlohaCare, Medicaid). Together, they are working on a variety of ways to improve the flow of information to: 1) improve healthcare; 2) improve health; and 3) reduce costs.

A key component of HIBC is innovation. Ms Hunt talked about a pilot project that started in 2011 that involves 10 offices that use a software program (more info at www.cozeva.com) as well as other measures to identify gaps in care and to obtain real-time feedback on quality care process measures. The success of that project has led to the adoption of Cozeva by all offices in the program.

The pilot programs seen in Montana as well as the various Beacon communities show that the use of EHRs and telemonitoring can improve both healthcare and patients' health, with the potential for reduced overall costs.

Ms Hunt ended her presentation by stating that HIBC is truly a community. Working together, the group has had great success in a number of other areas, as shown in the **Table**.

Western New York Beacon Community

The Western New York Beacon Community (www.wnyhealthelink.com/beacon) has been at the forefront of improving clinical outcomes and safety in patients with diabetes through the use of healthcare IT and health information exchange. Their efforts to improve care of patients with diabetes in the community were exemplified by Beacon project director Bob Hoover, who told the audience about "Kenneth," a 54-year-old patient who participated in one of their telemonitoring pilot programs (see **Patient Perspective** box).

One of the major advantages of telemonitoring is that it requires the patient to be compliant. Otherwise, the patient gets a phone call from a health professional to ask if there is a problem. The telemonitoring program currently has over 100 high-risk patients who have equipment in their homes to monitor glucose, blood pressure, and body weight. These patients belong to 1 of 3 participating home healthcare agencies and 1 of 6 practices. The data are monitored by nurses and other healthcare professionals who can report critical information to treating physicians if necessary. The data are also available through virtual health records to any of the participating patients' healthcare providers.

This program was initiated using funding from the Beacon Program. According to Mr Hoover, once that funding stops, healthcare providers in the community plan to continue to fund the telemonitoring program, based on its success.

The Western New York Beacon Program is a collaborative effort between HEALTHeLINK (regional health information organization for Western New York) and more than 40 partner organizations that are marrying clinical technology with clinical transformation to improve diabetes care at the practice level. So far, the involved organizations have embraced the use of EHRs. According to Mr Hoover, there has been a 650% increase in the usage of virtual health records from December 2010 to December 2011.

Mr Hoover ended his presentation with data from the diabetes registry they now have in place. At last count, there were 91 practices in the registry. Data from 3 phases of the program show a reduction in the percentage of patients that have poorly controlled diabetes and an increase in the percentage of patients that have control of LDL-C in just one 3-month period.

Patient Perspective: "Kenneth," 54-Year-Old Participant in Telemonitoring Pilot Program

"Telemonitoring has worked well for me because I know someone is monitoring me daily. If I don't monitor, I know that the nurse through telemonitoring will call me, which gives me incentive and motivation to do it. In the last few months my A1C has decreased remarkably and has been the best it has been in many, many years. My blood pressure has also decreased from 150s to 130s and although slower than I might like, my weight has decreased also. Nurses from the Visiting Nurses Association and Elmwood Health Center offer me encouragement, support, and assistance in obtaining supplies and medications. I see all of this as one big puzzle and without all of the pieces it falls apart. I have maintained better blood sugar control, blood pressure control, and weight loss since beginning on telemonitoring."

Concluding Remarks

Creating programs that allow patients, doctors, and providers to interact via electronic means provides benefits to all parties. The pilot programs seen in Montana as well as the various Beacon communities show that the use of EHRs and telemonitoring can improve both healthcare and patients' health, with the potential for reduced overall costs. **EBDM**

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Reprinted from A Special Report on Diabetes Innovation 2012. *Am J Manag Care*. 2012;18:14-16.

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Value-Based Care: What Do the Providers, Purchasers, and Payers Think?

A panel discussion at Diabetes Innovation 2012 entitled "Purchaser, Provider, and Payer Collaboration to Advance Value-Based Care in Diabetes" was moderated by Jeremy J. Nobel, MD, MPH, medical director at the Northeast Business Group on Health. Panelists included Jessica DiLorenzo, implementation leader at the Healthcare Incentives Improvement Institute; Robert Galvin, MD, chief executive officer of Equity Healthcare; and Thomas G. Lundquist, MD, MMM, FAAP, FACPE, president and chief executive officer of AnewCare Accountable Care Organization (ACO) and chief clinical integration officer of Integrated Health Solutions Network.

Moderator: **Where are we in terms of value-based payment? Where are we going, what's getting in the way, and how do we move faster?**

Jessica DiLorenzo of the Healthcare Incentives Improvement Institute addressed the question by referring to a program that they started 10 years ago called Bridges to Excellence. The program recognizes and rewards providers and clinicians who have demonstrated high-quality care in the area of diabetes and other chronic conditions. The pay-for-performance program was associated with better intermediate outcome measures (eg, hemoglobin A1C, blood pressure) and lower healthcare expenditures (eg, fewer hospital and emergency visits). Based on the results, there is a strong connection between quality care and lower costs.

Dr Thomas G. Lundquist of AnewCare ACO provided his perspective by stating that as CEO of an ACO, he is optimistic that the new medical home model that focuses on the patient and the primary care physician will greatly benefit patients, especially patients with diabetes. Dr Lundquist acknowledged, however, that the model still has to be fine-tuned and that some of the payment methods still need to be worked out. According to Dr Lundquist, the model requires a new way of looking at heathcare—one that is community-based rather than disease-based.

The medical home model that is starting to appear in many systems is in his opinion the future of healthcare. Dr Lundquist said, "I think it is a very exciting time in healthcare, especially for payment reform, despite the fact that it gives many of our colleagues in medicine tremendous heartburn." The medical home model will, in Dr Lundquist's opinion, transform the payment system and engage the communities with the providers to create a whole new healthcare platform.

