

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

Priority Area 08: Functional Limitations and Disability

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www.ahrq.gov

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Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS A290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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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.

Richard Kronick, Ph.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

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

Methods

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

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

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

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

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

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

Results

The table below lists the 15 topics for which (1) preliminary phase III data for drugs were available or phase II data for devices or off-label uses were available; (2) information was compiled and sent for expert comment before October 27, 2013, in this priority area; and (3) we received six to eight sets of comments from experts between April 9, 2012, and October 29, 2013. (Seventy-seven topics in this priority area were being tracked in the system as of October 29, 2013.) We present summaries on nine topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts’ comments. The material in this Executive Summary and the report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 08: Functional Limitations and Disability

Topic	High-Impact Potential
1. Alemtuzumab (Lemtrada) for treatment of relapsing-remitting multiple sclerosis	No high-impact potential at this time
2. *Corneal collagen cross-linking (VibeX Riboflavin/KXL System) for treatment of progressive keratoconus	Lower end of the high-impact-potential range
3. * Dimethyl fumarate (Tecfidera) for treatment of relapsing forms of multiple sclerosis	Lower end of the high-impact-potential range
4. * Eliglustat tartrate for treatment of Gaucher's disease	Moderately high
5. Handheld intracranial scanner (Infrascanner) for detection of intracranial hematomas	No high-impact potential at this time
6. * High-intensity focused ultrasound (EyeOP1 HIFU-system) for treatment-refractory glaucoma	Lower end of the high-impact-potential range
7. Northera (Droxidopa) for treatment of symptomatic neurogenic orthostatic hypotension	No high-impact potential at this time
8. * Ocriplasmin (Jetrea) treatment for symptomatic vitreomacular adhesion including macular hole	High
9. Off-label naltrexone for treatment of fibromyalgia	No high-impact potential at this time
10. * Pediatric Vision Scanner screening for strabismus or amblyopia	Moderately high
11. Pridopidine (Huntexil) for treatment of Huntington's disease	No high-impact potential at this time

Topic	High-Impact Potential
12. * RenalGuard for prevention of contrast media-induced nephropathy	High
13. Responsive neurostimulation system for treatment-refractory partial epilepsy	No high-impact potential at this time
14. * Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	High
15. *Wearable battery-powered exoskeletons (ReWalk and Ekso systems) to enable walking after spinal cord injury	Moderately high

Discussion

The AHRQ priority area of functional limitations encompasses a wide range of disease states and conditions. For purposes of horizon scanning, AHRQ defines this area using the U.S. Department of Health and Human Services definition of disability: “In general, disabilities are characteristics of the body, mind, or senses that, to a greater or lesser extent, affect a person’s ability to engage independently in some or all aspects of day-to-day life.” The horizon scanning team put this definition into operation by considering interventions in the context of conditions that impair activities of daily living (e.g., feeding, bathing, toileting/continence, transfers, such as those from bed to chair or wheelchair) or ambulation, dressing, or other independent activities of daily living (e.g., medication management, telephone use, leaving home without assistance, making meals, housekeeping).

Central Nervous System Disorder Intervention

Dimethyl Fumarate (Tecfidera) for Treatment of Relapsing Forms of Multiple Sclerosis

- Key Facts:** In many patients with relapsing forms of multiple sclerosis (MS), symptoms do not respond adequately to current therapies or patients are unable to tolerate the treatments, and no effective treatments are available to stop the long-term disease progression. Biogen Idec International GmbH (Zug, Switzerland), has developed dimethyl fumarate for treating relapsing forms of MS. Dimethyl fumarate is a homogenous fumaric acid ester formulation that purportedly has both immunomodulatory and neuroprotective effects. These effects have potential to reduce the number of active brain lesions that could contribute to disease progression. When used in treating MS, dimethyl fumarate is orally administered at a dosage of 120 mg twice daily for 7 days, followed by 240 mg twice daily as a maintenance dosage. In two completed, randomized controlled trials, about half as many patients in the dimethyl fumarate group had relapses as in the placebo group. One long-term safety and efficacy study is ongoing. In February 2013, the U.S. Food and Drug Administration (FDA) approved dimethyl fumarate for treating adult patients with relapsing forms of MS. A 30-day supply of dimethyl fumarate costs approximately \$4,800. The manufacturer offers a program, ActiveAccess™, to make the drug available to patients who meet eligibility criteria for a copayment of \$10 for a 1-month supply. Most third-party payers include the drug in their formularies as a specialty pharmaceutical requiring prior authorization and imposing quantity limits.
- Key Expert Comments:** Experts agreed a significant need exists for a treatment with fewer side effects and thought dimethyl fumarate could meet this need for patients in whom other treatments have failed. Data appear to show the side effects of dimethyl fumarate to be less severe than other treatment options, experts suggested. However, side effects could still limit acceptance and use, other experts noted. The experts thought that as an orally administered medication, dimethyl fumarate would be widely accepted by both clinicians and patients,

especially because many other MS treatments involve infusions. Experts suggested that dimethyl fumarate could reduce the need for infusion centers and reduce or delay the care burden and need for long-term care facilities by slowing disease progression. Experts overwhelmingly cited the need for long-term comparative-effectiveness data on the drug, which is being addressed in the long-term ongoing trial.

- **Potential for High Impact:** Lower end of the high-impact potential range

Genetic Disorder Intervention

Eliglustat Tartrate for Treatment of Gaucher's Disease

- **Key Facts:** FDA-approved oral drugs are not available as first-line treatment of Gaucher's disease, but intravenous (IV) therapy (e.g., enzyme replacement therapy [ERT]) is approved. ERT is expensive and requires lifelong IV infusions every 2–3 weeks. Eliglustat tartrate may provide an orally administered drug if it receives approval. The drug, by Genzyme Corp., a subsidiary of Sanofi (Paris, France), is under study as a first-line treatment for Gaucher's disease. Eliglustat tartrate purportedly partially inhibits the enzyme glucosylceramide synthase, resulting in reduced production of glucosylceramide. Three fully enrolled phase III trials of eliglustat tartrate are ongoing. In these trials, the drug is administered in 50, 100, or 150 mg doses, twice daily. Positive interim-analysis data have been reported from two of these trials. The manufacturer has indicated that it expects to submit a new drug application to FDA before the end of 2013, but had not announced making a submission as of early December 2013.
- **Key Expert Comments:** Experts cited a need for a more convenient treatment for Gaucher's disease and suggested this oral compound could increase patient adherence to treatment recommendations, leading to improved health outcomes and delaying disease progression. Experts anticipated widespread adoption and use of eliglustat tartrate, if approved, because of its convenient nature as an oral drug. Furthermore, experts suggested adoption of eliglustat tartrate would reduce the need for IV infusion centers and shift the care setting to self-administered homecare. Experts noted these shifts would be contingent on eliglustat tartrate being proved to be as effective as or more effective than the current standard of care.
- **Potential for High Impact:** Moderately high

