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

Priority Area 07: Diabetes Mellitus

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA290201000006C

Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

June 2013

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.

Disclaimer Regarding 508-Compliance

Individuals using assistive technology may not be able to fully access information in this report. For assistance contact info@ahrq.gov.

Financial Disclosure Statement

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

Public Domain Notice

Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 07: Diabetes Mellitus). (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. June 2013. http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Contents

Executive Summary ES-1
Background ES-1
Methods ES-1
Results ES-2
Discussion ES-3
Diabetes Mellitus Interventions 1
Artificial Pancreas for Treatment of Diabetes 2
New Exenatide Formulations (Bydureon; ITCA 650 with Match-Sized Pump) for Treatment of Type 2 Diabetes Mellitus 7
Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema 13
Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema 19
References 24

Figures

Figure 1. Overall high-impact potential: artificial pancreas device system for treatment of diabetes 5
Figure 2. Overall high-impact potential: new exenatide formulations (Bydureon; ITCA 650 with Duros pump) for treatment of type 2 diabetes mellitus 10
Figure 3. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema 16
Figure 4. Overall high-impact potential: ranibizumab (Lucentis) for treatment of diabetic macular edema 22

Executive Summary

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 identifying 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 4 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 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 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 annually. Topics eligible for inclusion are those interventions expected to be within 0–4 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 10 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 May 16, 2013, in this priority area; *and* (3) we received six to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Twenty-one topics in this priority area were being tracked in the system as of May 18, 2013.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present four summaries on five 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 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 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. *Exenatide subcutaneous pump (ITCA 650 with Duros pump) for treatment of type 2 diabetes mellitus	Lower end of the high-impact-potential range
5. *Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Moderate
6. Interactive text messaging program (Care4Life) to improve management of type 2 diabetes mellitus	No high-impact potential at this time
7. Off-label salsalate for treatment of type 2 diabetes	No high-impact potential at this time
8. *Ranibizumab (Lucentis) for treatment of diabetic macular edema	Moderate
9. Service dogs (diabetic alert dogs) for detection of hypoglycemia in patients with insulin-dependent diabetes mellitus	No high-impact potential at this time
10. 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 about 95% of cases. In 2011, the American Diabetes Association (ADA) published a fact sheet reporting that 25.8 million children and adults in the United States, or 8.3% of the total population, have diabetes mellitus. The ADA reported that approximately 18.8 million people have received a diagnosis of diabetes mellitus, and 7.0 million people have diabetes that has not been diagnosed. 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 USPSTF 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 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 level 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 excursions high or low, to improve patient adherence to treatment regimens, and to reduce acute excursions (i.e., hyperglycemia, hypoglycemia), weight gain, and secondary complications (i.e., nephropathy, neuropathy, retinopathy).

Artificial Pancreas 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 with insulin delivery. It is considered by many to be the ideal management strategy for patients with diabetes who require intensive insulin therapy. Researchers and manufactures are developing two types of systems: reactive or predictive low-glucose suspend systems. In reactive systems, patients or clinicians preset 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 although all the necessary component parts of a CLS exist, a truly portable CLS for routine use is several years from realization 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 some are in pilot studies. On November 9, 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. FDA placed development of APDSs on the agency's new Innovation Pathway, which seeks to enable a unique device that addresses a significant unmet need to be brought to market more quickly (i.e., within 4 years).
- **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.

- **Potential for High Impact**: High

New Exenatide Formulations (Bydureon; ITCA 650 with Duros Pump) 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, once-weekly formulation delivered 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 $354 to $469 per month or about $4,250 per year; the lower rates take into account availability of a $50 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 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

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) that leads to moderate or even to complete vision loss over time. The main treatment for DME had been macular focal/grid laser photocoagulation until August 2012, when FDA approved another therapy, Lucentis® (ranibizumab injection), that is administered as a once-monthly injection into the eye. Iluvien (Alimera Sciences, Inc.,

Alpharetta, GA) is a tiny tube containing 190 mcg of fluocinolone acetonide that is injected 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, patients need not return for monthly injections, as is required with Lucentis. The exact mechanism by which fluocinolone acetonide works in treating DME is unknown, but it is thought to work by the combined vasoconstrictive, anti-inflammatory, and antipruritic qualities inherent to corticosteroids such as fluocinolone. In November 2011, FDA issued a complete response letter requesting that the company provide two additional safety and efficacy studies before resubmitting a new drug application (NDA). The company resubmitted an NDA to FDA, and the new Prescription Drug User Fee Act date is slated for October 17, 2013. The drug/device has been approved in Europe. If approved in the United States, this drug would compete with the recently approved Lucentis and aflibercept (Eylea® injection); the latter is in phase III trials for treating DME. The product's history of regulatory rejections and potential risk of increasing intraocular pressure might dissuade other 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 other monthly injections for treating DME. Although some experts believe the risk of adverse events would affect patient and clinician adoption of this intravitreal 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**: Moderate

Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

- **Key Facts**: Until the approval of ranibizumab for DME in August 2012, the main treatment was macular focal/grid laser photocoagulation, because no other pharmacotherapies were FDA approved for DME. Ranibizumab (Lucentis, 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 has 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 action inhibits growth of new blood vessels under the macula. Because growth of new blood vessels 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. Reported cost of an injection is about $1,170. Some third-party payers reimburse for the drug, and some of those require prior authorization. Genentech offers payment assistance to qualified patients. This drug will compete with other drugs in phase III trials, such as Iluvien and aflibercept (Eylea injection).
- **Key Expert Comments**: Some experts thought that the frequency of intravitreal ranibizumab administration might pose a barrier to patient treatment adherence, limiting its

ability to significantly improve patient outcomes and potentially affecting patient acceptance. Experts thought that the per-patient cost of about $20,000 annually associated with ranibizumab use might pose a barrier to adoption by patients. 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**: Moderate

Diabetes Mellitus Interventions

Artificial Pancreas for Treatment of Diabetes

Unmet need: Traditional glucose meters and continuous glucose monitors (CGMs) help monitor blood glucose levels in patients with diabetes mellitus, yet two-thirds of patients requiring insulin do not achieve adequate glycemic control. CGMs are susceptible to errors that arise from incorrect calibration, rapid glucose changes, and glucose levels within the hypoglycemic range.[1] CGMs are also unable to protect a patient from nocturnal hypoglycemia (i.e., low blood sugar during sleep), and their value for lowering glycated hemoglobin (HbA_{1c}) in patients aged 25 years or younger is unclear.[1,2] Constantly fluctuating glucose levels makes diabetes management and control difficult, often requiring adjustments to insulin dosage. A major barrier to achieving adequate glycemic control for some patients is optimal access to health care providers to assist them in adjusting insulin dosages. The Diabetes Control and Complication Trial highlighted the importance of tight glucose control to prevent long-term diabetes-related complications (e.g., nephropathy, retinopathy, neuropathy, heart disease) in 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 combines several technologies currently used for diabetes management with a glucose sensor and using advanced computer algorithms to purportedly provide better glycemic control for this patient population.[5]

Intervention: Artificial pancreas device systems (APDSs) under development are intended to mimic the activity of a natural pancreas. An APDS consists of an external or implantable insulin pump and blood glucose monitoring system that can monitor blood glucose levels in real time through a small computing device that uses an algorithm to determine insulin dosage delivery.[5] An APDS aims to monitor patient blood glucose levels and automatically respond to these levels using a computerized algorithm and pumping out appropriate doses of insulin from an internally or externally worn pump.[6] In a November 2012 guidance document, the U.S. Food and Drug Administration (FDA) defined the components of APDSs as follows, stating also 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, and including, 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 insulin 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 both in the United States and internationally, and much of the research is supported by the Juvenile Diabetes Research Foundation (JDRF). In 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:[9]

> On nights when the artificial pancreas was used, versus nights when the sensoraugmented 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 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:[10]

> 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 2011, Zisser and colleagues released an evaluation of an APDS in 10 patients showing that this intervention can "safely regulate glycemia in patient with type 1 diabetes even following a meal challenge, without prior meal information."[11] 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."[11]

In a new trial, expected to complete in July 2013, children stay overnight with their parents at the U.K. Cambridge Clinical Research Facility (CRF), a joint venture between Cambridge University's School of Clinical Medicine, the Diabetes Research Network, National Institute for Health Research and the Wellcome Trust.[12] Several additional studies on the APDS are ongoing.[12]

Manufacturer and regulatory status: The separate components that compose an APDS—external insulin pumps and CGMs—have had marketing approval for some time.[6] In November 2012, FDA published guidelines, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems," to inform the sponsors of APDS IDE studies on how to support a PMA for "single patient use in the home environment."[7] Regarding clinical study progression, the guidelines provide 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 in-patient 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.