Dr Robert Galvin of Equity Healthcare reiterated what Ms DiLorenzo said about the Bridges to Excellence program being an excellent way to improve quality of care and reduce costs. Dr Galvin noted that while working at General Electric as an employer program director, he asked a diabetologist what he could do to help the diabetologist. The diabetologist stated that the payment system was set up so that if he provided better quality care, he made less money, and if he did a good job and his patients required fewer hospitalizations, hospitals were not happy. The diabetologist then said, "Bob, solve that problem—that is what you can do." According to Dr Galvin, Bridges to Excellence and similar programs have shown that people are starting to find ways to reward clinicians for doing their job well. That is, people understand that fee-for-value instead of fee-for-service is the way of the future. Dr Galvin also acknowledged, however, that while we all want to get to that system, it will take time and we are entering uncharted territory; it is difficult to know where the system is heading. It is not currently known where "true north" is, noted Dr Galvin. He is also concerned that while we all want to move toward the pay-for-value medical payment model, the new plan must be user friendly. If the plan requires more checks and balances, and more regulations, and more involvement of outside parties, clinicians will feel demoralized and less involved in the care of patients with diabetes.

If the plan requires more checks and balances, and more involvement of outside parties, clinicians will feel demoralized and less involved in the care of patients with diabetes.

Dr Galvin also noted that there are 160 million people using employer-based health plans. A group called Catalyze Payment Reform (CPR) is working with employers to give them a voice. CPR knows that each area and each company is different; an ACO may be perfect for a community in Tennessee, but a different model may be needed for a company in Boston. Dr Galvin said that CPR is encouraging private companies to adopt a fee-for-quality care model because it is in the best interests of the respective companies. Dr Galvin noted that the private sector is open to the concept of adopting plans that are flexible to meet the needs of different patients, different locations, and different companies; however, he is concerned that the public sector (ie, Medicare) is behind in that regard. More importantly, Dr Galvin is concerned that the private sector and the public sector are not coordinating as well as they should. Challenges may arise in the future if the private and public sectors adopt pay-for-quality payment systems, but implement these systems in different and/or incompatible ways.

On a positive note, Dr Galvin said he recently checked in with various chief executive officers and presidents of major companies; he noted that these leaders understand that it is their responsibility to keep their employees healthy and to create environments that promote healthy choices. Whether that means, for example, changes in the cafeteria menu or incentives to lower monthly fees will vary with each company; however, leaders are taking notice. Dr Galvin is excited about the change in thinking at the top level of management.

Audience member: **Some programs are converting from a pay-for-performance program to a more value-based, total cost of care incentive program and they are experiencing some "growing pains" during the transition. Are there ways to avoid these problems?**

Dr Lundquist addressed this question by acknowledging that there will be growing pains during this transition; one idea he proposed was to allow doctors and medical professionals to have more control over the money coming in so that they can distribute it in a way that best suits the community and medical team. That will require good metrics to measure success and will take a new way of looking at how funding is controlled. "If the right quality metrics and efficiency metrics are in place, we can do the right things, at the right time, for the right patient, with the right touch, and that will create a more efficient system," stated Dr Lundquist. **EBDM**

Reprinted from A Special Report on Diabetes Innovation 2012. *Am J Manag Care*. 2012;18:19-20.

"If the right quality metrics and efficiency metrics are in place, we can do the right things, at the right time, for the right patient, with the right touch, and that will create a more efficient system."

—Thomas G. Lundquist, MD, MMM
President/CEO, AnewCare ACO
Chief Clinical Integration Officer
Integrated Health Solutions Network

For appropriate patients with type 2 diabetes

NOW AVAILABLE: JANUMET XR

Same powerful efficacy as JANUMET (sitagliptin/metformin HCl), now available with convenient **once-daily** dosing

JANUMET XR is indicated, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin extended-release is appropriate.

JANUMET XR should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

JANUMET XR 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 of developing pancreatitis while taking JANUMET XR.

Selected Important Risk Information

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, JANUMET XR should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions]*.

JANUMET XR is contraindicated in patients with renal impairment (serum creatinine levels ≥1.5 mg/dL in men and ≥1.4 mg/dL in women or abnormal creatinine clearance); hypersensitivity to metformin hydrochloride; acute or chronic metabolic acidosis, including diabetic ketoacidosis; or history of a serious hypersensitivity reaction to JANUMET XR or sitagliptin, such as anaphylaxis or angioedema.

Temporarily discontinue JANUMET XR in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. Avoid use in patients with hepatic disease. Temporarily discontinue for intercurrent serious conditions, infection, or surgery.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis.

Measure renal function before initiation of therapy with JANUMET XR and at least annually thereafter. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Lactic acidosis is fatal in approximately 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking JANUMET XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiating JANUMET XR, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JANUMET XR and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUMET XR.

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving JANUMET XR.

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, JANUMET XR should be temporarily discontinued at the time of or before the procedure, withheld for 48 hours subsequent to the procedure, and reinstituted only after renal function has been re-evaluated and found to be normal.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET XR or any other antidiabetic drug.

Use With Medications Known to Cause Hypoglycemia

Sitagliptin

When sitagliptin was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or insulin. Therefore, patients also receiving insulin or an insulin secretagogue (eg, sulfonylurea) may require a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 16.4% (0.82 episodes/patient-year) for sitagliptin 100 mg in combination with metformin and glimepiride, 0.9% (0.02 episodes/patient-year) for placebo in combination with metformin and glimepiride, 8.2% (0.61 episodes/patient-year) for placebo in combination with metformin and insulin, and 15.3% (0.98 episodes/patient-year) for sitagliptin in combination with metformin and insulin.