Renal-Protection Intervention

RenalGuard for Prevention of Contrast-Induced Nephropathy

- **Key Facts:** In patients with chronic kidney disease, contrast-induced nephropathy (CIN) is a common cause of acute renal dysfunction or failure. It can occur after contrast media is administered during an imaging procedure such as computed tomography. Many CIN cases in these patients are not identified until 48–72 hours after contrast media exposure. When CIN occurs, the only treatment available is hydration and avoidance of additional nephrotoxic agents. The RenalGuard System is under development by PLC Systems, Inc. (Milford, MA), as a preventive measure for patients at risk of developing CIN while undergoing an imaging procedure that uses contrast media. RenalGuard purportedly reduces the risk of CIN by reducing the effects of contrast media on the kidneys. The system replaces fluid, actively synchronizing a patient's urine output with sterile saline solution IV infusion. The induction of high urine-flow rates purportedly limits contrast exposure time

and maintains renal blood flow, thereby limiting hypoxia from endothelin-mediated vasoconstriction. High urine flow also accelerates duct flow via reduced sludging and precipitation of contrast material in renal tubular cells. One phase III pivotal trial and one phase IV trial are ongoing. Two phase III trials have been completed and the study investigators reported positive data from both trials—about two to four times as many patients in the control groups developed CIN as in the RenalGuard groups in these studies. The RenalGuard System is not yet FDA approved; a phase III pivotal trial is ongoing to support the planned premarket approval filing. The manufacturer received Conformité Européenne (CE) mark for the system in December 2007 allowing marketing in Europe.

- **Key Expert Comments:** Experts unanimously agreed on the importance of preventing CIN, because no effective treatment is available. Overall, experts thought RenalGuard represents a viable option for clinicians to reduce the risk of CIN in patients at high risk of developing chronic kidney disease or who already have it. The intervention would also increase access to imaging procedures among patients at high risk of developing CIN who would otherwise be unable to undergo imaging procedures using contrast media. Experts thought RenalGuard would face very few barriers to adoption and could be easily implemented into the existing infrastructure.
- **Potential for High Impact:** High

Sensory Disorder Interventions

Corneal Collagen Cross-Linking (VibeX Riboflavin/KXL System) for Treatment of Progressive Keratoconus

- **Key Facts:** Keratoconus is characterized by a progressive thinning of the cornea, causing it to change from its normal shape and bulge out into a cone, leading to astigmatism and nearsightedness. The condition typically affects both eyes and can progress slowly for 10 or more years. It is the most common corneal dystrophy in the United States, affecting 1 in 2,000 people; it is more prevalent in teenagers and adults in their 20s than in older adults. Certain genetic risk factors play a role in its development. Signs and symptoms include blurred or distorted vision, sensitivity to light, night vision problems, headaches from eye strain, and sudden worsening or clouding of vision. Treatment depends on disease severity and progression. Specially fitted contact lenses are first-line treatment usually. Most cases stabilize after several years, but in some cases, extreme corneal thinning and scarring or occurs and corneal transplant or corneal ring insertion may be necessary. These interventions are associated with complications, such as graft rejection, permanent vision loss, and prolonged recovery. Corneal collagen cross-linking (CXL) is a less drastic option intended to strengthen the corneal structure by removing the corneal epithelium and applying drops of riboflavin to the eye. The eye is then exposed to ultraviolet A (UVA) light for a period of time to accomplish the CXL. Reactive oxygen molecules generated during irradiation purportedly cause chemical bonds to form between corneal collagen fibrils, increasing corneal rigidity. Avedro, Inc. (Waltham, MA), is developing its VibeX Riboflavin™/KXL™ System to perform accelerated CXL. No other system is available in the United States for performing CXL, although systems are available in Europe. Purported advantages of this system for accomplishing CXL are increased UVA power, reducing exposure time, and use of the company's proprietary riboflavin formula. The system consists of a battery-powered, touch-screen monitor for operation and an articulating arm to focus UVA irradiation on the patient's cornea. The system is not yet FDA approved, but received

the CE mark in Europe in 2010. In March 2012, the manufacturer announced that it had submitted a new drug application (NDA) to FDA for its KXL/VibeX Rapid system, which had been granted orphan drug designation in December 2011. In November 2013, the company announced that FDA had granted priority review status for the system. The scheduled decision date is March 15, 2014. The company stated that the proposed indications in the NDA are for treating keratoconus and corneal ectasia after refractive surgery, both of which are orphan drug indications.

- **Key Expert Comments:** Experts thought the system could fill the unmet need for a progressive keratoconus treatment that is less invasive than current standard treatment. The ease of performing CXL with the system was cited by experts as a main factor that would facilitate adoption and acceptance. However, other experts noted that the training and knowledge required to successfully use the technology could also serve as a barrier to adoption. Experts suggested the technology, if FDA approved, might not be available to some patients because of procedure costs, health insurance status, or access to the specialty clinicians offering it.
- **Potential for High Impact:** Lower end of the high-impact-potential range

High-intensity Focused Ultrasound (EyeOP1 HIFU system) for Treatment-Refractory Glaucoma

- **Key Facts:** Glaucoma, if left untreated or inadequately treated, can lead to irreversible blindness. The main goal of glaucoma management is reducing intraocular pressure (IOP), which is frequently accomplished using medications; however, these treatments may not adequately control IOP in all patients. The EyeOp1 high-intensity focused ultrasound (HIFU) system, developed by EyeTechCare, S.A. (Rillieux la Pape, France), is a novel approach to reducing the production of aqueous humor (and subsequently IOP) intended to avert the thermal complications that can occur with laser treatment or cryoablation. The rationale underlying the EyeOp1[®] procedure is similar to that underlying these other ablative procedures that target the ciliary bodies, the eye tissues responsible for production of aqueous humor. The system uses miniaturized piezoelectric transducers to perform controlled HIFU thermocoagulation of ciliary processes without affecting surrounding ocular tissue. This stands in contrast to laser ablation and cryoablation procedures, which use thermal energy that can damage surrounding tissues. The HIFU-generating transducers are placed in a ring to allow ablation of the full circumference of the eye during a single treatment session. The ablation itself takes about 1 minute. Three clinical trials of the EyeOp1 system for treatment-refractory glaucoma are ongoing, and two others have been completed. Study investigators of a 39-patient trial compared 4-second and 6-second exposure times using the EyeOp1 and reported that IOP significantly declined in both groups. In May 2011, the EyeOP1 obtained the CE mark, allowing marketing in Europe. The company's EyeMUST 2 international trial is expected to publish results in early 2014, and the company intends to register with FDA by the end of 2013 to pursue regulatory approval for the U.S. market.
- **Key Expert Comments:** Experts highlighted the need for less invasive glaucoma treatment options and options for medication-resistant disease and suggested the EyeOP1 could potentially fill this need. Experts further cited the minimally invasive nature of EyeOp1 as facilitating clinician and patient adoption. Experts indicated that for EyeOp1 to have a significant impact on glaucoma treatment, a general awareness campaign would be needed

to improve screening for and detection of the disease to increase early diagnosis and intervention.