At least three companies are pursuing APDSs.[13] Medtronic, Inc. (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.[14] Medtronic has promoted CGM integration by developing the MiniMed Paradigm Veo, a low-glucose suspend APDS.[15] The Veo, launched in 2009, is available in 50 countries outside the United States, including Canada.[14]

Medtronic received FDA approval at the end of 2011 to begin an in-home pivotal trial (Automation to Simulate Pancreatic Insulin Response [ASPIRE]) of a low glucose suspend APDS in the United States.[6,16] The ASPIRE clinical trial aims to evaluate the safety and efficacy of the systems in a home setting.[16] Medtronic and another company, Tandem Diabetes Care, Inc., of San Diego, CA, have formed a partnership with JDRF to advance technologies toward realizing a fully automated monitor/pump combination.[17]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 CE (Conformité Européene) mark in June 2011, and has been released in the United Kingdom.[16] In April 2013, Animas submitted a premarket approval (PMA) application to FDA for the device, and the company is working through a second feasibility study.[13,18]

Diffusion: An APDS is intended for patients on intensive insulin management who are suitable candidates for insulin pumps.[1] The most appropriate patients are those with T1DM who frequently experience hypoglycemia and are highly motivated to achieve control and are able to use an insulin pump.[19,20] Among patients who are suitable candidates, many are likely to use the automated technology if it becomes available, in particular those who have trouble maintaining normal nocturnal glycemia.[21] Data on the safety and efficacy of the APDS from ongoing and future clinical trials are likely to dictate the rate and extent of diffusion. Once the technology is developed and approved for use, its diffusion may be limited to centers of excellence due to the level of expertise and comprehensive training required.[14] However, if the APDS effectively slows the progression of diabetes, the device might become more widespread for both health and economic reasons.[4,22] For example, an estimated $174 billion 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 $23 million over 10 years by slowing progression of the disease in patients.[4,22]

FDA has approved about 20 IDEs for APDS trials. Most device prototypes are in early-phase development.[14,23] The development of an APDS capable of regulating bolus insulin injections remains an engineering obstacle.[15] In June 2013, five people with T1DM in the United Kingdom became the first in the world to use an APDS at home.[24] According to a report, 24 people will have taken part in home trials of the device by the end of 2013.[24] However, the device is not expected to become available as a treatment for T1DM for several years.

Clinical Pathway at Point of This Intervention

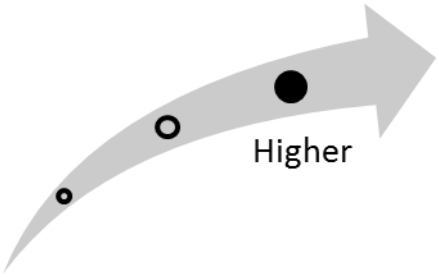
Patients with T1DM require insulin therapy. For T2DM, one or more self-administered oral antidiabetes agents taken alone or in combination are generally tried as first-line therapy.

Upon diagnosis, patients undergo medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan, including establishing target blood glucose levels and HbA_{1c} goals. The HbA_{1c} test measures the average amount of glucose in a patient's blood over a 3- or 4-month period with a single blood draw. It is the accepted standard for measuring successful diabetes management. Ongoing, patients are given a treatment plan and are taught how to self-manage their day-to-day care. Clinicians encourage

patients to achieve an HbA_{1c} level of 7% because this value has been shown to reduce some of the complications associated with T2DM.

Clinicians recommend insulin therapy for patients with T1DM. Some patients with T2DM also need insulin therapy, but most undergo treatment with pharmacotherapy (e.g., metformin) combined with lifestyle modifications.[2] Currently, patients work with their physicians to adjust insulin dosages using feedback from a blood glucose monitor.[6] Some patients with diabetes 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, if they are highly motivated and capable of using such devices.[1,25]

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



Overall, experts commented 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.[26-31] We 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 controlling blood glucose levels in an automated fashion and could be addressed by an APDS that would link CGMs and insulin pumps with seamless feedback, the experts agreed. "A gap exists," one research expert stated, "because we don't have a method of convincing the pancreas to once again produce insulin (for example) and [an] insulin pump and glucose monitor are important pieces of the solution, but we do need a software component that bridges the gap between the two pieces." 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 regarding glucose control for patients with T1DM, the experts generally agreed. One research expert stated that this device has potential to limit variable swings in glucose levels, thus improving short- and long-term glucose control. But the experts called for longer safety and efficacy studies to determine whether this system would significantly improve patient health outcomes, and one clinical expert said that APDS development is still in its infancy and needs refining before becoming appropriately available in the clinical setting.

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 highly complicated to operate and, thus, would be indicated only for a subset of patients who are highly motivated to learn to use the technology and who have access to a multidisciplinary diabetes care team trained in use of an APDS. Additionally, experts indicated that these systems would likely need significant maintenance by users and physicians to ensure their proper function. While experts thought that the initial use of these systems would be limited, they saw significant potential for these systems to become widely used after a period of refinement. One clinical expert explained, "A large percentage of patients with type 1 diabetes would very likely elect for implantation of an artificial pancreas if given the option. The benefits of tight glycemic control, reduction in the need for intermittent self glucose monitoring and self administration of insulin will place high demand for and rapid adoption of this technology."

Health care delivery infrastructure and patient management: If sufficient refinement of the systems should occur, most experts believe, it could eventually simplify diabetes care for patients and physicians by reducing the "need for intermittent self glucose monitoring and self administration of insulin…." Relative to current treatments, experts envisioned small care-setting shifts, noting the potential reduction in hospitalizations related to adverse events. However, one health systems expert explained that early versions of the artificial pancreas could require more monitoring by clinicians, at which point "provisions would also need to be made to reimburse clinicians for the increased time required to oversee the patients."

Early versions of the artificial pancreas will be expensive and its use most likely would lead to higher upfront costs for patients, the experts also thought. However, they believe that refinement of the systems and wider adoption would eventually reduce patients' upfront costs. Additionally, several experts noted that the high cost of the artificial pancreas system could be offset somewhat by improved glycemic control, which could result in fewer adverse health outcomes needing medical intervention in these patients.

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.

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 to aid patients with T2DM in improving glycemic control.[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.[32] 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 currently approved by FDA, exenatide (Byetta®) and liraglutide (Victoza®), require twice- or once-daily subcutaneous injection, respectively.[32,33] New treatments that provide a more constant dose of exenatide than repeated injection are needed and could improve patient compliance to therapy.

Intervention: Two GLP-1–receptor agonist therapies for treating T2DM, one in development and one approved in 2012, are intended to improve drug efficacy and tolerability as well as patient adherence to treatment recommendations. They are as follows:

- Extended-release exenatide (exenatide once-weekly [EQW]; Bydureon®)
- 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

EQW is a GLP-1 receptor agonist formulation that allows for once-weekly dosing rather than the once- or twice-daily dosing with current GLP-1 receptor agonist formulations. This formulation consists of injectable exenatide encapsulated in microspheres consisting of a biodegradable polymer (poly [D,L lactic-co-glycolic acid]).[33] As the microsphere degrades in the bloodstream, exenatide is slowly released.[33] The microsphere technology used in EQW has also been used in other extended-release drugs such as extended-release naltrexone (Vivitrol®) and extended-release risperidone (Risperdal®, Consta®).[33] In clinical trials, EQW was administered at a dose of 2 mg per week.[33]

ITCA 650, a proprietary form of exenatide delivered subcutaneously and continuously through a tiny implanted stick-shaped pump,[34,35] is purported to remain stable at body temperature for as long as a year, according to the most recently presented data.[36] The delivery system is a semipermeable, osmotic mini-pump that a physician or physician assistant implants into 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 (after which it must be reimplanted), potentially providing a more convenient dosing option for patients.[37] The system is also designed to minimize the nausea associated with twice-daily dosing.

Clinical trials: The manufacturer has completed the six-trial, Diabetes Therapy Utilization: Researching Changes in A1C, Weight, and Other Factors Through Intervention With Exenatide Once Weekly (DURATION) program evaluating the safety and efficacy of EQW compared with other diabetes therapies. The comparators for each study were the following:

- DURATION-1, twice-daily exenatide injection (Byetta)[38]
- DURATION-2, sitagliptin or pioglitazone[39]
- DURATION-3, once-daily subcutaneous insulin glargine (Lantus®)[40]
- DURATION-4, metformin, pioglitazone, or sitagliptin[41,42]
- DURATION-5, exenatide injection (Byetta)[43]
- DURATION-6, liraglutide[44]

In 2013, Buse and colleagues reported the following results from DURATION-6:[44]

> 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 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:[45]

> 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.