Adverse reactions with sitagliptin in combination with metformin and rosiglitazone through Week 18 were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54 they were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET XR, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUMET XR.

In clinical studies, the most common adverse reactions reported, regardless of investigator assessment of causality, in ≥5% of patients treated with either sitagliptin in combination with metformin or placebo were as follows: diarrhea (7.5% vs 4.0%), upper respiratory tract infection (6.2% vs 5.1%), and headache (5.9% vs 2.8%). In patients treated with sitagliptin in combination with metformin and sulfonylurea or placebo in combination with metformin and sulfonylurea: hypoglycemia (16.4% vs 0.9%) and headache (6.9% vs 2.7%). In patients treated with sitagliptin in combination with metformin and insulin or placebo in combination with metformin and insulin: hypoglycemia (15.3% vs 8.2%). Other adverse events with an incidence of ≥5% included nasopharyngitis for sitagliptin monotherapy and hypoglycemia (13.7% vs 4.9%), diarrhea (12.5% vs 5.6%), and nausea (6.7% vs 4.2%) for extended-release metformin vs placebo when added to glyburide.

Please see the adjacent Brief Summary of the Prescribing Information, including the Boxed Warning about lactic acidosis.

For more information, please visit JanumetXR.com

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ONCE-DAILY

Janumet® XR

(sitagliptin and metformin HCl extended-release) tablets

Brief Summary of Prescribing Information

JANUMET® XR (sitagliptin and metformin HCl extended-release) Tablets

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, JANUMET XR should be discontinued and the patient hospitalized immediately.
[See Warnings and Precautions.]

Important Limitations of Use. JANUMET XR should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. JANUMET XR 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 the development of pancreatitis while using JANUMET XR. *[See Warnings and Precautions.]*

CONTRAINDICATIONS

JANUMET XR is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia *[see Warnings and Precautions].*
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to JANUMET XR or sitagliptin, such as anaphylaxis or angioedema. *[See Warnings and Precautions; Adverse Reactions.]*

WARNINGS AND PRECAUTIONS

Lactic Acidosis. *Metformin hydrochloride.* Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET XR and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking JANUMET XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. JANUMET XR treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, JANUMET XR should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking JANUMET XR, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, JANUMET XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (in controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. *[See Drug Interactions; Clinical Pharmacology.]* The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis.

Patients should be educated to promptly report these symptoms to their physician should they occur. If present, JANUMET XR should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of JANUMET XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking JANUMET XR do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking JANUMET XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. *[See Contraindications.]*

Pancreatitis. There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiation of JANUMET XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUMET XR should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR.

Impaired Hepatic Function. Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Assessment of Renal Function. Metformin and sitagliptin are substantially excreted by the kidney.

Metformin hydrochloride. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, JANUMET XR is contraindicated in patients with renal impairment.

Before initiation of JANUMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Sitagliptin. There have been postmarketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with JANUMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Vitamin B_{12} Levels. In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JANUMET XR and any apparent abnormalities should be appropriately investigated and managed. *[See Adverse Reactions.]*

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Alcohol Intake. Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving JANUMET® XR (sitagliptin and metformin HCl extended-release) tablets.

Surgical Procedures. Use of JANUMET XR should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes. A patient with type 2 diabetes previously well controlled on JANUMET XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, JANUMET XR must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia. *Sitagliptin.* When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin *[see Adverse Reactions].* Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia *[see Dosage and Administration].*

Metformin hydrochloride. Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

Concomitant Medications Affecting Renal Function or Metformin Disposition. Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion *[see Drug Interactions]*, should be used with caution.

Radiologic Studies with Intravascular Iodinated Contrast Materials. Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography [CT] scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin *[see Contraindications].* Therefore, in patients in whom any such study is planned, JANUMET XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure, and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States. Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JANUMET XR therapy, the drug should be promptly discontinued.

Loss of Control of Blood Glucose. When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold JANUMET XR and temporarily administer insulin. JANUMET XR may be reinstituted after the acute episode is resolved.

Hypersensitivity Reactions. There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. *[See Adverse Reactions.]*

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUMET XR.

Macrovascular Outcomes. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET XR or any other anti-diabetic 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.

Sitagliptin and Metformin Immediate-Release Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise. The most common (≥5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and metformin immediate-release were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise were diarrhea (sitagliptin + metformin immediate-release [N=372], 7.5%; placebo [N=176], 4.0%), upper respiratory tract infection (6.2%, 5.1%), and headache (5.9%, 2.8%).

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release Alone. In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin immediate-release regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin immediate-release, 1.9%; placebo and metformin immediate-release, 2.5%).

Gastrointestinal Adverse Reactions. The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin immediate-release were similar to those reported for patients treated with metformin immediate-release alone.

Table 1: Pre-selected Gastrointestinal Adverse Reactions (Regardless of Investigator Assessment of Causality) Reported in Patients with Type 2 Diabetes Receiving Sitagliptin and Metformin Immediate-Release

	Number of Patients (%)					
	Study of Sitagliptin and Metformin Immediate-Release in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Immediate-Release Alone	
	Placebo	Sitagliptin 100 mg once daily	Metformin Immediate-Release 500 mg or 1000 mg twice daily*	Sitagliptin 50 mg bid + Metformin Immediate-Release 500 mg or 1000 mg twice daily*	Placebo and Metformin Immediate-Release ≥1500 mg daily	Sitagliptin 100 mg once daily and Metformin Immediate-Release ≥1500 mg daily
	N=176	N=179	N=364	N=372	N=237	N=464
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.2)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11 (3.0)	9 (3.8)	10 (2.2)

*Data pooled for the patients given the lower and higher doses of metformin.
†Abdominal discomfort was included in the analysis of abdominal pain in the study of initial therapy.