- **Potential for High Impact:** Lower end of the high-impact-potential range

Ocriplasmin (Jetrea) for Treatment of Symptomatic Vitreomacular Adhesion Including Macular Hole

- **Key Facts:** During the aging process, the gelatin-like vitreous humor that fills the space between the eye's lens and the retina may begin to break down through a process of liquefaction. This breakdown may reduce adhesion between the vitreous humor and the retina. The combination of liquefaction and loss of adhesion can lead to posterior vitreous detachment (PVD), in which the vitreous pulls away from the posterior retina. In some cases, PVD occurs abnormally, particularly when liquefaction and vitreoretinal-adhesion breakdown occur asynchronously. The adhesive forces between the retina and the vitreous humor are often strongest at a region of the retina called the macula, which is responsible for central vision and fine-detail perception. Regions of sustained adhesion are often located at the macula and result in vitreomacular adhesion (VMA). In this condition, rapid eye movements can place significant traction on the site of vitreal adhesion as the vitreous pulls or pushes on the retina, potentially damaging the macula and adversely affecting vision. Vitrectomy and membrane peeling followed by regeneration of the retinal architecture are the standard treatment approaches and are reserved for cases showing progression and signs of worsening visual function. The efficacy of vitreoretinal surgical procedures for treating symptomatic VMA is limited by the potential for incomplete vitreoretinal separation and removal, surgical complications (e.g., cataract development), and high costs. Nonsurgical approaches have been sought, and ocriplasmin (Jetrea[®]) is an agent developed to address this need. It was developed by ThromboGenics NV (Heverlee, Belgium) as a truncated form of plasmin and is produced using recombinant methods. Recombinant ocriplasmin retains the catalytic characteristics of human plasmin and purportedly offers several advantages as a therapeutic agent including increased stability over plasmin and smaller molecular size allowing for greater penetration of epiretinal tissues. Two phase III trials were completed and formed the basis of a submission to FDA for approval; approval was granted in October 2012 for treating VMA. In both trials, treatment was generally safe and well tolerated. Ocriplasmin is provided in a single-use, glass vial at a concentration of 2.5 mg/mL. The recommended dose is a single injection of 0.1 mL of solution at a concentration of 1.25 mg/mL. According to the manufacturer, the price of the single-use vial of ocriplasmin was \$3,950 at product launch.
- **Key Expert Comments:** Experts commenting on this intervention suggested ocriplasmin has the potential to fulfil the significant unmet need for minimally invasive treatment for VMA. Furthermore, experts thought ocriplasmin could reduce the need for invasive surgery and reduce the patient risks associated with surgery. The minimally invasive nature of the intervention, experts agreed, would facilitate clinician and patient acceptance and adoption. Experts thought ocriplasmin would shift the care setting for VMA from surgery centers to office-based care.
- **Potential for High Impact:** High

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

- **Key Facts:** The leading cause of preventable monocular vision loss in children is amblyopia, which is most often caused by strabismus. Early detection of amblyopia can be

difficult because standard screening methods lack sufficient sensitivity and specificity, thereby missing cases of children who should be referred for further evaluation and possible treatment. The Pediatric Vision Scanner (PVS) is under development by REBIScan, Inc. (Cambridge, MA), and is intended for use as a screening tool to enable earlier detection of amblyopia or strabismus so that patients can be more appropriately referred to specialist care. The screening device is intended to rule out strabismus and amblyopia and provide early referral to an ophthalmologist for children who have a positive test result. The system uses proprietary technology called retinal birefringence scanning to screen for amblyopia and strabismus. The PVS simultaneously assesses both eyes during a 2–5 second scan to detect both binocular alignment and the ability of the eyes to focus on a target. The system’s software then provides a result as to whether the patient’s eyes accurately fixated on the target (indicating a “pass” or passing grade). If they did not fixate, the patient is to be referred to an ophthalmologist for further evaluation. Three clinical trials evaluated the sensitivity and specificity of the PVS. Investigators from the largest and most recently reported PVS trial (2013), in children aged 2–6 years, reported that “PVS correctly identified 144 of 147 children with strabismus and/or amblyopia; sensitivity=98% (95% CI [confidence interval]: 95-100%)... [and] correctly identified 89 of 102 control children; specificity=87% (95% CI, 79%-96%).” FDA has determined the PVS to be a nonsignificant risk investigational device. This means the PVS has abbreviated requirements for labeling; institutional review board approval is all that is needed to conduct trials (i.e., not prior FDA approval to conduct a trial); and reporting rules are streamlined for the regulatory approval pathway.

- **Key Expert Comments:** Overall, experts thought the ability of PVS to be used in younger populations was a significant factor in its potential to fulfill the unmet need for early diagnostic tools for amblyopia and strabismus. Experts thought the early diagnostic capabilities of PVS would contribute to improved patient health outcomes. Experts especially liked the ease of use, quick scan time, low risks, and minimal training needed to successfully operate the device in a primary care setting. Experts believe that these factors will contribute to wide acceptance and adoption of this screening tool. They also suggested that utilization would be fueled by parent and caregiver awareness and demand for the screening tool.
- **Potential for High Impact:** Moderately high

Retinal Prosthesis System (Argus II) for Treatment of Retinitis Pigmentosa

- **Key Facts:** Medications or devices have not been available to restore lost vision or halt progression of vision loss that occurs because of retinitis pigmentosa (RP), a debilitating genetic vision disorder that eventually results in blindness. The implantable Argus® II Retinal Prosthesis System is the first device available that purportedly restores a level of vision that is sufficient to allow patients greater independent functioning, although it does not restore detailed vision such as facial recognition. The device is intended to stimulate the retina with electrical impulses that the patient perceives as images. In clinical studies, patients receiving the device implant were able to perform basic activities such as detecting motion, recognizing letters, detecting street curbs, and distinguishing certain colors. The most common adverse events reported in the studies included conjunctival dehiscence, conjunctival erosion, retinal detachment, inflammation, and hypotony (low intraocular pressure). Appropriate use of the device requires surgeon and technician training in patient

selection, device fitting, and implantation and patient training after the procedure. Argus II was FDA approved in February 2013 as the first implantable device for treating adult patients with advanced RP. Reported cost for the device is about \$115,000, which includes the device and the surgical procedure.

