AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 07: Diabetes Mellitus

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,200 leads about potential topics has resulted in identification and tracking of about 1,900 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 500 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the eight topics for which (1) preliminary phase III data for drugs, at least phase II or equivalent data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled by October 27, 2013, in this priority area; *and* (3) we received six to eight sets of comments from experts between April 9, 2012, and October 29, 2013. (Nineteen topics in this priority area were being tracked in the system as of October 29, 2013.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present five summaries on six topics (indicated below by an asterisk) that emerged as having higher-impact potential on the basis of experts' comments and assessment of potential impact.

The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 07: Diabetes

Topic	High-Impact Potential
1. *Artificial pancreas device systems for treatment of diabetes	High
2. Buccal insulin (Oral-lyn) for treatment of type 1 or type 2 diabetes	No high-impact potential at this time
3. *Exenatide extended-release (Bydureon) for treatment of diabetes	Lower end of the high-impact-potential range
4. *ITCA 650 (exenatide continuous subcutaneous delivery) for treatment of type 2 diabetes	Lower end of the high-impact-potential range
5. *Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Moderately high
6. Metabolic (bariatric) surgery for resolution of type 2 diabetes in mildly obese and nonobese patients	High
7. *Ranibizumab (Lucentis) for treatment of diabetic macular edema	Lower end of the high-impact-potential range
8. Ultra-long-acting insulin (Tresiba, degludec; Ryzodeg degludec plus aspart) for treatment of type 1 or 2 diabetes	No high-impact potential at this time

Discussion

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia (elevated blood sugar). Diabetes-associated hyperglycemia results from dysfunction in either insulin secretion or insulin action or both. Most diabetes mellitus cases fall into one of two broad categories: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). According to a 2012 report from the U.S. Centers for Disease Control and Prevention (CDC), T1DM accounts for about 5% of all diagnosed cases and T2DM makes up the rest. The American Diabetes Association (ADA) fact sheet on diabetes reports that about 25.8 million children and adults in the United States, or 8.3% of the total population, have diabetes mellitus. About 18.8 million of these people have received a diagnosis of diabetes, but in the other 7 million, the disorder is undiagnosed. Furthermore, about 79 million people in the United States have prediabetes or are at risk of developing T2DM. ADA stated that clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older in 2010.

The Mayo Foundation for Medical Education and Research (MFMER) states that T1DM risk factors include family history of T1DM and presence of certain genetics, whereas T2DM risk factors include being overweight, having a body that primarily stores fat in the abdomen, having a family history of the disease, or having another form of diabetes mellitus such as prediabetes or gestational diabetes. Being African American, Hispanic, American Indian, or Asian American is also a risk factor for T2DM. According to CDC, diagnosed T2DM is seven times as prevalent in adults aged 65 years or older as it is among adults aged 20–44 years. MFMER recommends diabetes screening for overweight children and adults who have risk factors; adults older than age 45 years should undergo screening every 3 years. The latter recommendation is controversial; the U.S. Preventive Services Task Force concluded that the evidence was insufficient for recommending screening for adults with normal blood pressure.

T1DM results from an absolute deficiency of insulin secretion. ADA states that the disease is caused by destruction of the pancreatic beta cells and that this destruction is either immune mediated or idiopathic, with immune-mediated destruction accounting for the majority of cases. T1DM can occur at any age but is most often diagnosed in children, adolescents, or young adults; as such, it is often referred to as juvenile-onset diabetes. MFMER states that all patients with T1DM require insulin therapy.

T2DM hyperglycemia is a result of insulin resistance or a diminished response to insulin. ADA states that patients with T2DM also often have a relative insulin deficiency and may have an insulin secretory defect in conjunction with insulin resistance. T2DM was previously referred to as noninsulin-dependent diabetes; as that name suggests, patients often do not require insulin to survive.

Clinicians use one of three tests to diagnose diabetes mellitus: fasting plasma glucose test, oral glucose tolerance test, and casual plasma glucose level measurement. A fasting plasma glucose level of 126 mg/dL or more, an oral glucose tolerance test reading of 200 mg/dL or more, or a casual plasma glucose level of 200 mg/dL or more in conjunction with hyperglycemia symptoms all signal a diabetes diagnosis.

Additionally, a glycated hemoglobin (HbA_{1c}) test may be performed. This test indicates the patient's average blood sugar level for the previous 2 or 3 months. MFMER considers an HbA_{1c} level of 6.5% or higher on two separate tests to indicate a diagnosis of diabetes.

Diabetes mellitus treatment and management to prevent complications requires patients to make a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and, in some cases, taking insulin. According to MFMER, the primary

treatment goal is to maintain blood sugar levels as close to normal as possible to delay or prevent complications.

After diagnosis and disease-type classification, patients undergo evaluation to detect complications, review glycemic control challenges, and establish treatment goals, including target HbA_{1c} levels. Patients receive a treatment plan and are taught how to self-manage day-to-day care. Clinicians generally encourage patients to achieve an HbA_{1c} level of 7% or lower because this value has been shown to reduce diabetes-associated microvascular complications. However, targets are individualized according to clinician judgment about the optimal goal for a specific patient, taking into account the patient's medical characteristics and age.

For T2DM, several self-administered, oral antidiabetes agents, alone or in combination, are generally tried as first-line therapy. These include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) agonist. Insulin supplementation has become increasingly common with T2DM.

New treatments in development for diabetes focus on delaying disease onset in at-risk patients and improving diabetes management and treatment adherence. New drugs, technologies, and drug-delivery modalities are intended to optimize efficacy to enable patients to meet and maintain near-normal glycemia without acute excursions high or low (i.e., hyperglycemia, hypoglycemia), to improve patient adherence to treatment regimens, and to avoid weight gain and secondary complications (i.e., nephropathy, neuropathy, retinopathy).

Diabetes Mellitus Interventions

Artificial Pancreas Device Systems for Treatment of Diabetes

- **Key Facts:** An artificial pancreas device system (APDS) consists of an external or implantable insulin pump, real-time continuous glucose monitor, and a small computing device with software and algorithms to detect glucose levels and coordinate insulin delivery. Many believe that the APDS will be the ideal management strategy for patients with diabetes who require intensive insulin therapy. Researchers and manufacturers are developing two types of systems: reactive and predictive low-glucose suspend systems. In reactive systems, patients or clinicians set a blood glucose threshold, and the pump automatically shuts off when that reading is reached. In predictive systems, the monitor uses control algorithms that predict when the patient's blood glucose is projected to decrease to a dangerously low level. Although many proof-of-concept studies of closed-loop systems (CLSs) have been performed and all the necessary component parts of a CLS exist, a truly portable CLS for routine use is several years from realization. This is because major advances in sensor technologies and artificial pancreas software algorithms are needed, as is a developer that is able and willing to integrate the disparate components into a single CLS. The Juvenile Diabetes Foundation has committed significant resources to developing a system, and several are in pilot studies. In November 2012, the U.S. Food and Drug Administration (FDA) issued guidance for developers titled, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems" to guide trial conduct and regulatory submissions. In September 2013, FDA approved a reactive system, the Medtronic MiniMed 530G® threshold system with Enlite®. It consists of a combined insulin pump and sensor purported to be the first step toward a fully artificial pancreas.

- **Key Expert Comments:** Overall, experts commented that an APDS has significant potential to simplify the way in which patients with T1DM manage the disease to achieve near-normal glycemia and avoid acute (i.e., hypoglycemia, hyperglycemia) and long-term complications (i.e., nephropathy, neuropathy, retinopathy). Such a system, they opined, would likely be indicated for only a subset of the T1DM and insulin-dependent T2DM populations, and success of operating such a system would largely depend on a multidisciplinary care team and a highly motivated patient capable of understanding the complexities of using the system. (Note: The MiniMed 530G system had not been approved as of the time expert comments were received.)
- **Potential for High Impact:** High

Metabolic (Bariatric) Surgery for Resolution of Type 2 Diabetes in Mildly Obese and Nonobese Patients

- **Key Facts:** Current guidelines specify that bariatric surgery is indicated for individuals who are morbidly obese (i.e., body mass index [BMI] >40 kg/m^2) or individuals with a BMI >35 kg/m^2 and an associated comorbidity. One such qualifying comorbidity is diabetes, which is highly correlated with obesity, and outcomes showing resolution of T2DM in patients who have undergone bariatric surgery has generated interest in the potential of bariatric surgery to treat T2DM in less-obese patients (i.e., BMI <35 kg/m^2). The cost of the surgery varies depending on the choice of procedure (e.g., Roux en Y; lap banding; sleeve gastrectomy). Currently, insurers generally do not cover bariatric surgery in patients at these BMIs. The average total cost for lap-band surgery is reportedly between $17,000 and $30,000, and the average cost for gastric bypass ranges from $20,000 to $35,000.
- **Key Expert Comments:** Experts commenting on this intervention opined that bariatric surgery had the potential to improve health outcomes in patients with T2DM. Many experts agreed that this intervention has the potential to fulfill the unmet need. However, some experts questioned long-term efficacy. Experts commented that this intervention should be used as a last resort in treating patients with T2DM and that its invasiveness would likely affect limit adoption by patients and clinicians. However, some experts noted that patients may be willing to undergo surgery if the need for lifelong medication adherence is eliminated. Experts generally agreed that this use of the surgery has high potential to disrupt how T2DM patients with BMI <35 mg/kg^2 are managed, citing a shift from self-administered medication to inpatient surgery.
- **Potential for High Impact:** High

New Exenatide Formulations (Bydureon; ITCA 650) for Treatment of Type 2 Diabetes Mellitus

- **Key Facts**: Two therapies for treating T2DM, one in development and one FDA-approved, are intended to improve efficacy, tolerability (reducing nausea), and patient treatment adherence. One of these therapies is extended-release exenatide for injection (Bydureon™, Amylin Pharmaceuticals, a wholly owned subsidiary of Bristol-Myers Squibb, New York, NY). The other is ITCA 650 (Intarcia Therapeutics, Inc., Hayward, CA), a proprietary formulation of exenatide delivered through proprietary subcutaneous delivery system comprising a "matchstick-sized osmotic pump" that is inserted subcutaneously to purportedly deliver a slow and consistent flow of medication.

  Extended-release exenatide is a controlled-release formulation delivered once weekly by subcutaneous injection. It is intended to mimic the function of GLP-1, a naturally occurring

hormone that stimulates release of native insulin and inhibits glucagon release, lowering blood glucose levels. GLP-1 also has been observed to promote a feeling of fullness and satiety, purportedly reducing intake of exogenous glucose. FDA approved once-weekly exenatide in January 2012 for treating T2DM. Reported costs of Bydureon from 11 U.S. pharmacies range from about $400 to $415 per month or about $4,800 per year, all with the use of a discount coupon. Many third-party payers provide coverage but require prior authorization and quantity limits.

ITCA 650 has been reported to remain stable at body temperature for delivery up to 12 months, based on data presented thus far when administered continuously using the implantable subcutaneous delivery system. The delivery system is inserted by a clinician into the patient's arm or abdomen during an outpatient procedure that takes about 5 minutes. In March 2013, Intarcia began phase III trials of the ITCA 650/pump system.