Sitagliptin in Combination with Metformin Immediate-Release and Glimepiride. In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and glimepiride (sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia (see Table 2) and headache (6.9%, 2.7%).

Sitagliptin in Combination with Metformin Immediate-Release and Rosiglitazone. In a placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and rosiglitazone (sitagliptin, N=181; placebo, N=97), the adverse reactions reported regardless of investigator assessment of causality

through Week 18 in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54, the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

Sitagliptin in Combination with Metformin Immediate-Release and Insulin. In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 2).

Hypoglycemia. In all (N=5) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required although most (77%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When the combination of sitagliptin and metformin immediate-release was co-administered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and metformin immediate-release co-administered with a sulfonylurea or with insulin (Table 2).

Table 2: Incidence and Rate of Hypoglycemia* (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Clinical Studies of Sitagliptin in Combination with Metformin Immediate-Release Co-administered with Glimepiride or Insulin

Add-On to Glimepiride + Metformin Immediate-Release (24 weeks)	**Sitagliptin 100 mg + Metformin Immediate-Release + Glimepiride**	**Placebo + Metformin Immediate-Release + Glimepiride**
	N=116	N=113
Overall (%)	19 (16.4)	1 (0.9)
Rate (episodes/patient-year)†	0.82	0.02
Severe (%)‡	0 (0.0)	0 (0.0)
Add-On to Insulin + Metformin Immediate-Release (24 weeks)	**Sitagliptin 100 mg + Metformin Immediate-Release + Insulin**	**Placebo + Metformin Immediate-Release + Insulin**
	N=229	N=233
Overall (%)	35 (15.3)	19 (8.2)
Rate (episodes/patient-year)†	0.98	0.61
Severe (%)‡	1 (0.4)	1 (0.4)

*Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required: Intent-to-treat population.

†Based on total number of events (i.e., a single patient may have had multiple events).

‡Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin immediate-release alone, and 1.6% in patients given sitagliptin in combination with metformin immediate-release. In patients with type 2 diabetes inadequately controlled on metformin immediate-release alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo.

In the study of sitagliptin and add-on combination therapy with metformin immediate-release and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on sitagliptin and 1.0% in patients given add-on placebo.

Vital Signs and Electrocardiograms. With the combination of sitagliptin and metformin immediate-release, no clinically meaningful changes in vital signs or in electrocardiogram parameters (including the QTc interval) were observed.

Pancreatitis. In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). *[See Warnings and Precautions.]*

Sitagliptin. The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Metformin Extended-Release. In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common (>5% and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs. 4.9%), diarrhea (12.5% vs. 5.6%), and nausea (6.7% vs. 4.2%).

Laboratory Tests

Sitagliptin. The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin immediate-release (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs. placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride. In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. *[See Warnings and Precautions.]*

Postmarketing Experience. Additional adverse reactions have been identified during postapproval use of sitagliptin with or without metformin, and/or in combination with other antidiabetic medications. Because these reactions 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.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome *[see Warnings and Precautions]*; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Indications and Usage; Warnings and Precautions]*; worsening renal function, including acute renal failure (sometimes requiring dialysis) *[see Warnings and Precautions]*; constipation; vomiting; headache.

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors. Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with JANUMET® XR (sitagliptin and metformin HCl extended-release) tablets, as the risk of lactic acidosis may increase.

Cationic Drugs. Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

The Use of Metformin with Other Drugs. Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET XR the patient should be closely observed to maintain adequate glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy. *Pregnancy Category B.*

JANUMET® XR (sitagliptin and metformin HCl extended-release) tablets. There are no adequate and well-controlled studies in pregnant women with JANUMET XR or its individual components; therefore, the safety of JANUMET XR in pregnant women is not known. JANUMET XR should be used during pregnancy only if clearly needed.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to JANUMET XR while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUMET XR by calling the Pregnancy Registry at 1-800-986-8999.

No animal studies have been conducted with the combined products in JANUMET XR to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin. Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Metformin hydrochloride. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, metformin hydrochloride should not be used during pregnancy unless clearly needed.

Nursing Mothers. No studies in lactating animals have been conducted with the combined components of JANUMET XR. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin or metformin are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET XR is administered to a nursing woman.

Pediatric Use. Safety and effectiveness of JANUMET XR in pediatric patients under 18 years have not been established.

Geriatric Use. *JANUMET XR.* Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. *[See Warnings and Precautions; Clinical Pharmacology.]*

Sitagliptin. Of the total number of subjects (N=3884) in premarketing Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride. Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. *[See Contraindications; Warnings and Precautions; Clinical Pharmacology.]*

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Can Financial Incentives Improve Self-Management Behaviors?

Kim Farina, PhD

For many health conditions and chronic diseases, positive outcomes are tightly linked to patient self-management behaviors. Yet, patients struggle to successfully self-manage their conditions.

The field of behavioral economics has grown over the years and is increasingly being applied by health policy makers and providers to improve health-related behaviors and decision making. Behavioral economists are partnering with healthcare professionals to study the rationale behind behavioral decision making and to use this information to develop methods for reducing unhealthy behaviors (eg, smoking or poor adherence to medication). Presenters at the "Should We Pay People to Change Their Behavior? Behavioral Economics and Diabetes" symposium of the 72nd Scientific Sessions of the American Diabetes Association discussed how behavioral economics can enhance diabetes management.

Incentivizing Through Reinforcement

Nancy Petry, PhD, professor of medicine, University of Connecticut Health Center, shared lessons learned from the field of substance abuse treatment during her presentation, "Moving From Behavioral Economic Theory to Medical Decisions." Incentive intervention programs rely on the promise of a tangible reinforcement reward for positive behavioral change. This technique has had proven success among substance abusers and accumulating evidence supports its use to encourage healthy behaviors (eg, weight loss and adherence to medication and exercise) among other populations. The US Department of Veterans Affairs (VA) is so convinced of its efficacy for substance abuse treatment that it has called for nationwide implementation of reinforcement interventions.