The cardiovascular outcomes in 9,500 T2DM patients after treatment with EQW is being investigated in an ongoing phase III clinical trial (Exenatide Study of Cardiovascular Event Lowering Trial [EXSCEL]).[46]

The safety and efficacy of ITCA 650 delivered via the pump system compared with twice-daily exenatide injections (Ex-BID) was evaluated in a randomized phase II trial in patients with T2DM inadequately controlled with metformin.[47] Stage I of the study involved 155 subjects who were randomly assigned to receive 12 weeks of treatment with 20 or 40 mcg/day of ITCA 650 or Ex-BID. For Stage II, 131 subjects were re-randomly assigned to receive 20, 40, 60, or 80 mcg/day of ITCA 650 for an additional 12 weeks, culminating in a 24 week-long study. In 2013, Henry and colleagues published the following results:[47]

> 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 clinical studies will cover a broad range of patients whose diabetes is not controlled by oral antidiabetes medications including metformin and metformin-based combinations.[48]

Manufacturer and regulatory status: Amylin Pharmaceuticals, now owned by 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. 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.[49] Basing its decision on data from the DURATION program, 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."[50-52] FDA issued a Risk Evaluation and Mitigation Strategy (REMS) to accompany the drug's approval.[51] The REMS included obligations for Amylin to conduct additional clinical trials to evaluate the risks of adverse events (e.g., medullary thyroid carcinoma [MTC], acute pancreatitis) with EQW and create a case-series registry to monitor the annual MTC incidence.[51,53,54] After approval of the REMS, FDA expects Amylin to submit assessment updates on extended-release exenatide after 1, 2, and 7 years.[51]

ITCA 650 was formulated by Intarcia Therapeutics, Inc., of Hayward, CA. ALZA Corp., a unit of Johnson & Johnson, Inc. of New Brunswick, NJ, licensed its drug delivery technology to various companies, including Intarcia; the technology has been used commercially since 2000.[55] After successfully completing phase II trials, Intarcia announced a collaboration with Quintiles, Inc. (Durham, NC), in September 2011 to begin a phase III program of six trials.[56,57] 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.[58] 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.[59]

Diffusion: EQW and ITCA 650 are most likely to compete with available GLP-1 receptor agonists, including exenatide (administered twice daily) and liraglutide (administered once daily).[32,33] The cost of EQW reported by 11 pharmacies in the United States ranges from $354 to $469 per month; the lower rates take into account availability of a $50 discount coupon.[60] For comparison, once-daily, liraglutide costs about $421 per month.[54] By offering extended-release exenatide at a relatively lower price, the company intends to overcome competition with other T2DM treatments and increase the drug's accessibility for patients in need.[54] Many third-party payers provide coverage requiring prior authorization and quantity limits.[61-68]

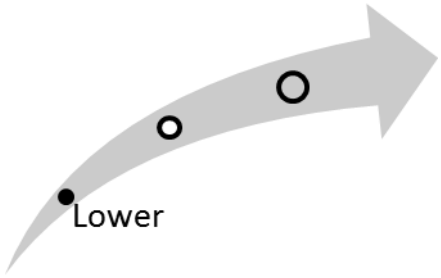
The cost for ITCA 650 has not been determined, but will likely be priced at a slight premium to the existing injectable exenatide formulations because of its novelty and convenience.[69] While ITCA 650 use would add to the upfront cost of drug therapy, it could potentially result in cost savings if it improves patient adherence to treatment, slows disease progression and the development of secondary complications, and eliminates the attendant health services needed to treat those complications.

Clinical Pathway at Point of This Intervention

T2DM is a chronic disease that typically occurs later in life, although incidence in a younger population has been growing as a result of obesity. T2DM results from development of peripheral insulin resistance and an insulin-secretory defect. 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. For some patients, a single oral agent is sufficient; however, if adequate glycemic control is not achieved, patients can be given a combination 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 one of two types of injected antidiabetes agents: subcutaneous insulin or a GLP-1 agonist.[70] If these measures are inadequate, physicians might also prescribe medication to control blood sugar levels.

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



Overall, experts opined that these new formulations of exenatide have potential to improve diabetes treatment by reducing injection frequency and nausea, 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).[71-77] Six experts, with clinical, research, and health systems backgrounds, provided perspectives on ITCA 650 (subcutaneous exenatide).[78-83] Given that these two therapies are geared toward extending release and improving efficacy of exenatide, we synthesized both sets of expert comments here. We organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: Whether EQW will be able to address the unmet need was a matter of mixed opinion. Although some experts agreed that any new therapy for treating diabetes would be welcome, this form of exenatide may be an incremental improvement and 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 opined, "Patients with T2D who are not well managed on metformin alone and who may benefit from GLP-1 [agonists] are often discouraged by the injection requirement-compliance can be low."

The underlying mechanisms for both modifications to exenatide appear sound, the experts generally agreed, citing currently approved forms of exenatide and other GLP-1 agonists already on the market. Several experts referred to early 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. In regards to extended-release exenatide, one research expert believes that although clinical studies show that this therapy could be marginally effective, it will not significantly improve patient health outcomes. However, one clinical expert noted, "In terms of improving glycemic control, extended-release exenatide is more effective than oral antidiabetic drugs, and twice daily exenatide injection, but slightly inferior to once daily liraglutide injection. Extended-release exenatide has an advantage of once weekly injection, which could potentially improve compliance." A research expert agreed that this formulation has potential to improve patient adherence to therapy but cautioned that "the microsphere technology in the extended-release formulation requires patients to use a larger-bore needle and may cause more injection-site adverse events [than] conventional daily dosings."

Health outcomes could improve with both modifications to exenatide because of better patient adherence to treatment recommendations 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 of exenatide via the Duros 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 types of exenatide, most experts agreed that patients and clinicians will welcome new treatment options that require fewer injections than available exenatide formulations. They thought that some patients might be hesitant to use EQW because it still requires injection and with a larger needle, but that injections once a week would be easier than comparators which require daily injections. Commenting on EQW, one expert with a health systems background thought that "the largest controversy would be the published boxed warning concerning the incidence in thyroid C-cell tumors in exposed rats and the increased risk of pancreatitis." This expert added that prescribing providers would need to be willing to monitor renal function in patients using EQW. Commenting on clinician acceptance of EQW, a clinical expert thought that "depending on effectiveness, this weekly form of injection may have some increased use with primary care physicians as it would be easier for the patient and GP [general practitioner] to implement. Among specialists, the key is whether it is likely to improve glucose control, weight loss as compared to the other available medications."

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." One research expert pointed out that an implantable device such as ITCA

650 might be appealing because it "gives the cognitive specialist a procedure, thus enhancing reimbursement."

But some experts pointed out that patients might not be as enthusiastic about ITCA 650 as physicians because of the "fear of a permanently implanted device." A clinical expert opined that "although the route of administration [is] innovative, patients most likely will be resistant to the insertion of the device subcutaneously," pointing out that concerns such as "infection or device malfunction are likely to influence patients from choosing this method." However, this expert also thought that "if exenatide delivered via the pump produces less nausea, it may lead to better acceptance."

Health care delivery infrastructure and patient management: Neither of the new formulations of exenatide will disrupt healthcare 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 will "disrupt the system by reducing the amount of day-to-day attention that will need to be paid to the health of those with diabetes" compared with drugs that require injection once or twice a day.

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. According to a health systems expert commenting on ITCA 650, "it is not difficult to implant this subcutaneous device which must be reimplanted annually so this should not be disruptive to the system. If it improves [diabetes] management...it will be very successful in reducing the medical care for complications." A clinical expert agreed, adding that insertion of the device "can be done within an office setting [and] would not require the use of a hospital facility." ITCA 650 has potential to improve patient adherence to treatment, this same expert thought, adding that "if this intervention is affordable, and its effectiveness is further demonstrated in subsequent trials, it could become as important as metformin is to the treatment of type 2 diabetes."

Opinions diverged on whether cost of care would rise or fall with these modifications to exenatide. Some experts believe that per-patient costs would increase with both forms of exenatide, but others noted that an increase in patient adherence to treatment and subsequent decrease in disease complications would lower long-term, per-patient costs. One expert summed up the differences, stating, "Initially, the cost would be increased for the patient and the third party payers when compared to cheaper generic products. It is cheaper than once daily competing product (Victoza). But overall, it would be less expensive for patients, third party payers, and healthcare facilities if the patient would be able better manage their diabetes."

In regards to subcutaneous exenatide, one clinical expert noted, "If this intervention provides significant long-term reduction in glycohemoglobin and prevents complications [of] diabetes, the cost of the device is likely to be minimal in comparison to the dollars saved from the complications of diabetes."

Health Disparities: Experts commenting on health disparities agreed that both forms of exenatide will have a minimal impact. They thought that access to the drugs would be limited to patients who are informed about their availability and 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." Another expert with a research background pointed out ITCA 650 "may offer therapy to patients unable to inject themselves or who don't have a reliable caregiver to do so." This expert added that ICT 650 could be "great for patients who live a long way from physicians" if it requires only a single annual implantation procedure.