- **Key Expert Comments:** Experts commenting on these topics believe that both formulations have potential to improve diabetes treatment by expanding access to exenatide while reducing frequency of injections and nausea, thereby potentially improving patient treatment adherence. However, some experts noted that the benefit would likely be incremental relative to existing forms of exenatide, other GLP-1 agonists, and other available adjunctive pharmacotherapies for T2DM treatment.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Diabetic Macular Edema Interventions

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

- **Key Facts:** According to the World Health Organization, people with diabetes who do not receive appropriate eye care have a 25% to 30% chance of developing clinically significant diabetic macular edema (DME). This condition leads to moderate or total vision loss over time. The main treatment was macular focal/grid laser photocoagulation until August 2012, when FDA approved another therapy, ranibizumab injection (Lucentis®), a once-monthly eye injection. Iluvien® (Alimera Sciences, Inc., Alpharetta, GA) is a tiny tube containing 190 mcg of fluocinolone acetonide that is injected once into the back of the eye with a 25-gauge needle in a single, in-office procedure. Over 2–3 years, the tube purportedly releases a constant, low flow of medication; thus, it does not require monthly injections as does Lucentis. The exact mechanism of action is unknown, but fluocinolone acetonide is thought to work through its combined vasoconstrictive, anti-inflammatory, and antipruritic activity, which is inherent to corticosteroids such as fluocinolone. After an initial review of the company's new drug application, FDA scheduled an advisory committee meeting for January 2014 to address clinical and statistical deficiencies in the application. The drug-device combination has been approved in Europe. If approved in the United States, it would compete with ranibizumab and aflibercept (Eylea®) injections; the latter is in phase III trials for treating DME. Fluocinolone acetonide's history of regulatory rejections and potential risk of increasing intraocular pressure might dissuade physicians from embracing fluocinolone acetonide implants to treat DME until a larger body of evidence becomes available.
- **Key Expert Comments:** Overall, experts thought this intervention could offer a long-lasting, single-procedure pharmacotherapy as an alternative to laser photocoagulation or monthly injections for treating DME. Although some experts believe the risk of adverse

events would affect patient and clinician adoption of this implant, other experts opined that some patients might be willing to accept this risk if it prevents vision loss. Experts thought that the intervention would reduce per-patient treatment costs, compared with costs of laser photocoagulation, noting it could reduce the need for in-hospital treatments. Experts expected costs to be substantially greater with this intervention than with off-label use of anti-VEGF (vascular endothelial growth factor) agents used for DME, but lower than the cost of laser photocoagulation.

- **Potential for High Impact:** Moderately high

Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

- **Key Facts:** Until ranibizumab's August 2012 approval, the main treatment for DME was macular focal/grid laser photocoagulation, because no other pharmacotherapies were FDA approved for DME. Ranibizumab (Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and Novartis International AG, Basel, Switzerland) is a humanized, recombinant, immunoglobulin G1, kappa isotope, monoclonal antibody fragment targeted against human VEGF-A. FDA had earlier approved it for treating wet age-related macular degeneration and macular edema with retinal vein occlusion. Ranibizumab's mechanism of action allows it to bind to multiple subtypes of VEGF-A. This binding inhibits growth of new blood vessels under the macula. Because new blood-vessel growth is prevented, the likelihood of vascular leakage and neovascularization is reduced; thus, vision loss as a result of fluid and protein buildup under the macula may be slowed. Investigators evaluated ranibizumab for DME in two phase III trials (RISE and RIDE) and reported positive results. The reported cost of a monthly injection is about $2,000. Some third-party payers reimburse for the drug, most requiring prior authorization. Genentech offers payment assistance to qualified patients. This injectable drug competes with other drugs in phase III trials, such as fluocinolone acetonide (Iluvien implant) and aflibercept (Eylea injection).
- **Key Expert Comments:** Some experts thought that the frequency of intravitreal ranibizumab injections might pose a barrier to patient treatment adherence, limiting its ability to significantly improve patient outcomes and potentially affecting patient acceptance. Experts also thought that the per-patient cost (about $24,000 annually) might pose a barrier to adoption by patients, depending on their insurance copayments. However, experts thought this intervention could significantly halt disease progression and improve visual acuity as a stand-alone or adjunctive therapy with laser photocoagulation.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Diabetes Mellitus Interventions

Artificial Pancreas Device Systems for Treatment of Diabetes

Unmet need: Several factors affect the ability of a patient with diabetes to achieve and maintain target blood glucose. Two-thirds of patients requiring insulin do not achieve adequate glycemic control; whether goals are reached can be affected by the equipment used to monitor glucose levels, patient access to appropriate care, and patient adherence to prescribed diabetes management regimens. Glucose monitors, including continuous glucose monitors (CGMs) are susceptible to errors that arise from incorrect calibration and rapid glucose changes that can result in hypoglycemia.[1] CGMs are also unable to protect a patient from nocturnal hypoglycemia (i.e., low blood sugar during sleep), and the usefulness of CGMs for helping patients aged 25 years or younger to lower glycated hemoglobin (HbA_{1c}) is unclear.[1,2] Constantly fluctuating glucose levels make diabetes management and control difficult, requiring frequent adjustments to insulin dosage. Access to health care providers is also a major barrier to achieving adequate glycemic control for some patients.

The Diabetes Control and Complications Trial highlighted the importance of tight glucose control to prevent long-term, diabetes-related complications (e.g., nephropathy, retinopathy, neuropathy, heart disease) in type 1 diabetes mellitus (T1DM); therefore, a medical need exists for reliable insulin delivery systems that autonomously respond to blood glucose levels.[1,3,4] The artificial pancreas device system (APDS) is intended to provide a complete system, known as a closed-loop system, to mimic pancreatic activity by combining several technologies—glucose monitoring device, external or implantable insulin pump, and glucose sensor device with advanced-algorithm software—to optimize diabetes management.[5]

Intervention: APDSs under development are intended to mimic the activity of a natural pancreas to monitor blood glucose levels in real time through a small computing device that uses an algorithm to determine and deliver the appropriate insulin dosage at the right time.[5,6] In a November 2012 guidance document on APDS development, the U.S. Food and Drug Administration (FDA) defined the components of APDSs as follows, stating that they are categorized as Class III devices:[7]

- Glucose monitoring devices—a CGM and blood glucose device used for calibrating the CGM (as applicable) and checking sensor performance as needed plus associated reagents/test strips
- APDS control algorithm
- Infusion pump—a fluid infusion set for the complete fluid pathway from the drug reservoir or fluid source container (e.g., bag, cassette, vial, syringe), infusion set, extension sets, filters and valves, clamps, up through the patient connection
- Components and accessories (e.g., power cord, wireless controller)

This definition includes a closed-loop system as well as first-generation systems referred to as low-glucose suspend systems. For an implantable APDS, an endocrinologist administers local anesthesia and surgically implants the pump and glucose monitor subcutaneously on opposite sides of the abdomen. The insulin reservoir is placed beneath the skin and is refilled every 2–3 months via transcutaneous injection.[5] In low-glucose suspend APDSs, insulin delivery automatically shuts off when blood glucose levels drop below a preset threshold indicating hypoglycemia (reactive), or the monitor uses control algorithms to predict and prevent potential hypoglycemic events (predictive).[8]

Clinical trials: Many proof-of-concept trials are ongoing in the United States and internationally. Much of the research is supported by the Juvenile Diabetes Research Foundation (JDRF). In July 2013, Bergenstal and colleagues published results from a pivotal, in-home study

assessing the safety and efficacy of a low glucose suspend APDS in 247 patients with T1DM. The authors reported the following results:[9]

> This multicenter, open-label, randomized, controlled trial showed that use of the threshold-suspend feature in sensor-augmented insulin-pump therapy significantly reduced the AUC for rigorously defined nocturnal hypoglycemic events (a proxy for the severity and duration of such events), the weekly rate of nighttime hypoglycemic events, and the percentage of nocturnal time spent with sensor glucose values in the hypoglycemic range. In addition, these reductions in measures of hypoglycemia with the threshold-suspend feature were observed for the full 24-hour period. Lower exposure to hypoglycemia was consistent in subgroups of patients stratified according to age, duration of diabetes, and glycated hemoglobin level at randomization and was achieved without significant changes in glycated hemoglobin levels, severe hypoglycemic events, ketosis, or diabetic ketoacidosis. The finding that there were no significant between-group differences in the number of study visits, insulin use, sensor wear and calibrations, or number of blood glucose determinations suggests that the reduction in hypoglycemia was due to the threshold-suspend feature itself.

In June 2013, results were announced from the ASPIRE in-home pivotal trial, which evaluated safety and efficacy of APDSs used in a home setting. According to the announcement, the ASPIRE study met safety and efficacy endpoints and provided clinical validation for threshold suspend systems.[10]

In February 2013, Phillip and colleagues published results from a multicenter, multinational, randomized, crossover trial assessing the safety and efficacy of an APDS for controlling nocturnal glucose levels in 56 patients with T1DM. In two consecutive overnight sessions, patients were randomly assigned to receive treatment with an APDS the first night and a sensor-augmented insulin pump (control) the second night or vice versa. The authors reported the following results:[11]

> On nights when the artificial pancreas was used, versus nights when the sensor augmented insulin pump was used, there were significantly fewer episodes of nighttime glucose levels below 63 mg per deciliter (7 vs. 22) and significantly shorter periods when glucose levels were below 60 mg per deciliter ($P = 0.003$ and $P = 0.02$, respectively, after adjustment for multiplicity). Median values for the individual mean overnight glucose levels were 126.4 mg per deciliter (interquartile range, 115.7 to 139.1 [7.0 mmol per liter; interquartile range, 6.4 to 7.7]) with the artificial pancreas and 140.4 mg per deciliter (interquartile range, 105.7 to 167.4 [7.8 mmol per liter; interquartile range, 5.9 to 9.3]) with the sensor-augmented pump. No serious adverse events were reported.

In August 2012, Nimri and colleagues published results of a feasibility study to establish overnight, closed-loop glucose control and reduce nocturnal hypoglycemia using an MD-Logic artificial pancreas algorithm in four adults and three adolescents (7 total patients) given a diagnosis of T1DM. The authors concluded the following:[12]

> The mean percentage of time spent in the near normal glucose range of 63–140mg/dL was 83±16%, and the median (interquartile range) was 85% (78–92%) for the overnight closed-loop sessions compared with 34±31% and 27% (6–57%) in the homecare open-loop setting, respectively. During the overnight closed-loop sessions at dinner alone 92±9% of the sensor values ranged within target range, compared with 73±19% for the sessions following exercise ($P = 0.03$). No hypoglycemic (<63 mg/dL) events occurred during the closed-loop sessions.

In June 2011, Zisser and colleagues released an evaluation of an APDS in 10 patients showing that this intervention can "safely regulate glycemia in patients with type 1 diabetes even following a meal challenge, without prior meal information."[13] The controller successfully brought subjects back to the euglycemic range, and the APDS "recognized all of the unannounced meals and gave appropriate meal boluses of insulin. The average percent time in the target glucose range (80 to 180 mg/dL) was 77% with one episode of mild hypoglycemia."[13]

In one ongoing trial, children stay overnight with their parents at the UK Cambridge Clinical Research Facility, a joint venture between Cambridge University's School of Clinical Medicine (Cambridge, UK), the Diabetes Research Network (London, UK), National Institute for Health Research (London, UK), and the Wellcome Trust (London, UK). These children, younger than 5 years of age, are treated with an insulin pump, continuous glucose sensor, and computerized algorithm to control the system's function in a closed-loop fashion.[14]

Manufacturer and regulatory status: The separate components that comprise an APDS have had marketing approval for some time.[6] FDA published guidance in November 2012 and sought comments on, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems," to inform sponsors of APDS IDE studies about what is needed for a PMA application for "single patient use in the home environment."[7] Regarding clinical study progression, the guidelines state the following:[7]

> FDA recommends that the APDS be studied in two general phases: feasibility and pivotal studies. Feasibility studies can be either exploratory in nature as part of device development and/or intended to demonstrate that the APDS functions as expected and has no obvious, unexpected safety concerns in either the inpatient or outpatient setting. Pivotal studies should be performed with a final device system and the study should evaluate the performance of the system in the intended setting.