- **Key Expert Comments:** Overall, experts commenting on this intervention agreed that a significant unmet need exists for RP treatment options because no therapies were available until approval of the device. Most experts who commented thought that this intervention has potential to fulfill that unmet need. Experts generally agreed that the potential to improve patient health was high because of the device's ability to restore some level of vision that improves patients' ability to function. Experts noted that although adoption may be limited because of the training required to implant the device and the technical challenges of surgery, patients with RP would be likely to seek this treatment because it may enable greater independence.
- **Potential for High Impact:** High

Spinal Cord Injury Intervention

Wearable Battery-Powered Exoskeletons (ReWalk and Ekso Systems) To Enable Walking After Spinal Cord Injury

- **Key Facts:** Conventional manual and powered wheelchairs are the primary assistive devices used to restore some degree of mobility in people with paraplegia. However, these devices do not help users walk or climb stairs. Two reciprocating gait orthosis systems in development, the ReWalk-I™ system (Argo Medical Technologies, Ltd., Yokneam Ilit, Israel) and the Ekso™ system (formerly eLegs; Ekso Bionics, Richmond, CA), are providing greater mobility and freedom to people with paraplegia from spinal cord injury. The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders and who have good bone density and cardiovascular health. The Ekso system incorporates technology similar to that of the ReWalk system. FDA classifies the ReWalk system as powered exercise equipment used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification and premarket application procedures. The ReWalk-I (institutional use) system is FDA-listed for institutional use only, and reported costs are about \$105,000 per system. The company expected to register the ReWalk-P system for personal use with FDA by the end of 2013; the system is available in Europe and Israel. Argo Medical has been quoted in lay press articles as stating that the personal system will cost one-third to one-half that of an institutional system. The company stated that patients seeking the device will be referred to ReWalk Rehabilitation Centers for training. The Ekso institutional system first became available in February 2012 and costs an estimated \$130,000, with anticipated costs for a personalized Ekso exoskeleton version estimated to be \$50,000–\$75,000.
- **Key Expert Comments:** Experts thought that this equipment could offer independence currently unavailable to these patients. However, they thought the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services for patients with paraplegia from spinal cord injury. Staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment. Also, the equipment would likely be appropriate only for patients whose health is robust enough to use it. Experts indicated that the intended

population has very limited treatment options, and they agreed upon the potential benefit of computerized walking systems.

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

Central Nervous System Disorder Intervention

Dimethyl Fumarate (Tecfidera) for Treatment of Relapsing-Remitting Multiple Sclerosis

Unmet need: Multiple sclerosis (MS) is a common cause of physical disability in the United States.¹ As the disease progresses, it can interfere with vision, speech, walking, writing, memory, sexual function, and bowel and bladder control.^{2,3} First-line therapies consist of immunomodulators that dampen autoimmune responses against the central nervous system.⁴ However, in many patients with relapsing forms of MS, symptoms do not respond adequately to current therapies or patients are unable to tolerate the treatments, and no effective treatments are available to stop the long-term progression of the disease.⁵⁻⁸ A strong demand exists for new, well-tolerated therapies for treating relapsing forms of MS that improve convenience through oral administration, slow disease progression, and provide symptomatic relief for patients.⁹

Intervention: Dimethyl fumarate is a homogenous fumaric acid ester formulation that purportedly has both immunomodulatory and neuroprotective effects. Dimethyl fumarate increases expression of Nrf2, a transcription factor known to upregulate cellular antioxidant pathways. Nrf2 upregulation brings about changes in the cellular redox system, leading to an increase in both reduced and intracellular glutathione, which could protect neurons and astrocytes from oxidative stress during inflammatory processes.^{10,11} These changes purportedly inhibit nuclear translocation of the proinflammatory transcription factor nuclear factor kappaB, potentially inhibiting downstream proinflammatory signaling in immune cells.¹² These anti-inflammatory and neuroprotective effects have potential to reduce the number of active brain lesions that could contribute to disease progression.^{9,13} Dimethyl fumarate is orally administered at a dosage of 120 mg twice daily for 7 days, followed by 240 mg twice daily as a maintenance dosage.¹³

Clinical trials: A long-term safety and efficacy study of dimethyl fumarate in patients with relapsing-remitting MS (RRMS) is ongoing. Two trials, DEFINE and CONFIRM, investigated the effects of dimethyl fumarate on MS relapses. In the DEFINE study (n=1,234), study authors reported, “The estimated proportion of patients who had a relapse was significantly lower in the two BG-12 [dimethyl fumarate] groups than in the placebo group (27% with BG-12 twice daily and 26% with BG-12 thrice daily [vs.] 46% with placebo, p<0.001 for both comparisons). The annualized relapse rate at 2 years was 0.17 in the twice-daily BG-12 group and 0.19 in the thrice-daily BG-12 group, as compared with 0.36 in the placebo group, representing relative reductions of 53% and 48% with the two BG-12 regimens, respectively (p<0.001 for the comparison of each BG-12 regimen with placebo).”⁹

In the CONFIRM study (n=1,417), study authors found, “At 2 years, the annualized relapse rate was significantly lower with twice-daily BG-12 [dimethyl fumarate] (0.22), thrice-daily BG-12 (0.20), and glatiramer acetate (0.29) than with placebo (0.40) (relative reductions: twice-daily BG-12, 44%, p<0.001; thrice daily BG-12, 51%, p<0.001; glatiramer acetate, 29%, p=0.01).”¹⁴ Side effects of dimethyl fumarate in these trials were mild and reversible. The most common adverse events (incidence 10% or more and 2% or more than placebo) were flushing, gastrointestinal symptoms, and nausea.¹³

Manufacturer and regulatory status: Biogen Idec International GmbH (Zug, Switzerland) is developing dimethyl fumarate for treating RRMS. Dimethyl fumarate received fast-track designation for treating RRMS from the U.S. Food and Drug Administration (FDA) in 2008.¹⁵ In February 2012, Biogen Idec submitted a new drug application (NDA) to FDA for dimethyl fumarate for treating RRMS.¹⁶ In February 2013, FDA approved dimethyl fumarate for treating adult patients with relapsing forms of MS.¹⁷

Diffusion: Based on a September 2013 query of a U.S.-based, online aggregator of prescription drug prices, a 30-day dose pack of dimethyl fumarate costs approximately \$4,800.¹⁸ However, a manufacturer-sponsored program, ActiveAccess,[™] makes dimethyl fumarate available for a copayment of \$10 for a 1-month supply.¹⁹ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found five policies that provide coverage for dimethyl fumarate with various preauthorization conditions.²⁰⁻²⁴ No specific policy was identified for the other payers.