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.[84] People with diabetes who go untreated for eye care have a 25% to 30% chance of developing moderate vision loss.[85] 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: Iluvien is a sustained-release, intravitreal corticosteroid insert intended for treating DME.[86] 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.[87] The insert consists of 190 mcg of the corticosteroid fluocinolone acetonide in a tiny, cylindrical, polymide tube designed for 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 through stable, long-term release of fluocinolone acetonide into the eye.[86,88] In clinical trials, two dosages 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.[86]

Clinical trials: In a 2013 analysis of two multinational trials in patients with DME previously treated with macular laser photocoagulation, authors reported the following:[89]

> 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 (Campochiaro et al., 2012) reported the following data from the completed 36-month trial:[90]

> 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 trial listed (Campochiaro et al., 2011) reported the following data at month 24:[91]

> 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."

This 24-month data is the data that was submitted in the manufacturer's original 2010 FDA new drug application (NDA).

In 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:[92]

> 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:[93]

> 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.[94] 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.[95]

According to a May 2013 company press release, a patient in Germany has become the first in the world to use the commercially available fluocinolone acetonide implant.[96] Iluvien is being marketed in Austria, France, Germany, Portugal, Spain, and the United Kingdom.[96] In these countries, Iluvien is approved for treating "DME considered insufficiently responsive to available therapies."[97]

Diffusion: The standard treatment for DME is laser photocoagulation; this treatment cannot reverse vision loss that has already occurred, and vision loss continues to progress in some patients despite treatment. [84,98,99] Additional vision loss is also a risk associated with the laser photocoagulation procedure.[98] Although the fluocinolone acetonide implant may compete with laser photocoagulation therapy, it is more likely that it will serve as a complementary intervention or alternative in cases in which laser photocoagulation treatment has failed. Off-label corticosteroid injections are being used by some retinal physicians to treat DME; however, multiple intravitreal injections are required for effective treatment.[100-102] The fluocinolone acetonide implant, a potentially more convenient and safer corticosteroid therapy, is likely to be an appealing treatment option for patients with DME whose condition does not respond to laser photocoagulation therapy.

Costs for the Iluvien implant are not yet established in the United States because the product has not received FDA marketing approval. However, the product is expected 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 was $18,250 as of August 6, 2012. The product is designed to deliver its drug payload over 30 months.[103] This estimated cost is comparable to other cutting-edge ophthalmic treatments, such as pegaptanib (Macugen®) injections, which are indicated to treat wet age-related macular degeneration and cost about $8,000–$9,000 per year (approximately $1,000 per injection).[103]

The fluocinolone acetonide implant will probably compete with the vascular endothelial growth factor (VEGF) inhibitor ranibizumab (Lucentis®), which is approved for treating DME with monthly intravitreal injections.[104] Ranibizumab costs an estimated $1,200 per month.[105]

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) than ranibizumab.[106-109] However, some researchers report that intravitreal

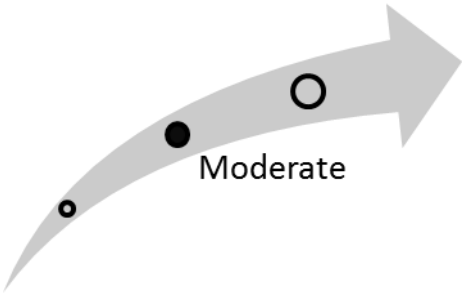
injections of bevacizumab are associated with a significantly higher rate of serious adverse events, which could pose an additional cost burden to treat. In one Canadian retrospective study, subjects who received bevacizumab for ophthalmic indications were 12 times as likely to develop severe intraocular inflammation following each injection as patients who received ranibizumab injections.[110]

The most common adverse event reported in the 3-year, phase III clinical trial for the fluocinolone acetonide implant was cataract formation, which occurred in 42.7% of the fluocinolone acetonide low-dose group and 51.7% of the high-dose group. Adverse events related to intraocular pressure were also found more frequently in the groups receiving fluocinolone acetonide compared with those adverse-event rates in the sham group. [90]

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, such as diabetic history (T1DM at higher risk), older age, poor glucose control, pregnancy, hypertension, and increased lipid levels.[85] 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 devices, pharmacotherapies, and surgical techniques have shown promise in treating DME.[85]

Figure 3. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema



Overall, experts thought that given the prevalence of DME among patients with diabetes, there is an important unmet need that the fluocinolone acetonide implant intends to address. Standard treatment for DME has been laser photocoagulation therapy, which neither reverses vision loss or completely prevents vision loss from worsening. One expert with a health systems and administration background pointed out that additional vision loss is a risk of photocoagulation therapy, highlighting the need for more effective therapies for treating DME. A couple of experts with research background were less optimistic about the implant because of the risk for adverse events, with one noting that the "negative benefit/risk (sic), cost, and lack of sufficient data" interfere with the therapy's potential. A clinical expert had similar concerns, adding that "larger clinical trials are needed to determine which subgroups of DME patients will benefit from Iluvien therapy [and] appropriate doses with 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.[111-116] We 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 includes laser photocoagulation therapy or corticosteroid therapy or both; therefore, "Iluvien doesn't seem to address an unmet need."

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 the therapy's safety and effectiveness for treating DME. The expert highlighted that FDA found the risk of patients developing treatment-emergent adverse events was not offset by the benefits of the fluocinolone acetonide implant and required the drug's manufacturer to conduct two additional clinical trials. The expert added that cataract formation was observed in about 42% of patients receiving low-dosage Iluvien and 52% of patients receiving the high dose. This expert and others also pointed out that adverse events related to IOP were reported and that these reasons limit the potential for the fluocinolone acetonide implant to improve health outcomes for patients with DME.

Other treatment options, such as anti-VEGF therapies are available for treating DME, and according to one research expert, "if VEGF [therapy] also increases vision why take the chance with this [the fluocinolone acetonide implant]?"

It should be noted that after the time of 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.[95] According to the manufacturer, the NDA addresses questions raised in the FDA's letter and provides additional analyses and new information supporting that the fluocinolone acetonide implant is safe and effective for treating DME.[95]

In an opinion based on available data indicating that the fluocinolone acetonide implant can improve visual acuity tests by 10% to 40% over 3 years, the clinical expert opined that "this chronic corticosteroid treatment has the potential to benefit patients in whom laser therapy has failed to improve visual acuity." Some experts also proposed that a treatment like the fluocinolone acetonide implant could improve quality of life for some patients with DME if, for example, as one systems expert offered, if it reduces the number of injections needed and provides continuous therapy.

Acceptance and adoption: Most experts thought that patient and clinician acceptance would rely heavily on the therapy's success compared with the success of other treatments available for treating DME, including more-frequent steroid injections. However, one systems expert opined, "the fact that you would need the procedure less often with Iluvien would be a key selling point." Several experts pointed out that the risks for adverse reactions observed with the fluocinolone acetonide implant might deter wide use of the therapy, at least until it is proved safe and effective in ongoing clinical trials. Other experts focused on the unmet need at hand, with one research expert commenting that "there would be wide acceptance…if the fluocinolone acetonide implant becomes an alternative to laser treatment for DME."

Commenting on the potential financial impact of the fluocinolone acetonide implant, expert opinion was mixed. Most experts thought that compared with other treatments for DME, it is likely to be costly. They thought that the impact would be large because adding another expensive therapy to the DME armamentarium would increase costs associated with treating the condition. 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 DME patients, 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 for treating DME. And an expert with a research background anticipates "it is highly likely that the cost will be lower than costs for some alternative treatments, such as laser surgery."

Health care delivery infrastructure and patient management: Experts agreed that the fluocinolone acetonide implant should 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 to treat DME. Some experts with research backgrounds pointed out that the fluocinolone acetonide implant might have a small impact on how care is delivered for patients who were previously being treated with laser photocoagulation therapy. But according to one research expert, the fluocinolone acetonide implant would be administered in the in-office setting and "could eliminate or reduce the need for in-hospital treatments, such as laser surgery." Further, prescribing the fluocinolone acetonide implant "will require resources for a careful evaluation of DME patients eligible for this therapy, and adequate follow-up and management of cataracts and glaucoma," noted a clinical expert.

Some experts commented on the fluocinolone acetonide implant's place in the current treatment paradigm for DME, opining that it is more likely to serve as a complementary treatment to laser photocoagulation therapy or as an alternative option when laser photocoagulation has failed. The fluocinolone acetonide implant is expected to compete with VEGF inhibitors, such as ranibizumab, also approved to treat DME.