The concept of behavior modification through reinforcement is nothing new, Dr Petry explained. "Reinforcers are used to change behaviors in everyday settings, for example, employee salaries, commission, and awards." Its underlying principles are: 1) frequent monitoring of a specific target behavior, 2) providing tangible positive reinforcement each time the target behavior occurs, and 3) withholding reinforcement if the target behavior does not occur.

"In terms of diabetes prevention and treatment," stated Dr Petry, "there are a lot of potential applications of these techniques." Improved attendance at clinic visits or group education sessions, self-monitoring of blood glucose, and adherence to medication and lifestyle changes are just some of the potential goals that can be supported.

"Reinforcement interventions can be powerfully effective in changing behaviors. The challenge is to effectively adapt and apply these techniques to improve patient outcomes in both the short and long term, while being cognizant of costs and patient and provider burden," said Dr Petry.

During his presentation "Behavioral Economic Interventions in Obesity, Smoking Cessation, and Diabetes," Kevin Volpp, MD, PhD, professor of medicine and healthcare management, Perelman School of Medicine and the Wharton School, University of Pennsylvania, and staff physician, Philadelphia VA Medical Center, explained that new technology is enabling incentive programs to be executed remotely. Dr Volpp's group is exploring the usefulness of what he calls automated hovering.

Physicians don't know what their patients are doing outside the clinics and do not have effective tools to influence the decisions patients make. "So, in a general sense, we need to figure out a more effective way of hovering over patients in a way that is well received," remarked Dr Volpp. This may be achieved, he explained, through the application of a variety of devices and platforms. In one program, participants are given a scale that is linked to a server. The server automatically calculates an incentive, delivers information to the participant, and initiates an electronic fund transfer to the participant when appropriate.

Dr Volpp emphasized the importance of considering decision errors during the design of any health management improvement program. Humans tend to be wired for immediate gratification and this leads to decision errors. "It is very hard to say no to something that is right in front of you and very present as opposed to some future increased risk," Dr Volpp said.

Ignoring the elements that underlie decision errors can lead to ineffective programs that may worsen outcomes and certainly increase costs. "There are a lot of mistakes people make and they are easy to make," cautioned Dr Volpp. "You can spend millions of dollars on a program that doesn't work."

Redesigning Health Insurance to Change Behavior

High copays and increased patient cost sharing decrease the use of preventative medicine and worsen socioeconomic disparities in healthcare utilization. Value-based insurance design (VBID) is being purported as an innovative approach to healthcare financing that increases utilization of high-value healthcare services while reducing that of low-value services. Allison Rosen, MD, MPH, ScD, associate professor, department of quantitative health sciences, University of Massachusetts Medical School, discussed the merits of VBID during her presentation "Redesigning Health Insurance to Change Behavior."

Practically speaking, implementation of many of the diabetes management improvement programs being developed would require a complete rework of primary care office flow at significant time-cost effort for the practice.

The question that always comes up, according to Dr Rosen, is whether VBID saves money; however, the more appropriate question is whether VBID improves patient outcomes (or health returns) relative to every dollar spent. For VBID to save money, the cost of increased utilization of high-value services can be subsidized by medical cost offsets, enhanced productivity, decreased disability costs, and higher cost sharing for services of lower value. Dr Rosen suggests that return on investment can be maximized by strategic targeting. For example, return on investment for measures that prevent adverse events will be greater if they are targeted to those most likely to have an event rather than the general population.

Evidence shows that as barriers to quality healthcare decrease, utilization increases. Those increases are modest, admits Dr Rosen, ranging from 1% to 7%, and their clinical significance has yet to be determined. However, she noted, "If you are getting some increases, at least you are not spending the money on other services that are getting you nothing or perhaps decreasing health." To date, most private-sector VBID programs have focused on removing barriers to evidence-based services for chronic disease. There is a growing recognition that improving value in healthcare will require increasing barriers to low value services as well.

A Primary Care Perspective

Michael Parchman, MD, MPH, director, MacColl Center for Health Care Innovation, talked about the building blocks required for high-performing primary care during his presentation "The Behavioral Economics of Improving Diabetes Management—A Primary Care Perspective."

Interventions being developed to improve diabetes care delivery need to be integrated with primary care, where most diabetes care takes place, explained Dr Parchman. "Too often, these programs are completely isolated from primary care or are not designed to work in the context of primary care," he stated. Practically speaking, implementation of many of the diabetes management improvement programs being developed would require a complete rework of primary care office flow at significant time-cost effort for the practice. **EBDM**

Funding Source: None.

Author Disclosure: The author reports receiving payment for involvement in the preparation of this manuscript with no associated conflicts of interest.

Authorship Information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

New Approaches to Defining and Measuring the Quality of Healthcare

Kim Farina, PhD

The widespread adoption of electronic health records is facilitating implementation of quality improvement measures across healthcare. As the US healthcare system becomes more quality focused, current methods of defining and measuring quality have come under scrutiny. Diabetes has been a major focus of early quality improvement initiatives. The speakers of a symposium titled "What Are the Ideal Quality Measures for Diabetes Care?" at the 72nd Scientific Sessions of the American Diabetes Association discussed the current state of quality measurement in diabetes.

"It is impossible to know how well we are doing without measuring something," said Sandeep Vijan, MD, MS, associate professor of internal medicine, University of Michigan. "There is little doubt that quality measurement is important and reasonably effective." He explained that systems do better in those areas that are measured and reported, with financial incentives clearly driving behavior. "What you measure becomes a driver of what you do," said Dr Vijan.