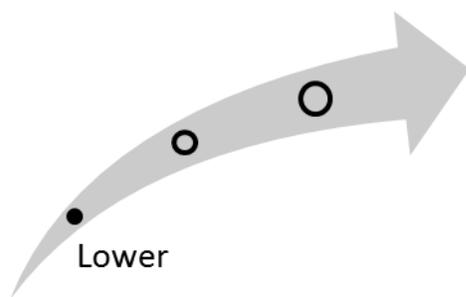
Clinical Pathway at Point of This Intervention

MS is an autoimmune disease in which the myelin sheath damage interrupts communication between the brain, spinal cord, and other areas of the body. There are four types of MS, three of which are relapsing MS: RRMS, secondary-progressive MS, progressive-relapsing MS (PRMS), and the non-relapsing form, primary-progressive MS.²⁵⁻²⁷

Manifestation of MS symptoms varies, depending on the amount of nerve damage and the affected nerves. Signs and symptoms include numbness or weakness in the limbs; partial or complete central vision loss, optic neuritis, and double or blurred vision; pain; electric-shock sensations that occur with specific head movements; tremor or unsteady gait; slurred speech; fatigue; and dizziness.²⁸ About half of patients with MS experience cognitive impairment, including difficulty concentrating, paying attention, remembering, and making judgments.²⁹

Treatment typically focuses on strategies to minimize attacks, manage symptoms, and reduce disease progression.²⁸ However, many medications used to treat MS have serious side effects.²⁹ If dimethyl fumarate is used as a monotherapy, competing oral drugs might include fingolimod (Gilenya[™]) and teriflunomide (Aubagio[®]), which are intended to treat RRMS.³⁰⁻³² FDA approved fingolimod in September 2010 as the first oral drug to reduce MS relapses,³⁰ and it approved teriflunomide in September 2012 for treating RRMS.³¹ Other drugs with which dimethyl fumarate may compete include the injectable agents natalizumab (Tysabri[™]) and mitoxantrone (Novantrone[®]), which can be used for RRMS or PRMS.⁵ Although natalizumab shows improved efficacy over other therapies in reducing RRMS relapses, it has also been associated with a potentially lethal brain infection. Mitoxantrone shows dose-limiting cardiac toxicity and a risk for acute myeloid leukemia as well as other side effects.³³

Figure 1. Overall high-impact potential: dimethyl fumarate (Tecfidera) for treatment of relapsing forms of multiple sclerosis



Experts agreed a significant need exists for a RRMS treatment with limited side effects and thought dimethyl fumarate could meet this need for patients in whom current treatment options fail. Side effects of dimethyl fumarate are less significant than in available treatment options, experts suggested. However, side effects could still limit use, other experts noted. As an orally administered

medication, experts thought dimethyl fumarate would be widely accepted by both clinicians and patients. Furthermore, experts suggested dimethyl fumarate could reduce the need for infusion centers and reduce the burden on long term care facilities. Experts overwhelmingly cited the need for long-term data and comparative effectiveness data on the intervention. 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

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.³⁴⁻³⁹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts indicated that a significant unmet need exists for an efficacious treatment for RRMS with minimal side effects and that requires less direct monitoring by health care professionals. In particular, experts noted that dimethyl fumarate is an additional option for patients in whom current treatment options fail. Conversely, some experts thought that dimethyl fumarate would offer only incremental benefit to patients with RRMS because other treatment options are available.

Experts agreed that there was substantial potential for this intervention to affect health outcomes in patients with RRMS, especial in patients in whom other treatments have been less effective. However, dimethyl fumarate is associated with gastrointestinal adverse events and experts were divided on the potential of these side effects to impact health outcomes. Some experts thought the adverse events were not significant, although others thought the effects could be possible deterrents to use. In general, experts suggested studies comparing dimethyl fumarate to active comparators are needed.

Acceptance and adoption: Experts anticipated dimethyl fumarate will be widely adopted by both clinicians and patients, citing its oral administration as the premier reason for its acceptance. Furthermore, the experts noted that patients on the drug do not need continued monitoring, which could further fuel adoption. However, one expert with a research perspective suggested, “trouble-free treatment for MS might negatively affect its diagnostic standards and might make clinicians more prone to initiate the treatment even when it is not necessarily the best option.”³⁷ Some experts highlighted the intervention’s potential gastrointestinal side effects and the lack of comparative effectiveness studies as barriers to acceptance and adoption.

Health care delivery infrastructure and patient management: Experts indicated that as an orally administered medication, dimethyl fumarate could reduce the need for infusion centers and reduce the burden on long-term care facilities. Furthermore, experts noted the potential to reduce the need for monitoring that is required with other comparable RRMS treatments. Experts agreed dimethyl fumarate, as an oral drug, could shift the RRMS treatment paradigm from injections to a more easily administered oral medication.

Health disparities: Experts concluded this intervention would have little impact on health disparities. One expert suggested that because MS is more prevalent in women, potential exists for dimethyl fumarate to improve women’s health overall.

Genetic Disorder Intervention

Eliglustat Tartrate for Treatment of Gaucher's Disease

Unmet need: Gaucher's disease is caused by a hereditary deficiency of glucocerebrosidase that leads to enlarged and malfunctioning organs, skeletal disorders, and painful neurologic complications due to accumulation of glucosylceramide in these tissues. The only oral drug approved (miglustat; Zavesca[®]) is not available as first-line treatment of Gaucher's disease, but intravenous (IV) enzyme replacement therapy (ERT) is approved as first-line therapy and is standard of care.⁴⁰ Eliglustat tartrate is being developed as a first-line oral therapy and is also intended to have fewer side effects than miglustat, which is known to cause side effects such as diarrhea, abdominal swelling, tremor, and weight loss. Treatment of Gaucher's disease has taken the two following basic forms:

- Supplying exogenous glucocerebrosidase enzyme (i.e., ERT)
- Inhibiting upstream components of the glucosylceramide biosynthetic pathway (i.e., substrate reduction)

ERT is expensive and requires lifelong IV infusions every 2–3 weeks.⁴¹ A temporary break from ERT due to personal issues or changes in lifestyle may lead to disease progression.

Intervention: Eliglustat tartrate, a self-administered oral compound, is under investigation as first-line treatment for Gaucher's disease. The drug purportedly partially inhibits the enzyme glucosylceramide synthase, resulting in reduced production of glucosylceramide.^{42,43} In phase III trials, eliglustat tartrate is administered in 50, 100, or 150 mg doses, twice daily.^{44,45} An additional phase III trial is ongoing and compares a once-daily dose of 100 or 200 mg with a twice-daily dose of 50 or 100 mg.⁴⁶

Clinical trials: Three phase III trials are ongoing.⁴⁴⁻⁴⁶ Positive interim-analysis data have been reported from two phase III trials.⁴² The ENCORE trial is evaluating the percentage of patients (n=160) who remain stable while taking eliglustat tartrate and interim results are available for the first 52 weeks of the study. As reported by a manufacturer press release, "Eliglustat tartrate met the pre-specified criteria for non-inferiority to Cerezyme [imiglucerase], with the majority of patients in both groups remaining stable one year after randomization (84 percent of eliglustat tartrate patients and 94 percent of Cerezyme patients). In an additional, pre-specified, efficacy analysis of the percent change in spleen volume from baseline, a mean change of minus six percent was observed in the eliglustat tartrate arm compared with minus three percent in the Cerezyme arm. This analysis also met the criteria for non-inferiority."⁴⁷