Health disparities: Most experts thought that if the fluocinolone acetonide 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 increase access to treatment for some patients compared to other DME therapies that require more frequent intravitreal injections (e.g., anti-VEGF therapies). On the other hand, 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 insurance and/or who are wealthy.

Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

Unmet need: FDA had not approved any pharmacotherapies for treating DME until its 2012 approval of ranibizumab (Lucentis®). This drug is now set to compete with or complement macular focal/grid laser photocoagulation as the primary treatment modality for DME and will compete with other DME treatments in development (e.g., Iluvien, Eylea) should they reach market.

Intervention: Ranibizumab is a humanized, recombinant, immunoglobulin G1 kappa isotope, monoclonal antibody fragment targeted against human VEGF A (VEGF-A).[117] VEGF-A is a protein responsible for acting on endothelial cells that increases vascular permeability, stimulates new blood vessel formation from preexisting vessels, induces endothelial cell proliferation, promotes cell migration, and inhibits apoptosis.[118] 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 vision damage or blindness.[84]

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.[117] As a result, ranibizumab purportedly reverses retinal thickening and halts retinal disease progression.

The recommended dose for ranibizumab is 0.3 mg (0.05 mL) once monthly (every 28 days) by intravitreal injection.[117] Treatment is often required indefinitely or until reversal of vision loss.[119]

Clinical trials: In 2012, Nguyen and colleagues published results from the combined randomized, phase III RIDE and RISE clinical trials evaluating ranibizumab in 759 patients receiving a diagnosis of DME with baseline visual acuity of 20/40 to 20/320. The authors reported the following results:[120]

> 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:[121]

> 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 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 with visual impairment due to DME who completed the RESTORE core study and entered the extension. The authors reported the following results:[122]

> 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 were nasopharyngitis (18.8%) and hypertension (10.4%). There were no cases of endophthalmitis, and the incidences of nonocular SAEs 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 May 2013 Novartis press release, a new 1-year study (REPAIR) suggests positive outcomes for patients across multiple retinal disease areas.[123] 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:[123]

> 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, a therapy that gained FDA approval in 2006 for treating wet age-related macular degeneration.[117,124] In June 2010, ranibizumab was approved in the United States for patients with macular degeneration following retinal vein occlusion.[117] In January 2011, the European

Commission granted approval of ranibizumab for DME treatment.[125] In August 2012, FDA approved ranibizumab injection for DME treatment based on the RISE and RIDE phase III trial results.[126] 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.[123]

Diffusion: Research suggests that treatment costs for patients with DME are 30% higher at 1- and 3-year followup than costs for patients with diabetes but no history of retinal disease;[127] therefore, cost is likely to be a major factor influencing ranibizumab diffusion. At the time of its approval, the estimated cost of an injection was reported to be about $1,170,[128] with one source quoting ranibizumab (0.5 mg/0.05 mL injection) at $2,437.50 per treated eye per month.[129]

The U.S. Centers for Medicare & Medicaid Services has not established a national coverage determination for ranibizumab for treating DME.[130] However, as of August 2012, several local coverage determinations for ranibizumab for treating DME were in effect.[131] Many payers, including Aetna,[132] GroupHealth,[133] and Rocky Mountain Health Plans,[129] have added ranibizumab (0.1 mg injection; bill 3 units) to their formularies.[134] Payers typically require preauthorization for coverage determination. Genentech has a patient assistance program to help defray costs for qualified patients.[135]

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[136] evaluated ranibizumab as either monotherapy or combined with laser therapy, compared with laser monotherapy, for treating DME. Basing their report on data from the phase III RESTORE trial, the authors noted the following:[136]

> 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."

But in another study, ranibizumab therapy was not deemed most cost-effective. Stein and colleagues (2013) 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.[137] 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."[137]

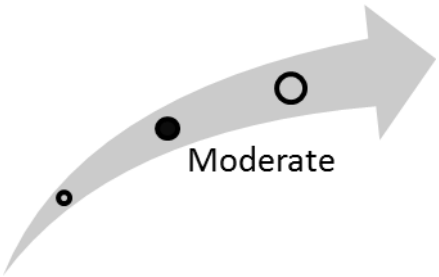
Bevacizumab (Avastin®)is a VEGF inhibitor and is reportedly used widely for off-label treatment of ophthalmic conditions, including DME, as a significantly less-expensive alternative (about $150 per dose) to ranibizumab.[106-109] However, some researchers report that intravitreal injections of bevacizumab 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 following each injection as were patients who received ranibizumab injections.[110]

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.[138]

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.[85] 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.[85]

Figure 4. 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. No FDA-approved pharmacotherapy existed before ranibizumab's approval for this indication. Some experts thought that the frequency of intravitreal injections might pose a barrier to patient adherence to treatment recommendations, 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. However, it has potential to restore vision or slow disease progression. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.[139-144]We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Treatment options for DME are limited, with laser photocoagulation being an invasive intervention with a variable degree of efficacy, all of the experts agreed. One research expert stated that with regards to photocoagulation, "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 warrants developing more treatment options for managing DME. Experts also agreed that

before Lucentis' approval, no FDA-approved treatments were available to improve vision in these patients. One clinical expert opined, "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 intra vitreal injections for [age-related macular degeneration] treatments with minimal side effects."

In terms of per-patient costs for ranibizumab, experts opined that costs are going to 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 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: This intervention's potential to affect health disparities is not clear; opinions were mixed, with several experts arguing 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.

References

1. Elleri D, Dunger DB, Hovorka R. Closed-loop insulin delivery for treatment of type 1 diabetes. BMC Med. 2011;9:120. Also available: http://www.biomedcentral.com/content/pdf/1741-7015-9-120.pdf. PMID: 22071283
2. Standards of medical care in diabetes - 2012. Diabetes Care. 2012 Jan;35 Suppl 1:S11-63.
3. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30;329(14):977-86. Also available: http://www.nejm.org/doi/pdf/10.1056/NEJM199309303291401. PMID: 8366922
4. O'Grady MJ, John PM, Winn A. Changes in Medicare spending for type 1 diabetes with the introduction of the artificial pancreas. New York (NY): JDRF; 2011 Jun 9. 3 p. Also available: http://www.jdrf.org/.
5. Gebel E. The artificial pancreas. [internet]. Alexandria (VA): Diabetes Forecast; 2010 Sep [accessed 2011 Dec 16]. [7 p]. Available: http://forecast.diabetes.org/print/2382.
6. Bylander J. FDA releases draft guidance on closed-loop artificial pancreas devices. Gray Sheet. 2011 Dec 5;37(49):article number 01111205019.
7. Guidance for industry and Food and Drug Administration staff: the content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) applications for artificial pancreas device systems. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Nov 9. 63 p. Also available: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259305.pdf.
8. Types of artificial pancreas device systems. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2011 Dec 1 [accessed 2012 Apr 10]. [2 p]. Available: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/ucm259555.htm.
9. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med. 2013 Feb 28;368(9):824-33. PMID: 23445093
10. Nimri R, Atlas E, Ajzensztejn M, et al. Feasibility study of automated overnight closed-loop glucose control under MD-logic artificial pancreas in patients with type 1 diabetes: the DREAM Project. Diabetes Technol Ther. 2012 Aug;14(8):728-35. PMID: 22853723
11. Artificial pancreas passes first test in patients with type 1 diabetes. In: Medical Economics [internet]. ModernMedicine; 2011 Jun 27 [accessed 2011 Aug 18]. [1 p]. Available: http://license.icopyright.net/user/viewFreeUse.act?fuid=MTM1MDc4OTM%3D.
12. The artificial pancreas that keeps tabs on sugar. [internet]. Medical Xpress; 2013 May 16 [accessed 2013 Jun 12]. [4 p]. Available: http://medicalxpress.com/news/2013-05-artificial-pancreas-tabs-sugar.html.
13. Garde D. Medtronic, J&J race toward artificial pancreas. In: Fierce Medical Devices [internet]. FierceMarkets; 2013 Apr 9 [accessed 2013 Jun 12]. [3 p]. Available: http://www.fiercemedicaldevices.com/story/medtronic-jj-race-toward-artificial-pancreas/2013-04-09.
14. Diabetes researchers say FDA is slowing artificial pancreas efforts. Gray Sheet. 2011 Jun 27;37(26):1, 5-6.
15. Miller M, Guthermann J. EASD 2010: innovations and challenges facing the diabetes care IVD industry. [internet]. Essex (UK): Informa UK Ltd.; 2011 Jan 18 [accessed 2011 Dec 14]. [6 p]. Available: http://www.clinica.co.uk/marketsector/other/EASD-2010-Innovations-and-challenges-facing-the-diabetes-care-IVD-industry-308765.
16. Guthermann J, Miller M. EASD 2011: the next-generation of diabetes management tools. [internet]. London (UK): Informa plc; 2011 Nov 2 [accessed 2011 Dec 14]. [2 p]. Available: http://www.clinica.co.uk/marketsector/ivds/EASD-2011-The-next-generation-of-diabetes-management-tools-323130.
17. Tandem Diabetes Care announces partnership with JDRF to develop novel dual-chamber infusion pump. [internet]. San Diego (CA): JDRF; 2013 Jan 8 [accessed 2013 Jun 13]. [7 p]. Available: http://jdrf.org/press-releases/tandem-diabetes-care-announces-partnership-with-jdrf-to-develop-novel-dual-chamber-infusion-pump/.