In August 2013, FDA finalized the guidance and added it to resources about APDS research and development on its Web site.[15]

At least three companies are pursuing APDSs.[16] Medtronic, Inc., of Minneapolis, MN, has released the Paradigm Real-Time System that links its Paradigm Revel Insulin Pump to the Guardian Real-Time CGM System through radiofrequency transmission.[17] In September 2013, FDA approved the Medtronic MiniMed 530G® threshold system with Enlite® (the U.S. version of the low-glucose suspend system known as the MiniMed Paradigm Veo and marketed in Europe) a combined insulin pump and sensor intended as the first step toward a fully artificial pancreas in the United States.[18,19] Medtronic has marketed the system since 2009 in Europe, Canada, and other countries outside the United States.[17,20,] Medtronic and Tandem Diabetes Care, Inc., of San Diego, CA, have formed a partnership with JDRF to advance technologies toward realizing a fully automated monitor and pump combination.[21]

Animas Corp., a unit of Johnson & Johnson, of New Brunswick, NJ, and DexCom, Inc., of San Diego, CA, have collaborated to develop the Animas Vibe combined insulin pump and CGM, which received the Conformité Européene (CE) mark in June 2011, allowing marketing in Europe. It has also been released in the United Kingdom.[22] In April 2013, Animas submitted a PMA application to FDA for the device, and the company is working through a second feasibility study.[16,23]

Diffusion: Diffusion of the newly approved Medtronic MiniMed 530G began as of late 2013. This is the first low-glucose suspend system in the United States and is said to "automatically stop insulin delivery when sensor glucose values reach a preset level and when the patient doesn't respond to the Threshold Suspend alarm."[24] The next generation of Medtronic APDS is the predictive type that suspends insulin delivery when the system predicts hypoglycemia in the patient.[19]

The most appropriate patients are considered to be those with T1DM who frequently experience hypoglycemia, are highly motivated to achieve control, and are able to use an insulin pump.[25,26] Among suitable candidates, patients who have trouble maintaining normal nocturnal glycemia are especially expected to want to adopt use of an APDS.[27] Diffusion may take place at centers of excellence because of the level of expertise and comprehensive training required for using and monitoring device function.[17] However, if the APDS effectively slows the progression of diabetes, the device might become more widely available as the most desirable method for diabetes management in patients who require daily insulin.[4,28]

An estimated $174 billion (2007 dollars) is spent annually in the United States for diabetes-related costs, and although a true APDS may raise the cost over that of standard CGM and insulin pumps, a study funded by JDRF projected the technology could reduce diabetes-related expenses by slowing progression of the disease.[4,28]

FDA has approved about 20 IDE protocols for APDS trials. Most devices are in phase I or II development.[17,29] The development of an APDS capable of regulating bolus insulin injections remains an engineering obstacle.[20]

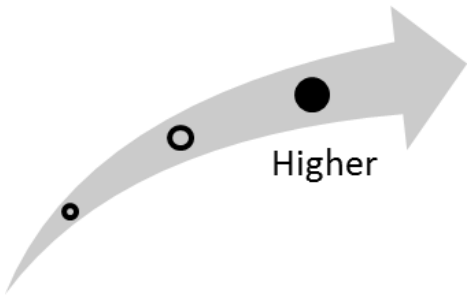
In June 2013, five people with T1DM in the United Kingdom were reported to be the first in the world to use a true APDS at home.[30] According to a report, 24 people were to have taken part in home trials of the device by the end of 2013.[30] However, the device is not expected to become available as a treatment for T1DM for several years.

Clinical Pathway at Point of This Intervention

Upon diagnosis, patients undergo medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan (depending on diabetes type and other medical factors), including establishing target glycated hemoglobin (HbA_{1c}) goals. HbA_{1c} is a measure of the average amount of glucose in a patient's blood over a 3- or 4-month period based on a single blood draw.

Patients with T1DM require insulin therapy. For T2DM, one or more self-administered oral antidiabetes agents taken alone or in combination are generally tried as first-line therapy. Some patients with T2DM also need insulin therapy.[2] Clinicians encourage patients to achieve an HbA_{1c} level of about 7% or slightly lower, depending on the patient. This value has been shown to reduce some secondary complications associated with T1DM and T2DM. Patients and their diabetes care team work to adjust patient insulin dosages using feedback from a blood glucose monitor.[6] Some patients who are unable to achieve the desired blood glucose levels within the desired time frame may be appropriate candidates for a CGM device and a continuous subcutaneous insulin infusion pump (or the new MiniMed 530G system), if they are highly motivated and capable of using such devices.[1,31]

Figure 1. Overall high-impact potential: artificial pancreas device system for treatment of diabetes



Overall, experts commenting on this intervention thought that APDSs have significant potential to simplify the way patients with T1DM manage the disease to achieve near-normal glycemia and avoid acute (i.e., hypoglycemia, hyperglycemia) and long-term complications (i.e., nephropathy, neuropathy, retinopathy). Such a system, they opined, would likely be indicated for only a subset of the population with T1DM, and patients would need to be highly motivated and able to operate the system. Experts thought that patients would also need access to a highly trained, multidisciplinary care team 24 hours a day, 7 days a week, to address any issues that might arise with operating an APDS. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.[32-37] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A long-standing, significant, unmet need exists for a device that mimics the pancreas to control blood glucose levels in patients with diabetes who need insulin. This need could be addressed by an APDS, the experts agreed, if the gap between the insulin pump and glucose monitor can be bridged with development of the missing components (automated glucose sensors and software algorithms). A significant need for a treatment that provides enhanced glycemic control without requiring burdensome glucose monitoring by patients is greatly needed, said one clinician. Preliminary data look promising, the experts generally agreed; one research expert stated that an APDS has potential to limit swings in glucose levels, thus improving short- and long-term glucose control. All expressed a desire for longer-term data.

Acceptance and adoption: Experts noted that both patients and physicians would widely accept and adopt this device for T1DM treatment. But the experts observed that early versions of an APDS might be complicated to operate and, thus, might be useful in only a subset of patients who are highly motivated, can learn to use the technology, and have access to a multidisciplinary diabetes care team trained in use of an APDS. Additionally, experts expected these devices would need significant maintenance by users and physicians to ensure their proper function. Although experts thought that the initial use of these systems would be limited, they saw significant potential for next-generation systems to become widely used after a period of refinement. One clinical expert noted he has a large proportion of patients with T1DM who he thought would likely want an APDS if given the option. The benefits of tight glycemic control, elimination of the need to self-monitor glucose and self-administer insulin would drive demand, the experts thought.

Health care delivery infrastructure and patient management: If sufficient refinement of the systems should occur, most experts believe, it could eventually simplify care for patients and their care teams because of the automated nature of the systems. Relative to current treatments, experts envisioned small shifts in the care setting, noting potential reductions in hospitalizations related to hypo- and hyperglycemia and long-term complications. However, one health systems expert explained that early APDSs could require even more monitoring by clinicians, which would require a different reimbursement paradigm.

Experts expect early versions of APDSs to be expensive with higher upfront costs for patients as well as third-party payers. However, experts believe that APDS refinement and wider adoption would eventually reduce upfront costs. Additionally, several experts noted that the high cost of an APDS could be offset somewhat by improved adherence to treatment plans for recommended insulin dosages and improved health outcomes.

Health disparities: In terms of health disparities, experts generally agreed that anticipated per-patient costs and access to the coordinated care needed to properly use and maintain this device could foster health disparities.

Metabolic (Bariatric) Surgery for Resolution of Type 2 Diabetes in Mildly Obese and Nonobese Patients

Unmet need: Two-thirds of diabetes patients, especially those requiring insulin therapy, do not achieve adequate glycemic control. This increases their risk of secondary complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy. Metabolic surgery has been proposed as a therapy for inducing remission of T2DM in patients who have been unable to achieve adequate control with first- or second-line therapy and whose body mass index (BMI) is lower than that typically required for patient eligibility for bariatric surgery.

Intervention: Metabolic surgery has become a therapy used to induce remission of T2DM in patients who have been unable to achieve adequate control with first- or second-line therapy. Although initially used for patients with T2DM with BMI >35 kg/m^2 (with comorbidities) or with BMI >40 kg/m^2, this approach has been used more recently for patients with BMI <35 kg/m^2 as well. Some clinical researchers believe that BMI-based criteria for bariatric surgery are not adequate for determining eligibility in patients with diabetes. Therefore, most obesity or bariatric surgery professional societies have added the term "metabolic" to their organization names.

Many clinicians (i.e., endocrinologists, metabolic surgeons) distinguish between bariatric and metabolic surgery because the goals of the surgery differ, although the same procedures are used to accomplish those goals. The goal of bariatric surgery is typically achieving weight loss, while the goal of metabolic surgery is achieving metabolic stability and diabetes remission. This difference has contributed to a paradigm shift in bariatric surgery for T2DM from interventions directed at obesity alone to restoring metabolic imbalances and has loosened the patient eligibility criteria from a focus purely on high BMI. A consensus is building that the metabolic improvements with surgery often precede weight loss in patients who are obese, and the improvements have occurred even in patients with a BMI lower than that used to define obesity.

Metabolic surgeries for T2DM are classified as purely restrictive, restrictive/malabsorptive, or purely malabsorptive. Purely restrictive procedures limit food consumption, while purely malabsorptive procedures reduce food absorption.[38,39] Today, most often the procedures are done laparoscopically; however, laparoscopic surgery may be difficult in patients with very high BMIs, intra-abdominal adhesions, or hernias. Therefore, surgery may still be performed as an open procedure.[40]

A purely restrictive procedure is adjustable gastric banding, in which surgeons place a band around the upper part of the stomach. This method is less invasive than some other metabolic surgeries, and the resulting pouch for food is smaller and empties into the lower stomach without bypassing the foregut. Gastric banding has been reported to be associated with excess weight loss of more than 30% (as much as 70%) and T2DM resolution (or improvement) in as many as 80% of patients in some studies.[38,41] Another restrictive procedure is the sleeve gastrectomy. This method is a vertical gastrectomy, an irreversible procedure in which a large portion of the stomach is surgically excised.[42]

Roux-en-Y gastric bypass (RYGB) surgery, a restrictive and malabsorptive procedure, is the most common type of metabolic surgery.[42] Although this procedure has both restrictive and malabsorptive features, it is primarily restrictive.[41] The surgeon partitions the stomach to form a small, 30 mL pouch where food will enter.[41] The surgeon then connects the distal small intestine to this gastric pouch. This connection creates the "Roux," or alimentary limb of the Y-shaped construction. Next, the surgeon connects the duodenum portion of the upper small intestine to a distal section of the small intestine. This construction results in the bypass of the duodenum and upper jejunum and creates the second limb of the "Y."[41,43] Biliopancreatic diversion with or without

duodenal switch is another restrictive and malabsorptive procedure. Surgeons perform a distal gastric resection and create a stapled closure of the duodenal stump to result in a stomach volume of around 300 mL. With the duodenal switch, the surgeon performs a proximal gastric resection leaving the pylorus to control food drainage. Food and digestive nutrients mix in the remaining 50 cm of the bowel.[41,42]

A purely malabsorptive procedure is the jejunoileal bypass, an ileal interposition linked to a diverted sleeve gastrectomy. The procedure connects the ileum, the lowest part of the small intestine, to the proximal intestine to keep digestive nutrients away from the bowel, in essence limiting small intestine length and absorptive surface area.[41] Another malabsorptive procedure is the duodenojejunal bypass. This is a stomach-sparing bypass in which surgeons partially transect the duodenum 2 cm distal to the pylorus and perform duodenojejunal anastomosis to manipulate the intestine.[42]

Clinical Trials: Many trials have been published reporting results that include patients with T2DM who are not considered to be morbidly obese. In a trial reporting 3-year followup in February 2013, Lanzarini and colleagues reported on 31 patients with T2DM and mild obesity.[44]

> This prospective clinical trial includes patients with T2DM with a body mass index (BMI) between 30 and 35 kg/m^2 who underwent laparoscopic RYGBP [Roux-en-Y gastric bypass] from July 2008 through October 2010. Thirty-one patients were included in the study, 15 men and 16 women, with an average age of 48.7 ± 8.6 years. The average time since onset of T2DM was 5.8 years. The average postoperative follow-up was 30.4 months. The average preoperative blood glucose and glycosylated hemoglobin were 152 ± 70 mg/dl and 7.7 ± 2.1 %, respectively. All of them were using oral hypoglycemic agents, and four patients were insulin dependent. Only one patient had a postoperative complication (hemoperitoneum). At 36 months follow-up, the average BMI decreased to 24.7 kg/m^2, all patients (31) showed improvement in their glycemic control, and 29 of them (93.6 %) met the criteria for remission of T2DM in the last control. Laparoscopic RYGBP is a safe and effective procedure that improves glycemic control in patients with T2DM and mild obesity at midterm follow-up.