The ENGAGE trial is evaluating improvement (i.e., reduction) in spleen size in patients (n=40) taking eliglustat tartrate. As reported in a manufacturer press release, "A statistically significant improvement in spleen size was observed at nine months in patients treated with eliglustat tartrate compared with placebo. Spleen volume in patients treated with eliglustat tartrate decreased from baseline by a mean of 28 percent compared with a mean increase of two percent in placebo patients, for an absolute difference of 30 percent (p<0.0001)."⁴⁷

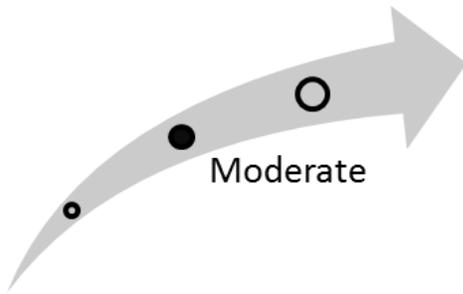
Manufacturer and regulatory status: Eliglustat tartrate is under development by Genzyme Corp. (Cambridge, MA), a subsidiary of Sanofi (Paris, France), for treating type 1 Gaucher's disease.⁴³ The manufacturer stated that it may submit an NDA to FDA by the end of 2013.⁴⁸

Diffusion: If approved, diffusion among the intended patient population would be expected to be brisk, because it would be the first oral treatment available; however cost might be a factor that affects access for some patients. As the first orally administered long-term therapy, cost is anticipated to be high and formulary coverage as a specialty pharmaceutical requiring preauthorization and quantity limits would be expected. However, because eliglustat tartrate is not yet FDA approved, no specific cost, coverage, coding, or payment information is available.

Clinical Pathway at Point of This Intervention

ERT (e.g., imiglucerase, taliglucerase alfa) is the standard first-line treatment.⁴⁹ Eliglustat tartrate is expected to compete with ERT as first-line treatment. Oral miglustat therapy for type 1 Gaucher's disease is approved only for use by patients who are ineligible for ERT.⁵⁰ Miglustat frequently causes side effects, such as diarrhea, abdominal swelling, tremor, and weight loss that affect patient acceptance of the drug. The associated clinical improvements are reported to be less effective and slower than that of ERT.⁴⁹

Figure 2. Overall high-impact potential: eliglustat tartrate for treatment of Gaucher's disease



Overall, experts cited a need for a more convenient treatment for Gaucher's disease and suggested the oral compound eliglustat tartrate could increase patient compliance and in doing so, lead to improved health outcomes and reduced disease progression. Experts anticipated widespread adoption of eliglustat tartrate, if approved, because of its convenient nature as an oral drug. Furthermore, experts suggested adoption of eliglustat tartrate could reduce the need for infusion centers and shift the care setting to homecare. Experts noted this to be contingent on eliglustat tartrate being proved as effective or more effective than the current standard of care. 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, health systems, and health administration backgrounds, provided perspectives on this intervention.⁵¹⁻⁵⁶ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts highlighted the need for a more convenient and well tolerated treatment for Gaucher's disease. The convenience of eliglustat tartrate, experts noted, could increase patient adherence with treatment, leading to better health outcomes and lessen the risk of disease progression. Additionally, experts suggested the ease of incorporating an oral therapy, rather than using standard bi-weekly IV infusion of ERT, could positively impact quality of life. However, experts also called for more comparative-effectiveness data to compare eliglustat tartrate with IV ERT. One expert with a health systems perspective questioned the potential overall benefit of the oral therapy, stating, "it is unclear whether there is any advantage to eliglustat [tartrate] over ERT in terms of safety, efficacy, and cost."⁵⁵ This expert proposed that data on these parameters would be important factors influencing the ability of eliglustat tartrate to fulfill the unmet need in Gaucher's disease treatment.

Acceptance and adoption: Experts unanimously agreed clinicians would readily accept a more convenient treatment for patients with Gaucher's disease. Experts cited the potential for increased compliance as an important factor contributing to clinician acceptance. However, experts remarked this potential for widespread acceptance and adoption would be contingent on eliglustat tartrate

being proved at least as effective as the standard of care. Experts anticipated patients would also welcome an oral treatment over bi-weekly IV infusions efficacy and safety were similar.

Health care delivery infrastructure and patient management: If adopted, eliglustat tartrate could reduce the demand for and burden on infusion centers, experts noted. Experts suggested eliglustat tartrate could shift the care setting from infusion centers to home care. One clinical expert noted that convenience of treatment might also allow for a shift in some of the aspects of patient management and monitoring from specialist care to primary care.

Experts were unclear on the cost impact of eliglustat tartrate. One expert with a research perspective noted that widespread adoption of a first-line oral therapy could reduce costs over time if a generic version became available. Another clinical expert suggested potential for cost savings exists because of increased patient adherence with treatment which could lead to fewer complications and emergencies, and a reduction in infusion center staffing demands.

Health disparities: Experts concluded eliglustat tartrate would have little effect on health disparities.

Renal-Protection Intervention

RenalGuard for Prevention of Contrast-Induced Nephropathy

Unmet need: Contrast-induced nephropathy (CIN) is a common cause of acute renal dysfunction that occurs after contrast media is administered (in the absence of other causes) to patients with chronic kidney disease (CKD).⁵⁷ Many cases are not identified until 48–72 hours after contrast media exposure, and the only treatment available is hydration and future avoidance of nephrotoxic agents.⁵⁸ Because no specific treatment for CIN exists, the primary goal is prevention in patients known to be at risk.⁵⁹

Intervention: The RenalGuard[®] System is under investigation as a system to reduce the risk of CIN in patients with CKD or who have known risk factors for CIN and who need to undergo imaging that requires use of contrast media. RenalGuard Therapy involves using a prescription-prescribed loop diuretic to induce the required level of high urine output. The system replaces fluid, actively synchronizing a patient's urine output with sterile saline solution IV infusion. This minimizes the risk of over- or underhydration; over- or underhydration can increase a patient's risk of CIN during imaging procedures.⁶⁰ Inducing high urine flow rates purportedly limits contrast exposure time, maintains renal blood flow, limits hypoxia from endothelin-mediated vasoconstriction, and accelerates duct flow through reduced sludging and precipitation of contrast material in renal tubular cells.⁶¹ RenalGuard is intended for temporary use (up to 14 days) to replace urine output in patients at high risk for CIN by matched infusion of sterile replacement solution to maintain intravascular fluid volume.⁶²

Clinical trials: One phase III pivotal trial and one phase IV trial are ongoing.^{63,64} Two phase III trials have been completed, and study investigators reported positive data from both trials.^{61,65-67} In the phase III REMEDIAL II trial (n=292), patients received care with either the RenalGuard system or IV sodium bicarbonate. Study authors reported, “Contrast-induced acute kidney injury occurred in 16 of 146 patients in the RenalGuard group (11%) and in 30 of 146 patients in the control group (20.5%; odds ratio, 0.47; 95% confidence interval, 0.24 to 0.92).”⁶¹