Quality measures may take the form of process measures of whether an action was performed (eg, glycated hemoglobin [A1C] measurement or eye examination), intermediate outcome measures (eg, A1C <7.0), or outcome measures (eg, hospital admissions for myocardial infarction). Defining quality is a significant challenge and prone to a number of problems.

Thus far, quality measures have generally been based on interpretations of trial evidence by clinical experts. This method poses a problem because the targets for continuous measures (eg, A1C and blood pressure) are based on mean clinical trial results. "If the mean A1C of a trial is 7.0%, then 50% of patients in the trial received less than optimal clinical care," stated Dr Vijan. Furthermore, intermediate outcomes are not always tightly linked to patient-important outcomes.

Often, quality measures are falsely dichotomized. For example, if A1C was set as a therapeutic target, a measurement of 7.1% would be equally unacceptable as a measurement of 13%. Dr Vijan raised concern that this type of quality measure will drive treatment of patients with milder elevations—who are more likely to reach target—rather than those with severe elevations. Without considering each patient's underlying risk profile, he said, "These types of measures provide a potential incentive to overtreat and possibly harm patients."

After reviewing some of the problems with existing quality measures, Dr Vijan spoke about new efforts to improve the science of quality measurement. According to him, quality measures should be based on rigorous interpretation of the evidence, incorporate reasonable exceptions, reward appropriate actions, consider how much benefit is gained, incorporate patient preference, and consider benefit and value. To date, patient involvement in defining and measuring quality has been very limited.

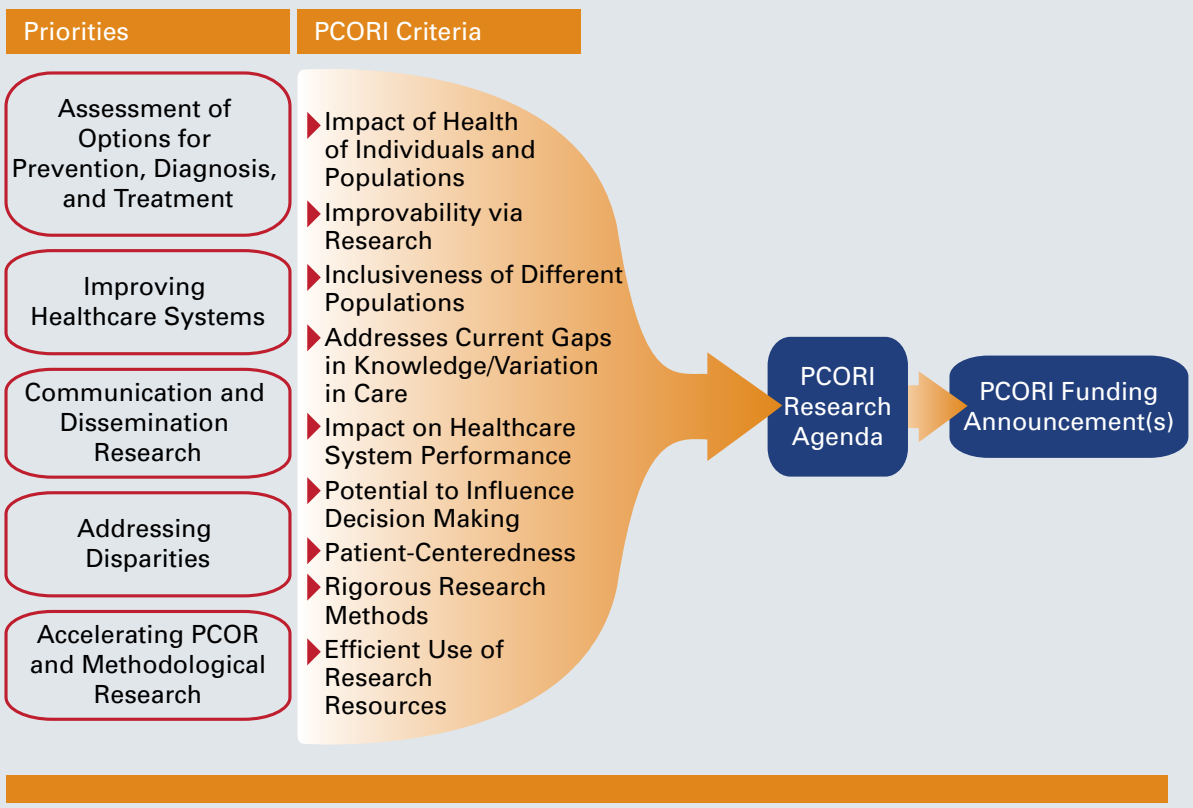
One potential improvement on the dichotomous quality measure is the linked action measure, also called a clinical action measure.[1] Linked action measures give credit for appropriate actions. For example, for a patient who is above goal (A1C >8 or systolic blood pressure >140), the provider would get credit if: new medication is added, existing dose is increased, or the therapeutic target is achieved within a certain time frame. This measure allows inclusion of reasonable exceptions. Linked action measures have already been developed, specified, and tested. Dr Vijan shared published and unpublished data demonstrating his institution's successful use of electronic medical records and linked action measures: 85% of providers from the system of more than 1 million patients were taking appropriate action or maintained patients at therapeutic target.[2]

The next step, explained Dr Vijan, is to develop and test patient-selected, personalized measures of quality. To exemplify the importance of patient preference in measuring quality, he presented data from a cost-effectiveness analysis of intensive glucose control among patients 65 years or older that considered patient preference.[3] Intensive glycemic control has been shown to be cost-effective among patients younger than 50 years. The results of this study suggest that among older patients, factoring in their patient preferences decreases quality-adjusted life-years of intensive glycemic control with insulin and makes treatment more harmful than beneficial. Factoring in patient preference regarding oral agents reduced cost-effectiveness. This type of study demonstrates how significantly patient experience can influence value.