In July 2012, Cohen and colleagues published results from a study assessing RYGB in 66 patients with T2DM and mild obesity, as follows.[45]

> For up to 6 years following RYGB, durable diabetes remission occurred in 88% of cases, with glycemic improvement in 11%. Mean HbA(1c) fell from 9.7 ± 1.5 to $5.9 \pm 0.1\%$ ($P < 0.001$), despite diabetes medication cessation in the majority. Weight loss failed to correlate with several measures of improved glucose homeostasis, consistent with weight-independent antidiabetes mechanisms of RYGB. C-peptide responses to glucose increased substantially, suggesting improved β-cell function. There was no mortality, major surgical morbidity, or excessive weight loss. Hypertension and dyslipidemia also improved, yielding 50-84% reductions in predicted 10-year cardiovascular disease risks of fatal and nonfatal coronary heart disease and stroke.

Manufacturer and regulatory status: Surgical procedures are not subject to marketing approval by FDA; however, the bands used in gastric banding (e.g., Lap-Band, Realize) are subject to FDA regulation. Searches identified four manufacturers that distribute and market devices used for gastric band procedures.[46-49] Commercially available technologies for metabolic surgery include:

- Lap-Band Adjustable Gastric Band by Allergan, Inc., Irvine, CA[46]

- Realize adjustable gastric band by Ethicon Endo-Surgery unit of Johnson & Johnson, New Brunswick, NJ[47]
- Heliogast HAGA, HAGE Gastric Band by Helioscopie, Vienne, France[48]
- Midband Adjustable Gastric Band by Médical Innovation Développement, Dardilly, France[49]

Of two devices that have been approved, only one has an indication that includes patients with a BMI <35 kg/m^2, the Lap-Band.[50,51] In June 2001, Allergan received FDA marketing approval through the PMA application process for the Lap-Band Adjustable Gastric Banding System.[52] The device is indicated for use in weight reduction for severely obese patients with BMI of at least 40 kg/m^2 or BMI of at least 35 kg/m^2 with one or more severe comorbidity. Since the original PMA, 26 supplements have been submitted involving process changes, changes in design, postmarket study modifications, and a change in the labeled indication. In February 2011, the Lap-Band received approval for the labeling change, which indicated its use for weight reduction for patients with a BMI ≥40 kg/m^2 or ≥30 kg/m^2 with one or more obesity-related comorbidity.[50]

Diffusion: Although metabolic surgery has been performed for many years for the obese population with T2DM, this option remains relatively new for nonobese patients with T2DM. The increase in publication of studies on this population suggests its use is increasing. The U.S. Centers for Disease Control and Prevention estimated the direct and indirect diabetes costs in the United States for 2007 at $174 billion; thus, a procedure that could induce permanent remission could affect and possibly reduce long-term costs.[53]

Metabolic surgery, however, is costly and complex. The average total cost for lap-band surgery ranges from $17,000 to $30,000, and the average cost for gastric bypass ranges from $20,000 to $35,000.[54] The cost generally includes preoperative lab work, x-ray fees, cardiac screening, and anesthesia, hospital, and surgeon fees. These costs vary by procedure, operating surgeon, location of health care provider, and length of recovery. Postsurgery costs are additional and may include dietary planning, a fitness regimen, potential behavioral modification, and lifetime nutritional supplementation.

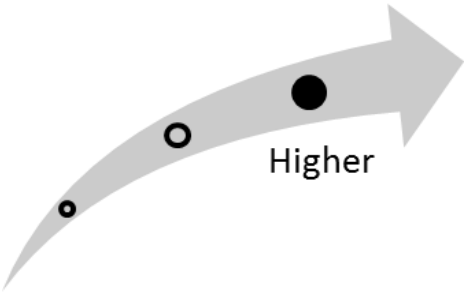
The U.S. Centers for Medicare & Medicaid Services has a national coverage determination titled "Surgery for Diabetes" that states, "Medicare currently covers bariatric surgery for persons with T2DM and BMI >35…and are non-covered for Medicare beneficiaries who have a BMI <35 and T2DM."[55] Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 10 outlining coverage, with only Wellmark having no policy listed. The other 10 have policies that indicate they provide coverage for surgical treatment of obesity when the patient has BMI >40 kg/m^2 or BMI >35 kg/m^2 with comorbidities.[56-65] Only HealthPartners' policy comments on BMI <35 kg/m^2, stating "weight loss surgery is not covered for BMI less than 35."[61]

Clinical Pathway at Point of This Intervention

T2DM typically occurs later in life, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action that might have additive therapeutic effects and result in better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.[66]

Bariatric surgery would provide another treatment option for T2DM in patients who are obese and not achieving adequate blood glucose control with medication or insulin.

Figure 2. Overall high-impact potential: metabolic (bariatric) surgery for resolution of type 2 diabetes in mildly obese and nonobese patients



Experts agreed on the potential of this intervention to meet the unmet need. Overall, experts commenting on this intervention opined that metabolic surgery has the potential to improve health outcomes in patients with T2DM and induce remission for a majority of patients in the short term. However, some experts questioned the long-term success and cited the need for more data to address this question. Experts commented that this intervention should be used as a last resort for patients who cannot achieve their target glucose goals with other, less drastic treatment options. Some experts noted that patients may be willing to undergo surgery if the need for lifelong medication adherence is eliminated and T2DM is resolved. Experts generally agreed on the potential of this intervention to disrupt how patients are currently managed, citing a shift from medication to surgery. The surgery could increase short-term costs of T2DM care but might offset costs over time if long-term remission can be achieved. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[67-72] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The majority of experts agreed on the unmet need for potentially curative treatments such as metabolic surgery. One expert with a research perspective noted, "The burden of T2DM and obesity is great. If life alteration or medication fail, surgery is an option to get off of meds and reduce the comorbidities associated with each."[67] Experts also generally agreed on the potential of this intervention to improve patient health outcomes. One research expert opined, "Overall, I think that metabolic surgery is a severe and extreme treatment option for most patients with diabetes, but a large proportion of those who have undergone the procedure seemed to have benefitted."[73] However, some experts noted the need for more long-term efficacy data to understand whether remission is maintained. A clinical expert opined, "A longer follow-up period may also be necessary to really assess for disease recurrence at 5 years-as even in morbidly obese patients."[71]

Acceptance and adoption: Although some experts agreed on the potential for clinician acceptance of metabolic surgery, some also commented that this intervention would likely be used only as a last resort. One research expert opined, "Metabolic surgery seems to be a serious and severe, extreme form of treatment relative to alternative options. Especially when you consider that lifestyle changes alone should be able to resolve the disease (T2DM). I believe clinicians will adopt metabolic surgery only as a last resort, and for patients who they deem ideal candidates."[69]

Alternatively, one expert with a research perspective noted, "Clinicians will accept it but will be concerned about potential side effects."[70] Additionally, one clinical expert opined, "The bariatric surgery market for morbidly obese patients has remained plateaued for the past 1-3 years despite ever increasing literature to support the efficacy and safety of metabolic procedures," and thought the same might be true for its use for treating T2DM in nonobese patients if made more widely available.[71]

Although comments regarding patient adoption were mixed, experts were generally more optimistic about patient acceptance. Some cited the lack of long-term efficacy studies as potential barriers for clinicians and patients alike. However, one clinical expert opined, "In our quick fix society, patients often want this procedure as a way of helping them achieve their goals."[72]

Health care delivery infrastructure and patient management: This intervention is a potentially disruptive treatment option compared with lifestyle management and pharmacotherapy, most experts thought. One research expert commented, "Patients who have diabetes are typically treated with lifestyle management, one or many pharmacotherapeutic options, and/or insulin therapy. Adding an invasive surgical procedure to the list of treatment options would be a large disruption to healthcare delivery, especially considering many of these procedures are performed inpatient. Relevant staff will also need training in the procedures, particularly in nonobese patients."[69]

One research expert opined that this option represented a "huge disruption in lifetime care patterns."[67] Another research expert elaborated, "Patients with diabetes will have a surgical adjunct (and possibly alternative) to their current treatment regimens, which typically include lifestyle intervention, pharmacotherapy, and/or exogenous insulin. This would likely increase patient volume at healthcare facilities. However, longterm, these procedures could reduce the burden of treating diabetes if they prove safe and effective."[69] Conversely, one clinical expert commented that patient management would not be disrupted until metabolic surgery is fully endorsed by numerous medical societies.[71]

Health disparities: Most experts agreed when commenting on the potential for this intervention to affect health disparities. One research expert commented, "Obesity is more prevalent in minority communities, and also is more prevalent in poorer communities. However, these communities may not have as much access to bariatric surgery, and so it could widen disparities."[70] Some experts cited limited access due to financial reasons. One research expert noted, "I would expect that given the cost for metabolic surgical procedures, and the fact that these procedures are generally only covered for certain indications, access to treatment could be limited to only those patients able to afford it."[69]

New Exenatide Formulations (Bydureon; ITCA 650 with Match-Sized Pump) for Treatment of Type 2 Diabetes Mellitus

Unmet need: Incretin mimetics (i.e., glucagon-like peptide 1 [GLP-1] receptor agonists) have become standard treatments for T2DM.[2] GLP-1 is a naturally occurring incretin hormone that stimulates insulin production in the presence of hyperglycemia, blocks the effects of glucagon (a hormone produced in the pancreas that signals the liver to release stored sugar into the bloodstream), and reduces appetite by delaying food absorption in the stomach.[74] Since the discovery that people with T2DM have reduced GLP-1 concentrations, it has been an important research focus. The clinical utility of natural GLP-1 is limited by its short action due to rapid enzymatic degradation. The GLP-1 receptor agonists approved by FDA, liraglutide (Victoza®) and exenatide (Byetta®), require once- or twice-daily subcutaneous injection, respectively.[74,75] New treatments that provide a more constant dose of exenatide than repeated injection are needed and could improve patient compliance to therapy.

Intervention: The two following GLP-1–receptor agonist therapies are intended to address this unmet need:

- Extended-release exenatide (exenatide once-weekly [EQW]; Bydureon®); FDA approved in January 2012
- Subcutaneously delivered exenatide (ITCA 650) with a proprietary subcutaneous delivery system comprising a "matchstick-sized osmotic pump" that is inserted subcutaneously to purportedly deliver a slow and consistent flow of medication; in development

EQW allows for once-weekly dosing rather than the once- or twice-daily dosing of other GLP-1 receptor agonists. The EQW formulation consists of injectable exenatide encapsulated in biodegradable polymer microspheres (poly [D,L lactic-co-glycolic acid]).[75] The microspheres degrade in the bloodstream to slowly release exenatide.[75] This microsphere technology has also been used in other extended-release drug formulations such as naltrexone (Vivitrol®) and risperidone (Risperdal®, Consta®).[75] In trials, EQW was given at weekly dose of 2 mg.[75]

ITCA 650 is exenatide delivered subcutaneously and continuously through a tiny implanted stick-shaped pump. It purportedly remains stable at body temperature for as long as a year, according to the most recently presented data.[76,77] The delivery system is a semipermeable, osmotic mini-pump that a physician or physician assistant implants in the patient's arm or abdomen during an outpatient procedure that takes about 5 minutes. The device is intended to deliver a steady dose for up to 12 months, potentially providing a more convenient dosing option for patients.[78] After 12 months, the implant is removed and replaced with a new one. The system is also designed to minimize the nausea associated with twice-daily exenatide dosing.