In an additional phase III trial, the MYTHOS trial, patients (n=170) received either furosemide with matched hydration (FMH) (via the RenalGuard) or IV sodium bicarbonate. Study authors reported, “In the FMH group, no device- or therapy-related complications were observed. Four (4.6%) patients in the FMH group developed CIN versus 15 (18%) controls (p=0.005). A lower incidence of cumulative in-hospital clinical complications was also observed in FMH-treated patients than in controls (8% vs. 18%; p=0.052).”⁶⁷

Manufacturer and regulatory status: The RenalGuard System is under development by PLC Systems, Inc. (Milford, MA).⁶⁸ The has not been approved by FDA; however, the manufacturer has indicated that a phase III pivotal trial is underway to support a premarket approval filing.⁶⁸ The manufacturer received the Conformité Européene (CE) mark for the system in December 2007 allowing marketing in Europe.⁶⁹

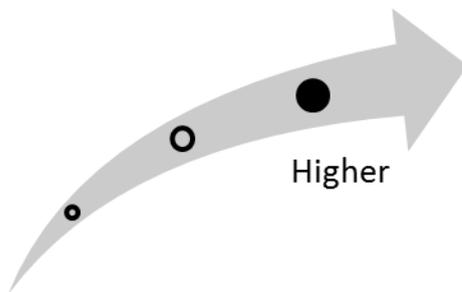
Diffusion: The system, if shown to be effective in preventing CIN in patients at high risk, would likely diffuse broadly for use during imaging in this patient population because no preventive therapy is available. Because the RenalGuard System is not yet approved by FDA, no specific cost, coverage, coding, or payment information is available.

Clinical Pathway at Point of This Intervention

No defined standard of care treatment for CIN exists; the primary goal is to prevent the occurrence in patients undergoing imaging procedures requiring contrast who are at high risk of CIN. Periprocedural hydration is often recommended as a simple and effective prevention technique; however, trial data are lacking on whether this approach is effective. Fluids can be administered orally or intravenously; current evidence supports periprocedural hydration, preferably

with intravenous isotonic saline or isotonic sodium bicarbonate solution, without furosemide, mannitol, or dopamine. N-acetylcysteine has had positive results in randomized studies as a preventative therapy in patients at higher risk of developing CIN. However, trial results conflict, using varying procedures, different types and volumes of contrast media, different timing and dosage of N-acetylcysteine administration, and different methods of administration. Overall, limited evidence exists supporting the use of a pharmaceutical agent (e.g., N-acetylcysteine, ascorbic acid, theophylline, fenoldopam, calcium antagonist).⁵⁷ Evidence does not support using postprocedural hemodialysis to prevent CIN. If approved in the United States, the RenalGuard System would compete with existing methods of prophylactic hydration to prevent CIN.

Figure 3. Overall high-impact potential: RenalGuard for prevention of contrast-induced nephropathy



Experts unanimously agreed on the importance of preventing CIN during imaging procedures in patients at high risk (i.e., those with CKD or history of CIN), because no effective prophylaxis is available, not is any standard effective treatment available after CIN occurs. Overall, experts thought RenalGuard seemed like a viable option to reduce the risk of CIN and increase access to imaging that requires contrast media in patients at high risk of developing CIN. Experts thought RenalGuard would face very few barriers to adoption and could be easily implemented into the existing infrastructure. 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, health systems, and health administration backgrounds, provided perspectives on this intervention.⁷⁰⁻⁷⁵ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Overwhelmingly, experts stressed the importance of preventative efforts in the absence of effective treatments for CIN. Experts indicated that RenalGuard presented an option for clinicians and patients to minimize risks associated with use of contrast media and also to make contrast media tests available to patients who may have previously been excluded from testing because of the potential for CIN. Specifically, one expert with a clinical perspective stated, “Preventing acute renal failure is not only important in and of itself, but also may allow some patients the option of having these contrast involved tests that are not able to have them at this time because of the fear of inducing CIN.”⁷² One expert with a health systems perspective highlighted the novelty of the mechanism of action of RenalGuard in preventing CIN and another expert with the same perspective noted the possible reduction in morbidity and mortality from CIN if the RenalGuard system were to be implemented.^{73,74} Overall, experts called for more data to further support RenalGuard’s purported efficacy in reducing CIN incidence.

Acceptance and adoption: Experts indicated that RenalGuard should face few barriers to adoption and would be readily accepted by clinicians and patients. Furthermore, experts agreed that

RenalGuard could become the standard of care in preventing CIN in patients with CKD who need imaging procedures with contrast media. Minimal training to implement the system and the minimal invasiveness of the system were cited by experts as reasons acceptance and adoption would be broad. The perceived benefits of RenalGuard, experts noted, would fuel patient acceptance as well. Several experts, however, remarked that widespread acceptance and adoption of the system would be contingent on conclusive data about safety and efficacy. If that is demonstrated, experts suggested the probable short-term costs of adding RenalGuard to imaging procedures would be offset by long-term savings from a decrease in CIN.

Health care delivery infrastructure and patient management: Experts did not anticipate a major disruption to delivery or infrastructure, largely because of the minimal training and direct patient-care time required for implementation. Overall, experts thought this innovation could be easily implemented. In regards to patient management, experts indicated the system could change patient management by reducing CIN incidence and resulting hospitalizations and followup care. One clinical expert countered that the potential reduction in hospital stays might be offset by an increase in imaging tests using contrast media in patients who were previously ineligible.⁷²

Health disparities: Four of six experts thought the RenalGuard system would have no impact on health disparities. However, two experts, both with health systems perspectives, suggested RenalGuard has the potential to protect marginalized populations and bridge existing barriers to health and wellness. Specifically, both experts noted that preexisting conditions that increase risk of CIN are more prevalent in health disparate populations. Use of RenalGuard to minimize risk of CIN in patients with CKD might therefore increase access to and use of imaging procedures with contrast media to aid diagnosis and treatment protocols.^{73,74}

Sensory Disorder Interventions

Corneal Collagen Cross-Linking (VibeX Riboflavin/KXL System) for Treatment of Progressive Keratoconus

Unmet need: Patients with progressive keratoconus or corneal ectasia currently face treatments that involve invasive procedures (e.g., corneal transplant, corneal ring insertion). Without treatment, blindness eventually occurs. These invasive interventions, such as corneal transplant, are also associated with complications, such as graft rejection, risk of permanent vision loss, and prolonged recovery after surgery. Minimally invasive treatment options are needed that can stabilize or slow the progression of keratoconus or corneal ectasia. The VibeX Riboflavin™/KXL™ System offers a less invasive option for accomplishing corneal collagen cross-linking (CXL), a procedure intended to preserve vision in patients with keratoconus or corneal ectasia and avoid the need for a corneal transplant. No systems for performing CXL are available in the United States at this time.