Measuring Quality of Care for Patients With Multiple Morbidities

Cynthia Boyd, MD, MPH, associate pro-

Figure. Framework for the Translation of the Patient-Centered Outcomes Research Institute's (PCORI's) National Priorities Into the Research Agenda



Through a process that sought public input, PCORI identified 5 National Priorities and developed a framework for translating these priorities into a research agenda. The resulting Research Agenda delineates specific research areas within each priority that each address unmet stakeholder needs across the healthcare system in making personalized healthcare decisions.

Source: Patient-Centered Outcomes Research Institute. National priorities for research and research agenda. http://www.pcori.org/assets/PCORI-National-Priorities-and-Research-Agenda-2012-05-21-FINAL.pdf. Published May 2012. Accessed July 10, 2012.

fessor of medicine, division of geriatric medicine and gerontology, Johns Hopkins University School of Medicine, presented "Measuring Quality of Care in Complex Patients." Multimorbidity is common—43% of Medicare enrollees 65 years or older have 3 or more chronic conditions.[4,5]

Decisions for patients with multimorbidity are complex. Most clinical practice guidelines are developed from a single-disease perspective, making them difficult to apply to patients with complex medical histories.[6]

The results of this study suggest that among older patients, factoring in their patient preferences decreases quality-adjusted life-years of intensive glycemic control with insulin and makes treatment more harmful than beneficial.

Dr Boyd discussed how clinicians need guidelines that help them navigate the treatment of patients living with multiple diseases or chronic conditions. Boyd explained that to best care for people with multimorbidities, clinicians need guidance on how to: maximize use of therapies likely to benefit patients with multimorbidity; minimize use of therapies unlikely to benefit or likely to harm patients with multimorbidity; and incorporate patient preferences and values regarding burdens, risks, and benefits.

The National Quality Forum has engaged its Consensus Development Process (CDP) toward a measurement framework that will assess the efficiency of care (defined as quality and cost) provided to individuals with multiple chronic conditions (MCCs).[7] The framework defines MCCs, identifies high-leverage measurement areas for the population with MCCs (to mitigate unintended consequences and measurement burden), presents a conceptual model that serves as an organizing structure for identifying and prioritizing quality measures, and offers guidance on methodological and practical measurement issues.

The framework is centered on patient and family goals and preferences for care and will allow for patient prioritization of disease-specific measures based on individual needs, preferences, and discussions with healthcare providers. Non–disease-specific measures that apply to all patients regardless of condition also factor into the model. Measurements fall under specific domains that are aligned with priorities of the US Department of Health and Human Services National Quality Strategy: person- and family-centered care, health and well-being, patient safety, effective communication and care, effective prevention and treatment, and affordable care.[8]

Patient-Centered Outcomes Research Institute

In recognition of the need to integrate patient preferences into the planning and execution of health research, the American Recovery and Reinvestment Act implemented the Patient-Centered Outcomes Research Institute (PCORI). According to its mission statement, PCORI "helps people make informed healthcare decisions—and improves healthcare delivery and outcomes—by producing and promoting high integrity, evidence-based information—that comes from research *guided by patients,* caregivers, and the broader health care community."

In May 2012, PCORI issued its National Priorities and Research Agenda, which lists 5 National Priorities: assessment of options for prevention, diagnosis, and treatment; improvement of healthcare systems; research on communication and dissemination; reduction of disparities; and acceleration of PCOR and methodological research (**Figure**).[9] That same month, PCORI issued its first 4 funding announcements.

Through its patient-driven research funding programs, PCORI aims to align research questions and methods with patient needs. According to Joe Selby, MD, MPH, PCORI, who presented "Insights on Quality of Care From Institutional Decision Makers," PCORI stipulates patient and stakeholder engagement from the earliest phases of study design through the final stages of research to: gain better understanding of the choices patients face, ensure that all elements of study design are truly relevant, keep research on track, and avoid changes in course that undermine the utility of the study to patients. Results of PCORI-funded studies will be disseminated to provide patients and providers with supplementary information to improve decision making. **EBDM**

Funding Source: None.

Author Disclosure: The author reports receiving payment for involvement in the preparation of this manuscript with no associated conflicts of interest.

Authorship Information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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Reexamining the Roles of Diabetes Educators

Kim Farina, PhD

The role of the diabetes educator is very different from what it was 5 years ago, Linda Siminerio, RN, PhD, CDE, associate professor of medicine, University of Pittsburgh, executive director, University of Pittsburgh Diabetes Institute, told attendees of the "Healthcare Delivery is Changing: Where Do Diabetes Educators Fit?" symposium at the 72nd Scientific Sessions of the American Diabetes Association. With medical reform on the horizon and new educational initiatives being implemented for patients discharged to home after hospitalization, she predicted that more changes will come for diabetes educators.

A common theme throughout the annual meeting was that effective diabetes self-management plays a critical role in positive outcomes. Patient self-care is becoming even more important as the numbers of people at risk for and diagnosed with diabetes increases while the number of physicians providing diabetes care wanes. Dr Siminerio calls for expansion of the roles of educators, nurses, pharmacists, and dieticians to the maximum allowed by licensing to help assuage the problem. With respect to di-

abetes care, diabetes educator support of patient self-management may be one of the most important roles these health professionals can play.

During a presentation titled "Can Patients Be Activated to Improve Self-Management Behavior?," Jessica Greene, PhD, associate professor, department of planning, public policy, and management, University of Oregon, talked about patient activation, how it is measured, and how diabetes educators can use it to individualize diabetes education strategies and facilitate patient self-management. Dr Greene discussed that by paying attention to patient activation, diabetes educators may improve outcomes and subsequently contain costs.