Clinical trials: The manufacturer has completed a six-trial program on EQW, the DURATION program. These studies evaluated the safety and efficacy of EQW compared with other diabetes therapies. The comparators in each study were as follows:

- DURATION-1, twice-daily exenatide injection (Byetta)[79]
- DURATION-2, sitagliptin or pioglitazone[80]
- DURATION-3, once-daily subcutaneous insulin glargine (Lantus®)[81]
- DURATION-4, metformin, pioglitazone, or sitagliptin[82,83]
- DURATION-5, exenatide injection (Byetta)[84]
- DURATION-6, liraglutide[85]

In January 2013, Buse and colleagues reported the following results from DURATION-6:[85]

> Of 912 randomised patients, 911 were included in the intention-to-treat analysis (450 liraglutide, 461 exenatide). The least-squares mean change in HbA(1c) was

> greater in patients in the liraglutide group (-1.48%, SE 0.05; n=386) than in those in the exenatide group (-1.28%, 0.05; n=390) with the treatment difference (0.21%, 95% CI [confidence interval] 0.08-0.33) not meeting predefined non-inferiority criteria (upper limit of CI <0.25%). The most common adverse events were nausea (93 [21%] in the liraglutide group vs 43 [9%] in the exenatide group), diarrhoea (59 [13%] vs 28 [6%]), and vomiting 48 [11%] vs 17 [4%]), which occurred less frequently in the exenatide group and with decreasing incidence over time in both groups. 24 (5%) patients allocated to liraglutide and 12 (3%) allocated to exenatide discontinued participation because of adverse events.

In May 2013, the manufacturer published an integrated analysis of the DURATION trial series, which included the six randomized, comparator-controlled, 24- to 30-week trials of EQW. The authors reported the following results:[86]

> The ITT [intent-to-treat] population experienced significant reductions from baseline (least-squares mean [95% CI]) in HbA1c levels (-1.4% [-1.5% to -1.4%]), fasting blood glucose levels (-36 mg/dL [-38.4 mg/dL to -33.8 mg/dL]), and body weight (-2.5 kg [-2.8 kg to -2.3 kg]) after 24 to 30 weeks of EQW treatment. Reductions in HbA1c and fasting blood glucose levels were observed across baseline HbA1c level strata; patients with higher baseline HbA1c levels experienced greater reductions. Treatment with EQW was associated with modest, significant reductions in blood pressure (systolic blood pressure, -2.8 mm Hg [-3.5 mm Hg to -2.1 mm Hg]; diastolic blood pressure, -0.8 mm Hg [-1.2 mm Hg to -0.4 mm Hg]), and fasting lipid levels (total cholesterol, -6.5 mg/dL [-8.2 mg/dL to -4.7 mg/dL]; low-density lipoprotein cholesterol, -3.9 mg/dL [5.3 mg/dL to -2.5 mg/dL]; and triglyceride [geometric least-squares mean percent change (95% CI)], -6% [-8% to -4%] levels). Similar reductions were observed in the completer population. Exenatide once weekly was generally well tolerated. Transient, mild-to-moderate gastrointestinal treatment-emergent adverse events and injection-site treatment-emergent adverse events were reported most frequently, but were seldom treatment limiting. No major hypoglycemic events were observed; minor hypoglycemic events occurred infrequently in patients not using a sulfonylurea.

Cardiovascular outcomes after EQW treatment in 9,500 patients with T2DM are being investigated in an ongoing, phase III trial, EXSCEL.[87]

The safety and efficacy of the ITCA 650 pump system compared with twice-daily exenatide injections (Ex-BID) was evaluated in a two-stage, phase II trial in patients with T2DM inadequately controlled with metformin.[88] Stage I (n=155) evaluated patient outcomes after 12 weeks of treatment with 20 or 40 mcg/day of ITCA 650 or Ex-BID. Stage II (n=131) re-randomly assigned patients to receive 20, 40, 60, or 80 mcg/day of ITCA 650 for an additional 12 weeks. Henry and colleagues published the following results in May 2013:[88]

> HbA1c was significantly lower in all groups after 12 and 24 weeks. Stage I: mean change in HbA1c from a mean baseline of 7.9-8.0% was -0.98, -0.95, and -0.72% for the 20 and 40 μg/day ITCA 650 and Ex-BID groups, respectively, with 63, 65, and 50% of subjects achieving HbA1c levels ≤7% ($P < 0.05$). Stage II: significant ($P < 0.05$) reductions in HbA1c (~1.4% from baseline) were achieved with 60 and 80 μg/day ITCA 650, and 86 and 78% of subjects achieved HbA1c ≤7% at 24 weeks; respectively. Weight was reduced by 2.8-3.7 kg ($P < 0.05$) at 24 weeks in all except the 20→20 μg/day group. ITCA 650 was well-tolerated; nausea was lower

and transient with 20 μg/day relative to Ex-BID; and 60 μg/day had the best profile of tolerability and HbA1c lowering.

In March 2013, ITCA 650's developer announced enrolling the first patients in its phase III FREEDOM clinical program, which is expected to include more than 4,000 patients at 500 clinical trial sites in more than 30 countries. The studies will include a broad range of patients whose diabetes is uncontrolled by oral antidiabetes medications including metformin and metformin-based combinations.[89]

Manufacturer and regulatory status: Amylin Pharmaceuticals (subsidiary of Bristol-Myers Squibb, of New York, NY) and Eli Lilly and Co., of Indianapolis, IN, developed EQW as a sustained-release therapy for the once-weekly treatment of T2DM. FDA approved EQW in January 2012 as "an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings."[90-92] The formulation incorporates the Medisorb® technology developed by Alkermes, plc, of Dublin, Ireland. In November 2011, Amylin and Eli Lilly agreed to terminate their alliance, transferring worldwide development and marketing rights to Amylin.[93] FDA's approval required a Risk Evaluation and Mitigation Strategy (REMS) program.[91] The REMS includes obligations for Amylin to conduct additional trials to evaluate the risk of adverse events (e.g., medullary thyroid carcinoma [MTC], acute pancreatitis) and create a case-series registry to monitor the annual MTC incidence.[91,94,95] FDA also required Amylin to submit assessment updates on extended-release exenatide after 1, 2, and 7 years.[91]

ITCA 650 was developed by Intarcia Therapeutics, Inc., Hayward, CA. ALZA Corp., a unit of Johnson & Johnson of New Brunswick, NJ, licensed its drug delivery technology to various companies, including Intarcia; the technology has been used commercially since 2000.[96] After successfully completing phase II trials, Intarcia announced a collaboration with Quintiles, Inc., of Durham, NC, in September 2011 to begin a phase III program of six trials.[97,98] In October 2012, the manufacturer stated plans to commence a phase III trial in January 2013, having completed analysis of phase II trial results to determine an optimal dosing regimen for the planned trial.[99] Intarcia reported that the phase III trial, with estimated enrollment of 450 patients, began in March 2013 and the company anticipates a July 2014 completion date.[100]

Diffusion: EQW and ITCA 650 are most likely to compete with exenatide (administered twice daily) and liraglutide (administered once daily) injections.[74,75] EQW retail cost reported by 11 U.S. pharmacies ranged from about $400 to $415 per month or about $4,800 per year, all with the use of a discount coupon.[101] By offering extended-release exenatide at a slightly lower price than other available GLP-1 receptor agonists, the company stated intentions to overcome competition and increase the drug's accessibility to patients.[95] Many third-party payers provide coverage requiring prior authorization and imposing quantity limits.[102-109]

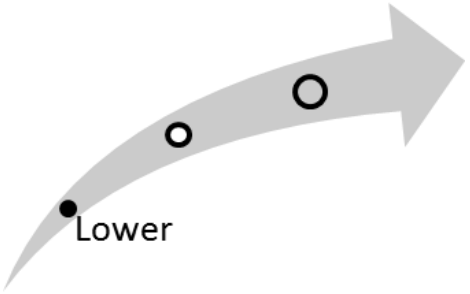
The cost for ITCA 650 has not been determined, but will likely be priced at a slight premium to the existing injectable exenatide formulations because of its novelty and convenience.[110] Although ITCA 650 use would add to the upfront cost of drug therapy, it could potentially save costs if it improves patient adherence to prescribed treatment, slows disease progression and development of secondary complications, and eliminates the attendant health services needed to treat those complications.

Clinical Pathway at Point of This Intervention

T2DM typically occurs later in life, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4

inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action that might have additive therapeutic effects and result in better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.[66]

Figure 3. Overall high-impact potential: new exenatide formulations (Bydureon; ITCA 650) for treatment of type 2 diabetes mellitus



Overall, experts opined that these new exenatide formulations have potential to improve diabetes treatment by reducing injection frequency and nausea and potentially improving patient adherence to treatment recommendations. However, experts noted that these benefits are incremental relative to existing exenatide formulations and other GLP-1 agonists. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on EQW (extended-release exenatide; Bydureon).[111-117] Six experts, with clinical, research, and health systems backgrounds, provided perspectives on ITCA 650 (subcutaneous exenatide).[118-123] Given that these two therapies are geared toward extending release and improving efficacy of exenatide, we synthesized both sets of expert comments here. We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: Expert opinions were mixed about whether EQW would address the unmet need. Although some experts agreed that any new therapy for treating diabetes would be welcome, some saw this form of exenatide as an incremental improvement that would minimally address the unmet need. The drug would simply join the list of adjunctive drugs for T2DM treatment, two research experts commented. But using EQW could significantly improve patient adherence to treatment recommendations, other experts believe. Although some experts referenced the existence of GLP-1 agonists on the market, one expert said that this therapy could better reduce HbA_{1c} and fasting glucose levels than similar medications.

Experts reviewing ITCA 650 generally agreed that subcutaneous delivery could improve patient adherence to therapy and therefore significantly address an unmet need. One research expert thought that patients with T2DM whose disease was not sufficiently managed by using metformin alone might benefit from GLP-1 agonists but that injection requirements could discourage use and adherence.

The underlying mechanisms for both modifications to exenatide appear sound, the experts generally agreed, citing previously approved forms of exenatide and other GLP-1 agonists already on the market. Several experts referred to clinical studies as evidence this delivery mechanism controls glucose levels in a fashion similar to injectable GLP-1 agonists while potentially improving treatment adherence. Subcutaneously released, long-term exenatide use could also result

in effective weight loss, several experts noted. One clinical expert noted that extended-release exenatide improved glucose levels more than oral antidiabetes drugs and twice-daily exenatide injection, but was slightly inferior to once-daily liraglutide injection. The advantage of once-weekly injection of extended-release exenatide could potentially improve adherence, thought that expert. A research expert agreed that this formulation had potential to improve patient adherence to treatment recommendations but cautioned that the microsphere technology in the formulation requires a larger needle and might cause more injection site reactions than conventional daily doses.

Health outcomes could improve with both formulations because of better patient adherence and better quality of life, the experts thought. But they noted benefits would be realized only if these therapies do not pose risk of serious adverse events (i.e., cardiac abnormalities, carcinomas). Referring to ITCA 650, one clinical expert was uncertain whether subcutaneous infusion via osmotic pump would improve patient health outcomes, compared with outcomes with twice-daily exenatide and other comparators but agreed it could improve adherence to treatment.