18. Newsflash: Animas Vibe finally submitted to FDA. In: Diabetes Mine [internet]. Salt Lake City (UT): Alliance Health Networks; 2013 Apr 16 [accessed 2013 Jun 13]. [5 p]. Available: http://www.diabetesmine.com/2013/04/newsflash-animas-vibe-finally-goes-to-fda.html.

19. Kern R. With 16 IDEs approved, FDA still questions artificial pancreas study designs. Gray Sheet. 2010 Nov 22;36(47):10-1.

20. Draft guidance for industry and Food and Drug Administration staff. The content of investigational device exemption (IDE) and premarket approval (PMA) applications for artificial pancreas device systems. Rockville (MD): U.S. Food and Drug Administration (FDA); 2011 Dec 6. 64 p.

21. Hovorka R, Kumareswaran K, Harris J, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. BMJ. 2011;342:d1855. PMID: 21493665

22. Gleason S. Lawmakers urge FDA to speed up review of diabetes. [internet]. New York (NY): Wall Street Journal; 2011 Jun 22 [accessed 2011 Dec 14]. [2 p]. Available: http://online.wsj.com.

23. Washington roundup: JDRF encouraged by FDA's artificial pancreas guidance. [internet]. Atlanta (GA): AHC Media LLC; 2011 Dec 2 [accessed 2011 Dec 16]. [3 p]. Available: http://medicaldevicedaily.com/.

24. Cooper C. Artificial pancreas promises to transform treatment of diabetes. [internet]. London: The Independent; 2013 Jun 10 [accessed 2013 Jun 12]. [10 p]. Available: http://www.independent.co.uk/news/science/artificial-pancreas-promises-to-transform-treatment-of-diabetes-8651455.html.

25. American Diabetes Association (ADA). Standards of medical care in diabetes. V. Diabetes care. Diabetes Care. 2010 Jan;33 Suppl 1:S16-29.

26. Expert Commenter 161. (External, Clinical). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Oct 10 [review date].

27. Expert Commenter 402. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 21 [review date].

28. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 13 [review date].

29. Expert Commenter 425. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 17 [review date].

30. Expert Commenter 547. (External, Clinical). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Sep 26 [review date].

31. Expert Commenter 651. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS55 - Artificial pancreas for treatment of diabetes. 2012 Oct 10 [review date].

32. Davidson JA. Incorporating incretin-based therapies into clinical practice: differences between glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors. Mayo Clin Proc. 2010 Dec;85(12 Suppl):S27-37. PMID: 21106865

33. DeYoung MB, MacConell L, Sarin V, et al. Encapsulation of exenatide in poly-(D,L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. Diabetes Technol Ther. 2011 Nov;13(11):1145-54. PMID: 21751887

34. Intarcia presents positive ITCA 650 phase 2 study results for type 2 diabetes at EASD. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2010 Sep 22 [accessed 2010 Dec 17]. [4 p]. Available: http://www.intarcia.com/IntarciaPresentsPositiveITCA650Phase2StudyResultsforType2DiabetesatEASD.html.

35. What is the DUROS technology? [internet]. Hayward (CA): Intarcia Therapeutics, Inc. [accessed 2010 Dec 17]. [1 p]. Available: http://www.intarcia.com/technology.html.

36. Yang B, D'Vaz R, Negulescu C, et al. ITCA 650 for zero-order continuous delivery of exenatide at therapeutic levels using 3-, 6-, and 12-month mini-pumps. In: Diabetes Technology Meeting; 2012 Nov 8-10; Bethesda (MD). Also available: http://www.intarcia.com/documents/Intarcia%201252D%20poster.pdf.

37. Intarcia platform technology. [internet]. Hayward (CA): Intarcia Therapeutics, Inc. [accessed 2011 Aug 18]. [4 p]. Available: http://www.intarcia.com/products-technology/intarcia-platform-technology.html.

38. Studies show effect of Bydureon on A1C and weight for up to three years. Duration-1 three-year and Duration-3 84-week data presented at ADA 2011. [internet]. San Diego (CA): Eli Lilly and Company; 2011 June 24 [accessed 2013 Jun 12]. [4 p]. Available: http://newsroom.lilly.com/releasedetail.cfm?releaseid=587236.

39. Bergenstal RM, Wysham C, Macconell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010 Aug 7;376(9739):431-9. PMID: 20580422

40. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010 Jun 26;375(9733):2234-43. PMID: 20609969

41. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2011 Dec 30;35(2):252-8. PMID: 22210563

42. DURATION-4 study results: Bydureon efficacy and tolerability profile extended to monotherapy treatment. [internet]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2010 Jun 15 [accessed 2011 Feb 22]. [3 p]. Available: http://phx.corporate-ir.net/phoenix.zhtml?c=101911&p=irol-newsArticle&ID=1438147&highlight=}.

43. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011 May;96(5):1301-10. Epub 2011 Feb 9. PMID: 21307137

44. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013 Jan 12;381(9861):117-24. PMID: 23141817

45. Grimm M, Han J, Weaver C, et al. Efficacy, safety, and tolerability of exenatide once weekly in patients with type 2 diabetes mellitus: An integrated analysis of the DURATION trials. Postgrad Med. 2013 May;125(3):47-57. PMID: 23748506

46. Amylin Pharmaceuticals. Exenatide study of cardiovascular event lowering trial (EXSCEL): a trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Feb 21]. [4 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01144338 NLM Identifier: 01144338.

47. Henry RR, Rosenstock J, Logan DK, et al. Randomized trial of continuous subcutaneous delivery of exenatide by ITCA 650 versus twice-daily exenatide injections in metformin-treated type 2 diabetes. Diabetes Care. 2013 May 3. PMID: 23645886

48. Intarcia enrolls first patients in "Freedom" global phase 3 program for ITCA 650 in type 2 diabetes. [internet]. Boston (MA): Intarcia Therapeutics, Inc.; 2013 Mar 21 [accessed 2013 Jun 12]. [5 p]. Available: http://www.intarcia.com/media/press-releases/2013-mar-21-itca650-phase3-trial-enrollment.html.

49. Lilly and Amylin mutually agree to end diabetes alliance and transition exenatide responsibility to Amylin. [internet]. Indianapolis (IN): Eli Lilly and Company; 2011 Nov 8 [accessed 2011 Nov 11]. [3 p]. Available: http://www.prnewswire.com/news-releases/lilly-and-amylin-mutually-agree-to-end-diabetes-alliance-and-transition-exenatide-responsibility-to-amylin-133424458.html.

50. FDA approves Bydureon -- the first and only once-weekly treatment for type 2 diabetes. [internet]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2012 Jan 27 [accessed 2012 Feb 20]. [4 p]. Available: http://phx.corporate-ir.net/phoenix.zhtml?c=101911&p=irol-newsArticle&ID=1653756.

51. Bydureon (exenatide extended-release for injectable suspension) risk evaluation and mitigation strategy (REMS). NDA 022-200. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2012 Jan 27. 11 p. Also available: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289674.pdf.

52. Bydureon FDA action date set for January 28, 2012. [internet]. Indianapolis (IN): Eli Lilly and Company; 2011 Aug 10 [accessed 2011 Aug 18]. [3 p]. Available: https://investor.lilly.com/releasedetail2.cfm?ReleaseID=598468.

53. Lowes R. Once-weekly exenatide okayed by FDA for T2DM after long look. [internet]. New York (NY): WebMD, LLC; 2012 Jan 27 [accessed 2012 Feb 20]. [2 p]. Available: http://www.medscape.com/viewarticle/757664.

54. Loftus P. FDA approves Amylin's Bydureon diabetes drug. [internet]. San Francisco (CA): MarketWatch, Inc.; 2012 Jan 27 [accessed 2012 Feb 21]. [3 p]. Available: http://www.marketwatch.com/story/fda-approves-amylins-bydureon-diabetes-drug-2012-01-27.