Patients who are activated are considered to have knowledge and skills competency for managing their own health. The extent of patient activation can be quantified with the patient activation measure (PAM).[1] PAM activation levels range from 1 to 4, with 1 being the lowest and 4 being the highest.

Patient activation is related to diabetes-related health outcomes and cost in cross-sectional studies, and in several intervention studies. Specifically, higher PAM levels were associated with certain healthy behaviors (eg, in physical activity and eating fruits and vegetables); appropriate use of healthcare; active chronic care self-management (eg, regular examinations for people with diabetes, keeping a diary of blood pressure readings); and better control of chronic conditions (eg, A1C reduction, fewer hospitalizations).[2] PAM predicted utilization and health outcomes 2 years into the future for patients with diabetes.[3] PAM is not only related to health outcomes, but to costs as well. A small number of long-term and prospective studies suggest patient activation can be increased and those increases are related to improvements in quality outcomes.

Not surprisingly, studies show that PAM levels vary from patient to patient. "Many of the behaviors we are asking people to do to self-manage chronic conditions are only done by those at the highest level of activation," said Dr Greene. Patients with lower activation levels become discouraged and overwhelmed when asked to take on the more complex and difficult behaviors. "If we start with behaviors more feasible for patients to take on, it has the potential to increase their ability to experience success," she explained. She suggests using activation levels to determine realistic *next steps* for individuals to take.

Dr Greene presented results from one study that supported the tailored-coaching approach.[4] Compared with a group receiving usual care, patients who received self-management coaching based on their level of activation had greater improvements over a 6-month period in: PAM, diastolic blood pressure, low-density lipoprotein cholesterol, medication adherence, reduced hospitalizations, and use of the emergency department (**Figure**). Dr Greene concluded, "Diabetes educators are well poised to improve patients' levels of activation, through tailoring education to patient activation and supporting skill development."

In a presentation titled "Should Diabetes Educators Be Care Managers in Primary Care?," Nadine Tomaino, RN, Med, CDE, practice-based care manager, University of Pittsburgh Medical Center (UPMC) Health Plan, talked about her experience as a diabetes educator in a patient-centered medical home (PCMH). Ms Tomaino spent the early part of her career working as a diabetes educator in a small community hospital. Now she functions as a practice-based care manager for the UPMC Health Plan. UPMC first started to realize the tremendous value of having certified diabetes educators (CDEs) in its physician practices about a decade ago. Since then, the UPMC Health Plan has steadily expanded the role to encompass practice-based case management. In 2010, UPMC Health Plan hired 27 practice-based nurse care managers at 44 of its physician practices. Continued expansion is planned throughout 2012. Currently, 2 full-time diabetes educators are employed to support 65 practice-based case managers. "We need to use our specialist CDEs strategically," stated Ms Tomaino.

Compared with non-PCMH practices, member medical costs decreased 4% (even with additional primary care physician office visits) and hospital readmissions decreased 13%...

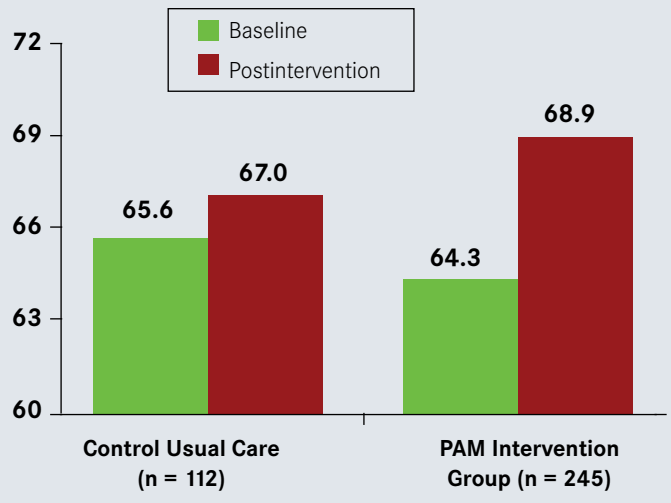
The chronic care/PCMH model gained attention in 2007. It incorporates 7 important principles: (1) personal physician point of contact, (2) physician-directed practice with a team leader, (3) whole-person orientation, (4) case management imbedded into practice, (5) coordinated and integrated care, (6) quality and safety, and (7) enhanced access to care.

"I have a number of tools available to me now within the practice that I did not have when I worked at a small community hospital education program," shared Ms Tomaino. For example, she now has direct access to physicians; electronic medical records; a database; patient claims data; medicine refill information; and alerts for overdue tests, physician visits, preventative screening, and admissions and discharges from hospital and emergency departments.

UPMC Health Plan data suggest that diabetes outcomes and cost benefits within its PCMH practices are better than those of the non-PCMH practices. Compared with non-PCMH practices, member medical costs decreased 4% (even with additional primary care physician office visits) and hospital readmissions decreased 13% among the PCMH practices from 2008 to 2009.

Ms Tomaino believes the keys to integrating successful self-management education into the PCMH are to have a motivated medical health system champion, as well as an active and engaged health team. Additionally, patients must be followed closely throughout every system of care. Barriers that prevent patient self-management should be addressed and educators need to think outside the box about how to deliver education in primary care and gain better access to patients. For example, she suggests asking, "How can I see this patient that never comes in? How can I get outside the practice to help this patient?" In her practice, this type of help may come with links to transportation services or social work. **EBDM**

Figure. Patient Activation Measure (PAM) Score After 6 Months of Tailored Coaching Versus Usual Care Coaching



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Funding Source: None.

Author Disclosure: The author reports receiving payment for involvement in the preparation of this manuscript with no associated conflicts of interest.

Authorship Information: Concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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 Printed in the U.S.A. 0313-00013774-3 March 2013

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