Acceptance and adoption: Commenting on both new types of exenatide, most experts agreed that patients and clinicians would welcome options that require fewer injections than available formulations. Commenting on EQW, one expert with a health systems background thought that the largest inhibition to adoption would be the boxed warning concerning risk of thyroid C-cell tumors in exposed rats and the increased risk of pancreatitis. This would require more patient followup to monitor renal function. Commenting on clinician acceptance of EQW, a clinical expert thought that the weekly injection might bring the therapy into use by primary care physicians, because it would be easier to implement. Among specialists, the key would be whether EQW adequately controls glucose and induces weight loss compared with other available medications, thought a clinical expert.

Patients would consider the ITCA 650 form of exenatide to be "a welcome relief to the concern regarding self-administered daily/weekly subcutaneous injections," noted one health systems expert. Clinicians "would be enthusiastic about not having to rely on patient compliance for medication delivery [with ITCA 650]," thought one research expert. A clinical expert agreed, commenting that physicians are likely to accept ITCA 650 because it has potential to improve patient adherence to treatment recommendations and improve patient outcomes. This clinical expert added that "for those providers who are willing to undergo training for device insertion, [there] would be minimal barriers to acceptance."

Other experts pointed out that patients might be less enthusiastic about ITCA 650 than physicians because of the fear of a permanently implanted device. A clinical expert opined that although the administration route is innovative, patients may resist having an inserted device and that concerns such as infection or device malfunction could affect patient acceptance. However, this expert also thought that a formulation that produced less nausea might lead to better patient acceptance.

Health care delivery infrastructure and patient management: Neither of the new formulations of exenatide will disrupt health care processes, most experts agreed; instead, they thought these drugs have potential to simplify patient management. Commenting on EQW, experts pointed out that clinicians would need to teach patients proper injection techniques but that this could be achieved in a single office visit. Clinical experts agreed that EQW is similar to other available injectable treatments for T2DM. One research expert thought that EQW would disrupt the system by reducing the amount of day-to-day attention needed by patients with diabetes compared with daily management with other diabetes injectable drugs.

One research expert commenting on ITCA 650 pointed out that patients would experience a shift in responsibility, from complying with injection requirements and re-medication obligations to monitoring their implant. One health systems expert and one clinical expert commenting on ITCA

650 thought the implant procedure would not be disruptive because the procedure for a subcutaneous implant is not difficult and is conducted in a physician's office. ITCA 650 has potential to improve patient adherence to treatment, this same clinical expert thought, adding that if the cost is affordable and its long-term safety and effectiveness is further demonstrated in trials, it could become as important as metformin in treating T2DM.

Opinions diverged on whether costs of care would rise or fall with these exenatide formulations. Some experts believe that per-patient costs would increase with both forms of exenatide because they are new, but others noted that improved patient adherence to treatment and subsequent decreases in complications would lower long-term, per-patient costs for both patients and third-party payers.

Health disparities: Experts commenting on health disparities agreed that both forms of exenatide would have minimal impact. They thought that access to the drugs would be limited in part by patient lack of knowledge about their availability and also be limited to patients who have the resources to afford newer forms of exenatide. In reference to EQW, one research expert suggested, "this is an injectable drug which reduces patient willingness to use, making it even less likely to reduce care disparities." Conversely, ITCA 650 "may offer therapy to patients unable to inject themselves or who don't have a reliable caregiver to do so," noted another expert with a research background. This expert added that ITCA 650 could be "great for patients who live a long way from physicians" if it requires only a single, annual implantation procedure.

Diabetic Macular Edema Interventions

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

Unmet need: Diabetic macular edema (DME) is a thickening or swelling of the retina caused by fluid leaking from blood vessels within the macula in patients with diabetes mellitus. The swelling that occurs as a result of fluid buildup distorts central vision, mainly affecting an individual's ability to see form, color, and detail. Patients gradually lose their ability to focus on objects in their central field of vision over a period of months or years as the disease progresses.[124] People with diabetes who go untreated for eye care have a 25% to 30% chance of developing moderate vision loss.[125] Until the August 2012 approval of another drug, ranibizumab (Lucentis®), no pharmacologic treatment was approved for treating DME. New effective therapies are needed that can improve the quality of life of patients with the disease; particularly needed are options that could restore vision loss.

Intervention: Fluocinolone acetonide (Iluvien®) is a sustained-release, intravitreal corticosteroid insert intended for treating DME.[126] The exact mechanism by which fluocinolone acetonide functions in DME treatment is unknown, but it is thought to be due to the combined vasoconstrictive, anti-inflammatory, and antipruritic qualities inherent to corticosteroids such as fluocinolone.[127] The insert consists of 190 mcg of the corticosteroid fluocinolone acetonide in a tiny, cylindrical, polymide tube designed for stable, sustained release of the corticosteroid into the eye. The insert is delivered by intravitreal injection to the back of the eye with a 25-gauge needle, a needle size that purportedly allows natural physiologic sealing of the injection site. Iluvien is designed to have a therapeutic effect for up to 36 months.[126,128] In clinical trials, two dosage regimens of Iluvien were administered to patients with DME: a high dosage with an initial release rate of 0.45 mcg per day and a low dosage with an initial release rate of 0.23 mcg per day.[126]

Clinical trials: In a February 2013 analysis of two multinational trials in patients with DME previously treated with macular laser photocoagulation, authors reported the following:[129]

> Fluocinolone acetonide intravitreal implant 0.2 μg/day was significantly more efficacious than sham injection in improving visual acuity. At 24 months post injection, 29 % of fluocinolone acetonide intravitreal implant 0.2 μg/day recipients had an improvement in the best-corrected visual acuity (BCVA) letter score of ≥15 compared with 16 % in the sham injection group ($p = 0.002$) [primary endpoint]. Treatment benefit was most evident in the subgroup of patients whose duration of [DME] was ≥3 years. In this subgroup at 36 months, 34 % of fluocinolone acetonide intravitreal implant 0.2 μg/day recipients had an increase in the BCVA score of ≥15, compared with 13 % of sham injection recipients ($p < 0.001$). Fluocinolone acetonide intravitreal implant recipients also had generally greater benefits than sham injection recipients on secondary endpoints. In patients who were phakic in the study eye at baseline, cataracts occurred in 82 % of fluocinolone acetonide intravitreal implant 0.2 μg/day recipients and 51 % of sham injection recipients. Overall, 37 % and 12 % of patients in the fluocinolone acetonide intravitreal implant and sham injection groups developed raised intraocular pressure (IOP), which was generally controlled with IOP-lowering drugs.

Two Campochiaro publications reported on the same phase III clinical trial (FAME™), which evaluated 953 patients over 36 months. The first listed trial (June 2012) reported the following data from the completed 36-month trial:[130]

> At month 36, the percentage of patients who gained ≥15 in letter score using the last observation carried forward method was 28.7% (low dose) and 27.8% (high dose)

in the FAc [fluocinolone acetonide] insert groups compared with 18.9% (P = 0.018) in the sham group, and considering only those patients still in the trial at month 36, it was 33.0% (low dose) and 31.9% (high dose) compared with 21.4% in the sham group (P = 0.030). Preplanned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported duration of DME ≥3 years at baseline; the percentage who gained ≥15 in letter score at month 36 was 34.0% (low dose; P<0.001) or 28.8% (high dose; P = 0.002) compared with 13.4% (sham). An improvement ≥2 steps in the [ETDRS] retinopathy scale occurred in 13.7% (low dose) and 10.1% (high dose) compared with 8.9% in the sham group. Almost all phakic patients in the FAc insert groups developed cataract, but their visual benefit after cataract surgery was similar to that in pseudophakic patients. The incidence of incisional glaucoma surgery at month 36 was 4.8% in the low-dose group and 8.1% in the high-dose insert group."

The second Campochiaro trial (April 2011) reported the following data at month 24:[131]

> The percentage of patients with improvement from baseline ETDRS letter score of 15 or more at month 24 was 28.7 and 28.6 in the low- and high-dose insert groups, respectively, compared with 16.2 in the sham group (P = 0.002 for each). Benefit occurred for both doses compared with sham at 3 weeks and all subsequent time points. The mean improvement in BCVA letter score between baseline and month 24 was 4.4 and 5.4 in the low- and high-dose groups, respectively, compared with 1.7 in the sham group (P = 0.02 and P = 0.016). At all time points compared with sham, there was significantly more improvement in FTH (foveal thickness). Subjects requiring cataract surgery were more frequent in the insert groups, and their visual benefit was similar to that of subjects who were pseudophakic at baseline. Glaucoma requiring incisional surgery occurred in 3.7%, 7.6%, and 0.5% of the low-dose, high-dose, and sham groups, respectively."

These 24-month data were submitted in the manufacturer's original 2010 FDA new drug application (NDA).

In August 2011, Pearson and colleagues published 3-year results from a 4-year, multicenter, randomized controlled clinical study that evaluated the safety and efficacy of fluocinolone acetonide intravitreal implants in eyes with refractory DME. Patients (196 eyes) were randomly assigned in a 2:1 ratio to receive the implant or standard of care (SOC; additional laser or observation). The authors reported the following results:[132]

> Overall, VA [visual acuity] improved ≥3 lines in 16.8% of implanted eyes at 6 months (P=0.0012; SOC, 1.4%); in 16.4% at 1 year (P=0.1191; SOC, 8.1%); in 31.8% at 2 years (P=0.0016; SOC, 9.3%); and in 31.1% at 3 years (P=0.1566; SOC, 20.0%). The number of implanted eyes with no evidence of retinal thickening at the center of the macula was higher than SOC eyes at 6 months (P<0.0001), 1 year (P<0.0001; 72% vs 22%), 2 years (P=0.016), and 3 years (P=0.861). A higher rate of improvement and lower rate of decline in DRSS [Diabetic Retinopathy Severity Score] occurred in the implanted group versus the SOC group at 6 months (P=0.0006), 1 year (P=0.0016), 2 years (P=0.012), and 3 years (P=0.0207). [IOP] ≥30 mmHg was recorded in 61.4% of implanted eyes (SOC, 5.8%) at any time and 33.8% required surgery for ocular hypertension by 4 years. Of implanted phakic eyes, 91% (SOC, 20%) had cataract extraction by 4 years.

Manufacturer and regulatory status: Alimera Sciences, Inc., of Alpharetta, GA, developed and manufactures Iluvien. In June 2010, after completing the FAME study, Alimera submitted an NDA to FDA for the low-dose formulation of the drug. The application was granted priority review

status, but in December 2010, FDA requested that 36-month FAME data be delivered and that manufacturing, packaging, and product sterilization processes be reported before it would consider approval. The 36-month trial results were provided to FDA in May 2011. In November 2011, the company stated the following about the complete response letter it received from FDA:[133]

> FDA stated that it was unable to approve the ILUVIEN NDA because the NDA did not provide sufficient data to support that ILUVIEN is safe and effective in the treatment of patients with DME. The FDA stated that the risks of adverse reactions shown for ILUVIEN in the FAME® Study were significant and were not offset by the benefits demonstrated by ILUVIEN in these clinical trials. The FDA has indicated that Alimera will need to conduct two additional clinical trials to demonstrate that the product is safe and effective for the proposed indication.