55. Rohloff CM, Alessi TR, Yang B, et al. DUROS technology delivers peptides and proteins at consistent rate continuously for 3 to 12 months. J Diabetes Sci Technol. 2008 May;2(3):461-7. PMID: 19885211

56. Intarcia and Quintiles sign letter of intent for innovative global collaboration to advance ITCA 650 in type 2 diabetes. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2011 Oct 21 [accessed 2011 Nov 14]. [3 p]. Available: http://www.intarcia.com/media/press-releases/2011-oct-21-LOI-Quintiles.html.

57. Intarcia presents positive phase 2 48-week results from ITCA 650 study at the American Diabetes Association 71st Scientific Sessions. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2011 Jun 28 [accessed 2011 Aug 18]. [4 p]. Available: http://www.intarcia.com/media/press-releases/2011-jun-28-itca-650.html.

58. Intarcia announces presentation of analysis used for dose selection for global ITCA 650 phase 3 program for type 2 diabetes at EASD. [internet]. Hayward (CA): Intarcia Therapeutics, Inc.; 2012 Oct 3 [accessed 2012 Nov 14]. Available: http://www.intarcia.com/media/press-releases/10%2003%2012%20ITCA%20650%20EASD%20Ph3%20Dose%20Select%20FINAL.html.

59. Intarcia Therapeutics. A study to evaluate ITCA 650 for the treatment of type 2 diabetes. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2013 Jun 13]. [3 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT01455857 NLM Identifier: NCT01455857.

60. Bydureon. [internet]. Santa Monica (CA): GoodRx, Inc.; 2012 Nov [accessed 2012 Nov 15]. [4 p]. Available: http://www.goodrx.com/bydureon.

61. Pharmacy clinical policy bulletins. Aetna non-Medicare prescription drug plan. Subject: insulins. [internet]. Hartford (CT): Aetna, Inc.; 2012 Mar 9 [accessed 2012 Apr 4]. [6 p]. Available: http://www.aetna.com/products/rxnonmedicare/data/2012/ENDO2012/insulins_2012.html.

62. Anthem Insurance Companies, Inc. Bydureon (exenatide extended release) prior authorization. North Haven (CT): Anthem Insurance Companies, Inc.; 3 p. Also available: http://www.anthem.com.

63. Blue Cross and Blue Shield of Alabama. Clinical program updates. East Birmingham (AL): Blue Cross and Blue Shield of Alabama; 2012 Apr 1. 5 p. Also available: https://www.bcbsal.org/providers/pdfs/ClinicalProgramUpdate.pdf.

64. CIGNA Corporation. Drug list search results: bydureon. [internet]. Bloomfield (CT): CIGNA Corporation [accessed 2012 Apr 4]. [1 p]. Available: https://my.cigna.com/teamsite/cgi-bin/customer_care/member/drug_list/DrugList.cgi?class_name=Antihypergly-%20Incretin%20Minetuc%20(GLP-1%20RECEP.%20AGONIST)&Pid=&search_by=class&LeanIndicator=&referer=.

65. Humana, Inc. Medicare plans: provider drug search results for Bydureon. [internet]. Louisville (KY): Humana, Inc.; [accessed 2012 Apr 4]. Available: http://apps.humana.com/prescription_benefits_and_services/execreq.asp?processcode=3&srcsite=physician&productid=4&ndc=66780021904&view=m.

66. Regence Group. Regence BlueShield (Washington) retail medication quantity limits. [internet]. Portland (OR): Regence Group; 2012 Feb 2 [accessed 2012 Apr 4]. [3 p]. Available: http://www.regencerx.com/learn/priorAuth/washingtonPriorAuth.html.

67. Regence Group. Regence BlueCross BlueShield of Oregon retail medication quantity limits. [internet]. Portland (OR): Regence Group; 2012 Feb 13 [accessed 2012 Apr 4]. [3 p]. Available: http://www.regencerx.com/learn/priorAuth/oregonPriorAuth.html.

68. Wellmark, Inc. Prior authorization request: GLP-1 agonists (Byetta/Victoza/Bydureon). Des Moines (IA): Wellmark, Inc.; 1 p. Also available: www.wellmark.com.

69. Intarcia bets it will shake up diabetes treatment with implantable device. [internet]. San Francisco: Xconomy; 2010 Nov 29 [accessed 2010 Dec 17]. [3 p]. Available: http://www.xconomy.com/san-francisco/2010/11/29/intarcia-bets-it-will-shake-up-diabetes-treatment-with-implantable-device/.

70. Eckman AS. Type 2 diabetes. In: MedlinePlus [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2010 May 10 [accessed 2011 Mar 17]. [7 p]. Available: http://www.nlm.nih.gov/medlineplus/ency/article/000313.htm.

71. Expert Commenter 809. (External, Clinical). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 24 [review date].

72. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 26 [review date].

73. Expert Commenter 660. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 26 [review date].

74. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 26 [review date].

75. Expert Commenter 1169. (PRI, Clinical). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 25 [review date].

76. Expert Commenter 420. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Apr 24 [review date].

77. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS190 - Extended-release exenatide (Bydureon) for treatment of diabetes. 2012 Jul 31 [review date].

78. Expert Commenter 161. (PRI, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 29 [review date].

79. Expert Commenter 404. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 6 [review date].

80. Expert Commenter 420. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Jul 31 [review date].

81. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Jul 31 [review date].

82. Expert Commenter 433. (External, Health Systems). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 22 [review date].

83. Expert Commenter 547. (External, Clinical). Horizon Scanning Structured Comment Form. HS180 - Subcutaneous exenatide (DUROS) for treatment of type II diabetes. 2012 Aug 14 [review date].

84. Callanan D, Eliott D, Ip M, et al. Diabetic macular edema: update and treatment options. In: Medscape Education [internet]. New York (NY): WebMD, LLC; 2007 Jun 18 [accessed 2011 Mar 29]. [7 p]. Available: http://www.medscape.org/viewarticle/557986.

85. Hampton R Sr, Mavrikakis E. Macular edema in diabetes: overview. In: Medscape Reference [internet]. New York (NY): WebMD, LLC; 2011 Mar 29 [updated 2011 Oct 10]. [accessed 2011 Mar 29]. [1 p]. Available: http://emedicine.medscape.com/article/1224138-overview.

86. Iluvien for diabetic macular edema (DME). [internet]. Alpharetta (GA): Alimera Sciences, Inc. [accessed 2013 Jan 30]. [1 p]. Available: http://www.alimerasciences.com/Products/iluvien.aspx.

87. Grover DA, Li T, Chong CC. Intravitreal steroids for macular edema in diabetes. Cochrane Database Syst Rev. 2008;(1):art. no.:CD005656.

88. Alimera Sciences' Iluvien receives marketing authorization in Spain for the treatment of chronic diabetic macular edema. [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2013 Jan 17 [accessed 2013 Jan 30]. [2 p]. Available: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=734042.

89. Sanford M. Fluocinolone acetonide intravitreal implant (Iluvien): in diabetic macular oedema. Drugs. 2013 Feb;73(2):187-93. PMID: 23335133

90. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology. 2012 Jun 21;Epub ahead of print. PMID: 22727177

91. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology. 2011 Apr;118(4):626-635.e2. PMID: 21459216

92. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. Ophthalmology. 2011 Aug;118(8):1580-7. PMID: 21813090

93. Alimera Sciences receives complete response letter from FDA for Iluvien. [internet]. Alpharetta (GA): Alimera Sciences, Inc.; 2011 Nov 11 [accessed 2011 Dec 6]. [3 p]. Available: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=623128.

94. Alimera Sciences reports third quarter 2012 financial results. [internet]. Atlanta (GA): Alimera Sciences, Inc.; 2012 Nov 7 [accessed 2012 Nov 15]. [4 p]. Available: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=719464.

95. Alimera Sciences announces new PDUFA date for Iluvien. [internet]. Atlanta (GA): Alimera Sciences, Inc.; 2013 May 1 [accessed 2013 Jun 12]. [2 p]. Available: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=760859.

96. Alimera Sciences announces first patient treated with commercially available Iluvien. [internet]. Atlanta (GA): Alimera Sciences, Inc.; 2013 May 7 [accessed 2013 Jun 12]. [2 p]. Available: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=762751.

97. Corporate overview. [internet]. Alpharetta (GA): Alimera Sciences [accessed 2013 Jan 30]. [1 p]. Available: http://www.alimerasciences.com/About-Us.aspx.

98. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes Care. 2003 Sep;26(9):2653-64. PMID: 12941734

99. Schwartz SG, Flynn HW Jr. Fluocinolone acetonide implantable device for diabetic retinopathy. Curr Pharm Biotechnol. 2011 Mar 1;12(3):347-51. PMID: 20939799

100. Funatsu H, Noma H, Mimura T, et al. Association of vitreous inflammatory factors with diabetic macular edema. Ophthalmology. 2009 Jan;116(1):73-9. PMID: 19118698

101. Diabetic macular edema (DME). [internet]. Alpharetta (GA): Alimera Sciences [accessed 2013 Jan 30]. [1 p]. Available: http://www.alimerasciences.com/Areas-of-Focus/Diabetic-Macular-Edema.aspx.