The company met with FDA in June 2012 and based on the outcome of that meeting, declared intentions to resubmit data from two previously completed phase III trials (FAME studies) to address FDA's concerns.[134] In May 2013, Alimera announced that FDA had received its NDA resubmission and set October 17, 2013, as the therapy's new Prescription Drug User Fee Act (PDUFA) date.[135] However, after initial review of the NDA, FDA scheduled an advisory committee meeting for January 27, 2014, to address clinical and statistical deficiencies. FDA also indicated that the manufacturer would need to submit new clinical trial data to address concerns of risk and safety profiles.[136]

According to a May 2013 company press release, a patient in Germany became the first in the world to use the commercially available fluocinolone acetonide implant. Iluvien is being marketed in Austria, France, Germany, Portugal, Spain, and the United Kingdom[137] for treating "DME considered insufficiently responsive to available therapies."[138]

Diffusion: The drug has just begun to diffuse in some countries outside the United States where it has marketing approval. If approved in the United States, the drug would compete with laser photocoagulation and off-label corticosteroid injections for DME;[139-141] but these treatments cannot reverse vision loss that has already occurred, and vision loss continues to progress in some patients despite treatment.[124,142,143] Additional vision loss is also a risk associated with the laser photocoagulation procedure.[142] Fluocinolone acetonide could also complement laser therapy. The fluocinolone acetonide implant might be potentially more convenient and safer than corticosteroid therapy because it would not require the ongoing intravitreal injections of steroid therapy. Thus, it could be more appealing to patients than steroid therapy.

Costs for the Iluvien implant in the U.S. market are not yet known. However, some industry analysts expect the product to be priced comparably to Retisert®, a fluocinolone acetonide ophthalmic implant that is FDA-approved to treat uveitis. According to ECRI Institute's PriceGuide Database, the price of a single Retisert implant is about $18,250. The product is designed to deliver its drug payload over 30 months.[144] Other cutting-edge ophthalmic treatments, such as pegaptanib (Macugen®) injections, which are indicated to treat wet age-related macular degeneration, cost about $8,000–$9,000 per year (approximately $1,000 per injection).[144]

The fluocinolone acetonide implant will also probably compete with ranibizumab (Lucentis®), a vascular endothelial growth factor (VEGF) inhibitor approved for treating DME with monthly intravitreal injections.[145] Ranibizumab is discussed later in this report. It costs an estimated $2,000 per vial with the use of a coupon.[146]

Another VEGF inhibitor, bevacizumab (Avastin®), is reportedly used widely for off-label treatment of ophthalmic conditions, including DME, as a significantly less-expensive alternative (about $150 per dose) to ranibizumab.[147-150] However, some researchers report that intravitreal injections of bevacizumab are associated with a significantly higher rate of serious adverse events (because of the dose-preparation requirements for ophthalmic administration), which could pose an

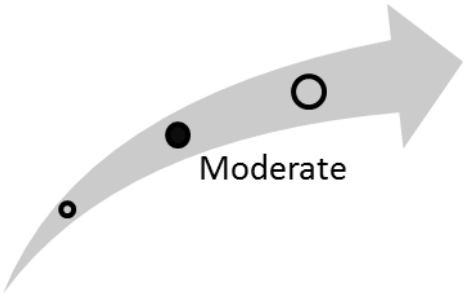
additional cost burden to treat. In one Canadian retrospective study, subjects who received bevacizumab for ophthalmic indications were 12 times as likely to develop severe intraocular inflammation following each injection as patients who received ranibizumab injections.[151]

The most common adverse event reported in the 3-year, phase III trial for the fluocinolone acetonide implant was cataract formation, which occurred in 42.7% of the low-dose group and 51.7% of the high-dose group. Adverse events related to increased IOP were also found more frequently in fluocinolone acetonide groups than in the sham implant group.[130]

Clinical Pathway at Point of This Intervention

A patient who presents with symptoms suggesting DME undergoes a history and physical examination pertaining to diabetes history, vision and eye disease history, and other risk factors (i.e., older age, poor glucose control, pregnancy, hypertension, and increased lipid levels).[125] Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. DME treatment focuses on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Standard therapy has been laser photocoagulation and use of ranibizumab or off-label bevacizumab.[125]

Figure 4. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema



Overall, experts thought the unmet need is significant for effective treatment for DME that the fluocinolone acetonide implant might be able to address. However, a couple of experts with research backgrounds were less optimistic about the implant because of the risk of adverse events, with one noting that the negative benefit-risk profile so far, the anticipated cost, and lack of sufficient data diminish the therapy's potential. A clinical expert had similar concerns and wanted more data from larger and longer-term trials to determine which subgroups of DME patients could benefit and have minimal side effects. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems and administration backgrounds, provided perspectives on the fluocinolone acetonide implant.[152-157] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: DME is one of the leading causes of blindness and an important unmet need exists for safe and effective therapies for patients with this condition, most of the experts agreed. However, one expert with a research background noted that standard therapy for DME is available through laser photocoagulation, corticosteroids, or anti-VEGF therapies making this new intervention just another treatment option. As for health outcomes, a health systems and

administration expert pointed out that FDA was unable to approve the fluocinolone acetonide implant because of insufficient data supporting safety and effectiveness. The expert noted that FDA found the risk of treatment-emergent adverse events to not be offset by the benefits of the fluocinolone acetonide implant and required the drug's manufacturer to conduct two additional clinical trials. The expert cited cataract formation (in about 42% of patients receiving low-dose and 52% of patients receiving high dose Iluvien). This expert and others also pointed out that adverse events related to IOP were reported and that the adverse event profile limits the implant's potential to improve health outcomes for patients with DME.

It should be noted that after the time of expert review, the manufacturer received market authorization for the fluocinolone acetonide implant in several countries around the world, and it has been granted a new PDUFA date in the United States.[135] According to the manufacturer, the NDA addresses questions raised in the FDA letter and provides additional analyses and new information supporting the fluocinolone acetonide implant's safety and effectiveness.[135] FDA has scheduled a meeting with an FDA advisory committee to discuss the NDA.[136]

One clinical expert opined that the fluocinolone acetonide implant could improve visual acuity tests by 10% to 40% over 3 years, demonstrating its potential to benefit patients in whom laser therapy has failed to improve visual acuity. Some experts also proposed that the fluocinolone acetonide implant could improve quality of life if, for example, as one systems expert offered, it reduces the number of injections needed and provides continuous therapy.

Acceptance and adoption: Patient and clinician acceptance would rely heavily on the therapy's success relative to other treatments, most of the experts thought. One systems expert opined that the less frequent dosing would be quite a selling point for patients relative to other ophthalmic drug injections for DME. Conversely, the adverse-event profile could be a barrier to adoption, noted several experts, at least until more data on good outcomes are available. Other experts thought the implant would be readily accepted because of the unmet need for effective treatment.

Commenting on the potential financial impact of the fluocinolone acetonide implant, expert opinion was mixed. On one hand, most experts thought that compared with other treatments for DME, Iluvien is likely to be costly and that it would have a large impact because it would be additive, not replacement therapy for DME. A clinical expert pointed out that a 30-month supply of corticosteroid therapy for treating uveitis costs $18,250, which might provide a pricing benchmark for the fluocinolone acetonide implant. According to this expert, given the large number of people with DME, the "enormous costs" will negatively affect patients and payers. On the other hand, one research expert opined that the fluocinolone acetonide implant would not affect costs if it is priced similarly to other available therapies. And an expert with a research background thought the implant might be less costly than laser surgery.

Health care delivery infrastructure and patient management: Experts agreed that the fluocinolone acetonide implant would not disrupt health care delivery infrastructure or the way cases of DME are managed. The therapy is delivered in a fashion similar to available intravitreal injections commonly used by retinal specialists. Some experts with research backgrounds pointed out that the fluocinolone acetonide implant would have a small impact on how care is delivered for patients who were previously treated with laser photocoagulation therapy, by switching care setting from an inpatient laser surgery to a physician office-based implant procedure. But a clinical expert thought some additional patient management would be needed to identify the appropriate patients for treatment and to conduct adequate followup and management of cataracts and glaucoma that could occur from the treatment.

Some experts commented on the fluocinolone acetonide implant's place in the current treatment paradigm for DME, opining that it is more likely to complement laser photocoagulation than

replace it. The implant is expected to compete with VEGF inhibitors, such as ranibizumab, also approved to treat DME.

Health disparities: Most experts thought that if the implant becomes available, it would have minimal impact on health disparities. However, one research expert pointed out that the administration schedule for the fluocinolone acetonide implant (i.e., every 3 years) might provide better access to treatment for some patients than other DME therapies that require more frequent intravitreal injections (e.g., anti-VEGF therapies). But an expert with a health systems and administration background thought that high costs for the fluocinolone acetonide implant would limit access, making it available only to patients with prescription insurance and/or who could afford its cost.

Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

Unmet need: FDA had not approved any pharmacotherapies for treating DME until approving ranibizumab (Lucentis) in 2012. However, a similar drug used in oncology, bevacizumab (Avastin®), could be used off-label for DME treatment.

Intervention: Ranibizumab is a humanized, recombinant, immunoglobulin G1 kappa isotope, monoclonal antibody fragment targeted against human VEGF-A.[158] VEGF-A is a protein responsible for acting on endothelial cells—cells that increase vascular permeability, stimulate new blood vessel formation from preexisting vessels, induce endothelial cell proliferation, promote cell migration, and inhibit cell death (apoptosis).[159] In DME, VEGF-A activation stimulates angiogenesis and endothelial cell proliferation, causing fluid leakage from these blood vessels, resulting in retinal thickening or swelling and consequent deterioration in vision or blindness.[124] Ranibizumab is designed to inhibit VEGF-A interaction with its receptors on the endothelial cell surface, leading to inhibition of both angiogenesis and endothelial cell proliferation. As a result, ranibizumab purportedly halts retinal thickening and halts and reverses retinal disease progression. The recommended dosage for ranibizumab is 0.3 mg (0.05 mL) once monthly (every 28 days) by intravitreal injection.[158] Treatment is often required indefinitely or until reversal of vision loss.[160]

Clinical trials: In April 2012, Nguyen and colleagues published results from the combined randomized, phase III RIDE and RISE clinical trials evaluating ranibizumab in 759 patients with DME and baseline visual acuity of 20/40 to 20/320. The authors reported the following results:[161]

> In RISE (NCT00473330), 377 patients were randomized (127 to sham, 125 to 0.3 mg, 125 to 0.5 mg). At 24 months, 18.1% of sham patients gained ≥15 letters versus 44.8% of 0.3-mg (P<0.0001; difference vs sham adjusted for randomization stratification factors, 24.3%; 95% confidence interval [CI], 13.8 to 34.8) and 39.2% of 0.5-mg ranibizumab patients (P<0.001; adjusted difference, 20.9%; 95% CI, 10.7 to 31.1). In RIDE (NCT00473382), 382 patients were randomized (130 to sham, 125 to 0.3 mg, 127 to 0.5 mg). Significantly more ranibizumab-treated patients gained ≥15 letters: 12.3% of sham patients versus 33.6% of 0.3 mg patients (P<0.0001; adjusted difference, 20.8%; 95% CI, 11.4 to 30.2) and 45.7% of 0.5 mg ranibizumab patients (P<0.0001; adjusted difference, 33.3%; 95% CI, 23.8 to 42.8). Significant improvements in macular edema were noted on OCT [optical coherence tomography], and retinopathy was less likely to worsen and more likely to improve in ranibizumab-treated patients. Ranibizumab-treated patients underwent significantly fewer macular laser procedures (mean of 1.8 and 1.6 laser procedures over 24 months in the sham groups vs 0.3 to 0.8 in ranibizumab groups). Ocular safety was consistent with prior ranibizumab studies; endophthalmitis occurred in 4 ranibizumab patients. The total incidence of deaths from vascular or unknown causes, nonfatal myocardial infarctions, and nonfatal cerebrovascular accidents, which are possible effects from systemic vascular endothelial growth factor inhibition, was 4.9% to 5.5% of sham patients and 2.4% to 8.8% of ranibizumab patients.

Then, in May 2013, Brown and colleagues published long-term outcomes data from the combined RIDE and RISE trials. The authors reported the following:[162]

> Visual acuity (VA) outcomes seen at month 24 in ranibizumab groups were consistent through month 36; the proportions of patients who gained ≥15 letters from baseline at month 36 in the sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab

> groups were 19.2%, 36.8%, and 40.2%, respectively, in RIDE and 22.0%, 51.2%, and 41.6%, respectively, in RISE. In the ranibizumab arms, reductions in CFT [central foveal thickness] seen at 24 months were, on average, sustained through month 36. After crossover to 1 year of treatment with ranibizumab, average VA [visual acuity] gains in the sham/0.5 mg group were lower compared with gains seen in the ranibizumab patients after 1 year of treatment (2.8 vs. 10.6 and 11.1 letters). Per-injection rates of endophthalmitis remained low over time (~0.06% per injection). The incidence of serious adverse events potentially related to systemic vascular endothelial growth factor inhibition was 19.7% in patients who received 0.5 mg ranibizumab compared with 16.8% in the 0.3 mg group.

In May 2013, Lang and colleagues published interim results from the phase IIIb RESTORE extension study, evaluating the 2-year safety and efficacy of ranibizumab 0.5 mg in DME. The study included 240 of 303 patients who completed the RESTORE core study and entered the extension. The authors reported the following results:[163]

> Two hundred twenty patients (92%) completed the month 24 visit. Over 2 years, the most frequent ocular serious AE [adverse event] (SAE) and AE were cataract (2.1%) and eye pain (14.6%), respectively. The main nonocular AEs [adverse events] were nasopharyngitis (18.8%) and hypertension (10.4%). There were no cases of endophthalmitis, and the incidences of nonocular SAEs [serious adverse events] were low. Of the patients entering the extension, 4 deaths were reported in the second year, none of which were related to study drug or procedure. Mean BCVA gain, central retinal thickness (CRT) decrease, and National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) composite score observed at month 12 were maintained at month 24 (prior ranibizumab: +7.9 letters, -140.6 μm, and 5.6, respectively; prior ranibizumab plus laser: +6.7 letters, -133.0 μm, and 5.8, respectively), with an average of 3.9 (prior ranibizumab) and 3.5 ranibizumab injections (prior ranibizumab plus laser). In patients treated with laser alone in the core study, the mean BCVA, CRT, and NEI VFQ-25 composite score improved from month 12 to month 24 (+5.4 letters, -126.6 μm, and 4.3, respectively), with an average of 4.1 ranibizumab injections.

According to a manufacturer press release, a new 1-year study (REPAIR) suggests positive outcomes for patients across multiple retinal disease areas.[164] At the 2013 Association for Research in Vision and Ophthalmology annual meeting, the company presented the following data pertaining to the drug's DME indication:[164]

> The response rates were evaluated in patients with DME in the RESTORE trial. Patients were treated with Lucentis 0.5 mg (monotherapy or combined with laser) or laser alone for a duration of 12 months, at 12 months all patients were eligible for Lucentis 0.5mg as-needed and the study was extended to 36 months. The patients who responded better to Lucentis treatment were the ones who were more recently diagnosed with DME, highlighting the need for prompt therapy.

Manufacturer and regulatory status: Genentech, a subsidiary of F. Hoffmann-La Roche, Ltd. (Basel, Switzerland), and Novartis International AG (Basel, Switzerland) have developed ranibizumab. Ranibizumab has a long approval record, as follows:

- In 2006, it gained FDA approval for treating wet age-related macular degeneration.[158,165]
- In 2010, it was FDA approved for treating macular degeneration after retinal vein occlusion.[158]
- In 2011, the European Commission granted approval for treating DME.[166]

- In August 2012, FDA approved ranibizumab injection for treating DME, basing its decision on the RISE and RIDE phase III trial results.[167]

Genentech has the commercial rights to Lucentis in the United States, and Novartis has exclusive rights to the therapy in the rest of the world.[164]

Diffusion: Cost is likely to be a major factor influencing ranibizumab diffusion, especially because the competing drug bevacizumab can be used off-label at a much lower cost. At the time of its approval, the estimated cost of a ranibizumab injection was reported to be about $1,170, with one source quoting ranibizumab (0.5 mg/0.05 mL injection) at $2,437.50 per treated eye per month.[168,169] As of December 2013, a U.S.-based, online aggregator of pharmacy pricing listed ranibizumab cost at about $2,000 per vial with the use of a coupon.[146]

The U.S. Centers for Medicare & Medicaid Services has not established a national coverage determination for ranibizumab.[170] However, as of August 2012, several local coverage determinations for ranibizumab for treating DME were in effect.[171] Many payers, including Aetna, GroupHealth, and Rocky Mountain Health Plans, have added ranibizumab (0.1 mg injection; bill 3 units) to their formularies.[169,172-174] Payers typically require preauthorization for coverage. Genentech has a patient-assistance program to help defray costs for qualified patients.[175]

Several studies assessing the cost-effectiveness of ranibizumab compared with other available treatments for DME have been reported. A 2012 study by Mitchell and colleagues in the United Kingdom evaluated ranibizumab as either monotherapy or combined with laser therapy, compared with laser monotherapy. They used data from the phase III RESTORE trial and reported the following results:[176]

> Ranibizumab monotherapy resulted in a 0.17 QALY [quality-adjusted life-years] gain at an incremental cost of £4191 relative to laser monotherapy, yielding an incremental cost-effectiveness ratio (ICER) of £24 028. Probabilistic sensitivity analysis showed a 64% probability of being cost-effective at a threshold of £30 000 per QALY. Combined ranibizumab and laser therapy resulted in a 0.13 QALY gain at an incremental cost of £4695 relative to laser monotherapy (ICER £36 106; 42% probability of ICER <£30 000).

According to the authors, "ranibizumab monotherapy appears to be cost-effective relative to laser monotherapy."[176]

But in another study, published in September 2013, ranibizumab therapy was not deemed most cost-effective. Stein and colleagues compared the incremental cost-effectiveness of treating patients with newly diagnosed clinically significant DME (CSDME) using focal laser photocoagulation alone, focal laser plus intravitreal ranibizumab, focal laser plus intravitreal bevacizumab, or focal laser plus intravitreal triamcinolone injections.[177] Using a hypothetical cohort of patients (aged 57 years) with newly diagnosed CSDME and data from the DRCRnet randomized controlled trial, the Medicare fee schedule, and the medical literature, the authors concluded that "with bevacizumab and ranibizumab assumed to have equivalent effectiveness and similar safety profiles when used in the management of CSDME, [focal laser plus] bevacizumab therapy confers the greatest value among the different treatment options for CSDME."[177]

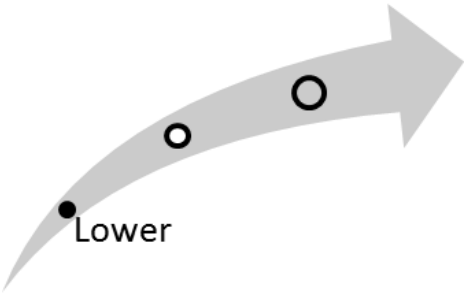
Bevacizumab is a VEGF inhibitor and is reportedly used widely for off-label treatment of ophthalmic conditions, including DME, as a significantly less-expensive alternative (about $150 per dose) to ranibizumab.[147-150] However, some researchers report that intravitreal injections of bevacizumab are associated with a significantly higher rate of serious adverse events, which could pose an additional cost burden to treat. In one Canadian retrospective study, subjects who received bevacizumab for ophthalmic indications were 12 times as likely to develop severe intraocular inflammation after each injection as were patients who received ranibizumab injections.[151]

Ranibizumab is being investigated in 660 patients in an ongoing phase III comparative effectiveness study (with intravitreal aflibercept and intravitreal bevacizumab); results from this trial, slated to end in January 2016, are expected to affect the therapy's diffusion among patients with DME.[178]

Clinical Pathway at Point of This Intervention

A patient who presents with symptoms suggesting DME undergoes a history and physical examination, including an assessment of his or her history of vision and eye disease and risk factors for DME, including diabetic history (T1DM at higher risk), older age, poor glucose control, pregnancy, hypertension, and increased lipid levels.[125] Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. DME treatment focuses on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Standard therapy is laser photocoagulation, which can reduce the risk of moderate visual loss, but some patients experience permanent vision loss even after intensive treatment. New advances in pharmacotherapy and surgical techniques have shown promise in treating DME.[125]

Figure 5. Overall high-impact potential: ranibizumab (Lucentis) for treatment of diabetic macular edema



Experts thought ranibizumab could offer a desirable alternative to laser photocoagulation for treating DME because no FDA-approved pharmacotherapy for DME existed before its approval for this indication. Some experts thought that the frequency of the intravitreal injections might pose a barrier to patient acceptance, limiting ranibizumab's ability to significantly improve patient outcomes and potentially affecting patient acceptance. Experts thought significant costs would be associated with this intervention, particularly if it is used as adjunctive therapy to laser photocoagulation and because it would likely be additive to laser therapy and also because a less costly off-label alternative is available (bevacizumab). However, experts thought ranibizumab's potential to restore vision or slow disease progression was significant. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[179-184] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Pharmacotherapy options for DME are limited, said the experts; laser photocoagulation offers an invasive intervention with a variable degree of efficacy and does not restore vision as does ranibizumab, all of the experts agreed. One research expert stated that, "preliminary data suggests limited effectiveness of laser treatment at [1] year and an

unknown risk of permanent visual loss." Another research expert stated that the increasing number of people receiving a diagnosis of diabetes makes treatment pharmacotherapy options for managing DME an important need. One clinical expert opined that at this time this is the only successful treatment available with high-yield success.

Regarding ranibizumab's potential to improve patient health outcomes, one clinical expert expressed satisfaction with this drug's efficacy not only in research, but also in the clinical setting. Another clinical expert mentioned this drug's potential efficacy, shown in two phase III trial results, but cautioned that the disease responded to therapy in only 30% to 40% of subjects and expressed concern over potential selection bias in trials because the drug was not directly compared with laser therapy. Altogether, experts generally agreed that ranibizumab for treating DME has the potential to significantly improve patient health outcomes, believing this drug could be a more practical, less expensive option than laser photocoagulation.

Acceptance and adoption: This intervention's potential for clinician and patient acceptance is high because more-effective therapy to treat DME is needed, all of the experts agreed. Regarding clinician acceptance, one clinical expert said adoption is likely, given the "convenience and ease of delivery. Most ophthalmologists are probably using intravitreal injections for [age-related macular degeneration] treatments with minimal side effects."

In terms of per-patient costs for ranibizumab, experts opined that costs would be significantly higher than costs for laser photocoagulation. But one clinical expert stated that although costs are currently high, per-patient costs and costs to insurers will probably decrease over time. A health systems expert opined that despite its cost, this drug will "probably become a standard procedure either independently or (more likely) along with photocoagulation."

Health care delivery infrastructure and patient management: Expert opinions were mixed on this intervention's potential to disrupt the current health care delivery infrastructure. Some suggested that an effective intravitreal drug would not significantly affect current care settings, while others argued that the increase in physician visits to receive a monthly intravitreal injection and followup compared with a one-time outpatient laser photocoagulation procedure could significantly change the health care delivery infrastructure.

Health disparities: Opinions were mixed on this intervention's potential to affect health disparities; several experts argued that the frequency of intravitreal injections would increase nonadherence to treatment recommendations among patients in rural and poor areas, increasing disparities. Several experts thought the cost of ranibizumab in terms of dollars per QALY would be significantly more expensive than laser photocoagulation, therefore widening the barrier for the economically disadvantaged. However, one researcher stated that intravitreal injections would be more accessible for disadvantaged patient populations than surgical options, therefore reducing health disparities.

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