102. Ciulla TA. Corticosteroids for diabetic macular edema. [internet]. Newtown Square (PA): Review of Ophthalmology; 2009 Feb 20 [accessed 2013 Jan 30]. [10 p]. Available: http://www.revophth.com/content/d/retinal_insider/i/1219/c/22960/.

103. Karmel M. Get drugs straight to the eye. [internet]. San Francisco (CA): American Academy of Ophthalmology (AAO) [accessed 2011 Sep 20]. [5 p]. Available: http://www.aao.org/publications/eyenet/200601/feature.cfm.

104. Lucentis (ranibizumab injection) intravitreal injection. South San Francisco (CA): Genentech, Inc; 2012 Aug. 8 p. Also available: http://www.gene.com/download/pdf/lucentis_prescribing.pdf.

105. Warner J. New drug for diabetes-related vision loss. [internet]. New York (NY): WebMD, LLC; 2012 Aug 14 [accessed 2012 Sep 13]. [3 p]. Available: http://diabetes.webmd.com/news/20120814/new-drug-for-diabetes-related-vision-loss.

106. Maugh TH II. Avastin cheaper than Lucentis for AMD, but has higher risks. [internet]. Los Angeles (CA): Los Angeles Times; 2012 Jun 20 [accessed 2012 Sep 26]. [2 p]. Available: http://articles.latimes.com/2012/jun/20/science/la-sci-sn-lucentis-avastin-20120620.

107. Nwanze CC, Akinwale A, Adelman RA. Bevacizumab vs. ranibizumab in preserving or improving vision in patients with wet, age-related macular degeneration: a cost-effectiveness review. Clin Med Insights Ther. 2012;4:29-38.

108. Raftery J, Clegg A, Jones J, et al. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol. 2007 Sep;91(9):1244-6. PMID: 2007429446

109. Rosenfeld PJ. Intravitreal Avastin: the low cost alternative to Lucentis? Am J Ophthalmol. 2006 Jul;142(1):141-3. PMID: 16815262

110. Sharma S, Johnson D, Abouammoh M, et al. Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections. Can J Ophthalmol. 2012 Jun;47(3):275-9. PMID: 22687306

111. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2013 Apr 16 [review date].

112. Expert Commenter 408. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2013 Mar 26 [review date].

113. Expert Commenter 428. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2013 Mar 19 [review date].

114. Expert Commenter 675. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2013 May 13 [review date].

115. Expert Commenter 849. (External, Clinical). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2013 May 16 [review date].

116. Expert Commenter 1193. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS849 - Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema. 2013 Mar 25 [review date].

117. Lucentis (ranibizumab injection) highlights of prescribing information. [internet]. South San Francisco (CA): Genentech, Inc.; 2012 Aug [accessed 2012 Nov 14]. [8 p]. Available: http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf.

118. Vascular endothelial growth factor A. In: GeneCards [internet]. Rehovot (Israel): Weizmann Institute of Science [accessed 2012 Apr 9]. [19 p]. Available: http://www.genecards.org/cgi-bin/carddisp.pl?gene=VEGFA.

119. Lucentis (ranibizumab) injection, solution. [internet]. South San Francisco (CA): Genentech, Inc.; 2012 [accessed 2012 Sep 6]. [15 p]. Available: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=de4e66cc-ca05-4dc9-8262-e00e9b41c36d.

120. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012 Apr;119(4):789-801. PMID: 22330964

121. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. 2013 May 22. PMID: 23706949

122. Lang GE, Berta A, Eldem BM, et al. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the RESTORE extension study. Ophthalmology. 2013 May 29. PMID: 23725735

123. Real-world data at ARVO highlight transformational outcomes seen with Lucentis, including lower injection frequency than in original clinical trials. [internet]. Basel (Switzerland): Novartis AG; 2013 May 8 [accessed 2013 Jun 11]. [4 p]. Available: http://www.novartis.com/newsroom/media-releases/en/2013/1700148.shtml.

124. Lucentis (ranibizumab injection) labeling. [internet]. San Francisco (CA): Genentech USA, Inc.; 2006 June [accessed 2007 Aug 20]. [7 p]. Available: http://www.fda.gov/cder/foi/label/2006/125156lbl.pdf.

125. Novartis gains new indication for Lucentis in EU for vision loss due to diabetic macular edema, a leading cause of blindness. [internet]. Basel (Switzerland): Novartis International AG; 2011 Jan 7 [accessed 2012 Apr 9]. [4 p]. Available: http://www.novartis.com/newsroom/media-releases/en/2011/1477848.shtml.

126. FDA approves Lucentis to treat diabetic macular edema. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2012 Aug 10 [accessed 2012 Aug 30]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm315130.htm.

127. Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. Arch Ophthalmol. 2008 Dec;126(12):1748-54. PMID: 19064859

128. Moore A. FDA approves eye drug for diabetics. [internet]. New York (NY): Medical Daily; 2012 Aug 11 [accessed 2012 Nov 15]. [4 p]. Available: http://www.medicaldaily.com/articles/11448/20120811/diabetes-eye-disease-fda-us-lucentis.htm.

129. Lucentis (ranibizumab) formulary coverage policy and prior authorization form. [internet]. Grand Junction (CO): Rocky Mountain Health Plans; 2013 Apr [accessed 2013 Jun 11]. [4 p]. Available: http://www.rmhp.org/docs/provider/lucentis_(ranibizumab).pdf?sfvrsn=4.

130. MEDCAC meeting 3/21/2012 - anti-VEGF treatment of diabetic macular edema. [internet]. Baltimore (MD): Centers for Medicare & Medicaid Services (CMS); 2012 [accessed 2013 Jun 11]. [6 p]. Available: http://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=60&MCDId=6&McdName=Factors+CMS+Considers+in+Opening+a+National+Coverage+Determination&mcdtypename=Guidance+Documents&MCDIndexType=1&bc=AAAIAAAAAAAA&.

131. Local coverage determination (LCD): ranibizumab (Lucentis). [internet]. Baltimore (MD): Centers for Medicare & Medicaid Services (CMS) [accessed 2013 Jun 11]. [3 p]. Available: http://www.cms.gov/medicare-coverage-database/search/search-results.aspx?CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=lucentis&KeyWordLookUp=Title&KeyWordSearchType=And&CptHcpcsCode=J277&type=article&page=results_index.asp&fr.

132. Aetna, Inc. Clinical policy bulletin: vascular endothelial growth factor inhibitors for ocular neovascularization. Policy #0701. [internet]. Hartford (CT): Aetna, Inc.; 2013 May 7 [accessed 2013 Jun 11]. [19 p]. Available: http://www.aetna.com/cpb/medical/data/700_799/0701.html.

133. Group Health Cooperative. Drug formulary. [internet]. Seattle (WA): Group Health Cooperative; 2013 Apr [accessed 2013 Jun 11]. [50 p]. Available: http://www.ghc.org/all-sites/images/drugFormulary.pdf.

134. Billing and coding for Lucentis (ranibizumab injection). [internet]. South San Francisco (CA): Genentech, Inc. [accessed 2013 Jun 11]. [3 p]. Available: http://www.genentech-access.com/lucentis/hcp/see-how-we-can-help/our-services/reimbursement.

135. Benefits investigation. [internet]. South San Francisco (CA): Genentech USA, Inc. [accessed 2012 Nov 15]. [2 p]. Available: http://www.genentech-access.com/lucentis/hcp/see-how-we-can-help/our-services.

136. Mitchell P, Annemans L, Gallagher M, et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: Evidence from the RESTORE trial. Br J Ophthalmol. 2012 May;96(5):688-93. PMID: 22399690

137. Stein JD, Newman-Casey PA, Kim DD, et al. Cost-effectiveness of various interventions for newly diagnosed diabetic macular edema. Ophthalmology. 2013 May 1. PMID: 23642372

138. Diabetic Retinopathy Clinical Research Network. Comparative effectiveness study of intravitreal aflibercept, bevacizumab, and ranibizumab for DME (protocol T). In: ClinicalTrials.gov [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2013 Jun 11]. [5 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT01627249 NLM Identifier: NCT01627249.

139. Expert Commenter 405. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 17 [review date].

140. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 5 [review date].

141. Expert Commenter 428. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Sep 13 [review date].

142. Expert Commenter 433. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 17 [review date].

143. Expert Commenter 935. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Sep 26 [review date].

144. Expert Commenter 1171. (External, Clinical). Horizon Scanning Structured Comment Form. HS737 - Ranibizumab (Lucentis) for treatment of diabetic macular edema. 2012 Oct 8 [review date].