Intervention: CXL is intended to strengthen the corneal structure by subjecting it to ultraviolet A (UVA) light after a riboflavin (vitamin B₂) photosensitizing solution has been applied to the cornea. CXL is intended to inhibit the progression of corneal ectasias, including keratoconus.⁷⁶ CXL is accomplished by removing the corneal epithelium and applying drops of riboflavin to the eye. The eye is then exposed to UVA light to produce a reaction with the applied solution. Reactive oxygen molecules generated during irradiation cause chemical bonds to form between corneal collagen fibrils, increasing corneal rigidity.^{76,77} The procedure is performed in the outpatient setting with the patient awake while topical anesthesia is used for pain management.⁷⁷ Currently, the CXL surgical technique reported to be most often used (in Europe) requires removing the corneal epithelium to expose the stroma, thus allowing for adequate riboflavin absorption.⁷⁸ However, CXL surgery has also been performed without removing the corneal epithelium in clinical trials.^{78,79}

The VibeX Riboflavin/KXL system for performing CXL consists of a portable, battery-powered touch-screen monitor for operation and an articulating arm to focus UVA irradiation on the patient's cornea. VibeX Rapid is the riboflavin solution used. The system purportedly can complete the CXL procedure much more quickly than other systems on the market in Europe for performing CXL because it uses higher UVA power to reduce the exposure time needed to achieve CXL.^{80,81}

Clinical trials: Three registered phase III trials of the system are ongoing in the United States.⁸²⁻⁸⁴ Data have been reported from 2 completed trials, UVX-002 and UVX-003;⁸⁵⁻⁸⁷ however, these data are from trials performed only in the United States and using the KXL system. Many manufacturers of systems to perform CXL distribute systems in Europe, but only one manufacturer (Avedro) appears to be pursuing regulatory approval in the United States.⁸⁸ Additional data and a large body of literature has been published on using CXL in treatment performed outside the United States using the cross-linking systems of multiple manufacturers. Most recently, study investigators reported on uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and Keratometry values (K) at 1 year after CXL treatment of 76 patients who underwent CXL treatment (patients were divided into 3 groups based on maximum K location: central cone group, paracentral cone group, and peripheral cone group). As reported by study investigators, "In the combined cohort, maximum K and uncorrected and corrected distance visual acuity significantly improved by -1.60 ± 3.40 diopters (D) ($P < 0.001$), -0.08 ± 0.25 logMAR [logarithm of the minimum angle of resolution] ($P = 0.001$), and -0.10 ± 0.18 log-MAR ($P < 0.001$), respectively. Comparing cone groups, maximum K decreased by 2.60 ± 4.50 D ($P < 0.001$) in the central cone group, 1.10 ± 2.50 D ($P = 0.02$) in the paracentral cone group, and 0.40 ± 1.20 D ($P = 0.08$) in the peripheral cone group. Differences among groups were statistically significant ($P < .001$). Uncorrected distance visual acuity improved by -0.07 ± 0.3 logMAR ($P = .1$) (central cone group), -0.1 ± 0.17 logMAR ($P = 0.004$) (paracentral cone group), and -0.1 ± 0.25 logMAR ($P = 0.04$) (peripheral cone group). Corrected

distance visual acuity improved by -0.14 ± 0.21 logMAR ($P < 0.001$) (central cone group), -0.08 ± 0.17 logMAR ($P = 0.01$) (paracentral cone group), and -0.08 ± 0.12 logMAR ($P = 0.002$) (peripheral cone group).⁸⁵ These differences were not significant between the groups for UDVA and CDVA outcomes.⁸⁵

For a trial of 71 eyes of patients with either keratoconus ($n = 49$) or post-LASIK ectasia ($n = 22$), study investigators reported, “In the entire patient cohort, there were significant improvements in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature at 1 year compared with baseline (all $P < 0.001$).”⁸⁶ Procedure-related adverse events reported in clinical trials of CXL procedures included: corneal haze, corneal edema, infection, pain, perforation, striae, sterile keratitis, and stromal scar.⁸⁹

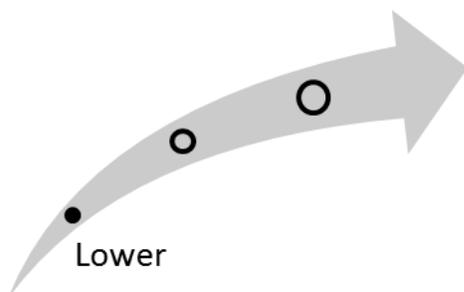
Manufacturer and regulatory status: Avedro, Inc. (Waltham, MA), is developing the system for the U.S. market.⁸⁰ The system a CE mark in 2010 in Europe.⁸⁰ In December 2011, the manufacturer announced that FDA had granted an orphan drug designation for the system for treating keratoconus and corneal ectasia after refractive surgery.⁸¹ In March 2012, the manufacturer announced that it had submitted an NDA to FDA.⁸¹ In November 2013, the company announced that FDA had granted priority review status for the system; the scheduled date for a decision is March 15, 2014. The company stated that the proposed indications in the NDA are treating keratoconus and corneal ectasia following refractive surgery, both of which are orphan drug indications.⁹⁰

Diffusion: The system is in an innovative phase of diffusion in the United States (i.e., under development); no specific coverage, coding, or payment information is available at this time. Cost information for the U.S. market is also not yet available. However, the cost of surgery at one Singapore location was listed at about \$3,500 per eye.⁹¹ Although not currently for sale in the United States, the Avedro KXL machine reportedly costs approximately \$35,000 in markets outside the United States.⁹¹

Clinical Pathway at Point of This Intervention

Keratoconus is typically treated using rigid, gas-permeable contact lenses; however, the progressive form usually requires surgical intervention with corneal transplantation.⁷⁶ Intracorneal ring segments can be implanted to enhance the effectiveness of contact lenses, but a corneal transplant may still be required.⁷⁶ If approved for marketing, the VibeX/KXL system would likely compete with these interventions or, in some cases, be used in combination with them (e.g., with corneal ring segment implantation).

Figure 4. Overall high-impact potential: corneal collagen cross-linking (VibeX/KXL System) for treatment of progressive keratoconus



Overall, experts thought the system could fill the unmet need for minimally invasive treatment of progressive keratoconus. The ease of performing CXL procedures with the system was cited by several experts as facilitating adoption and acceptance; however, others noted that the required training and knowledge base could serve as a barrier because it would be a new treatment in the United States. Experts suggested that costs associated with CXL procedures could negatively affect health disparate populations and might limit access. 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

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.⁹²⁻⁹⁷ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts agreed that CXL would fulfill the need for a minimally invasive option for progressive keratoconus that is not satisfied by the current standard of care. Experts highlighted the time intensity of available treatment options and noted the potential for CXL to reduce treatment time and associated risks. One expert with a clinical perspective noted, “CXL is expected to be revolutionary” and thus far has proven to positively impact patient health outcomes.⁹² Other experts called for more data to prove CXL’s long term efficacy and outcomes sustainability. Experts indicated CXL is associated with less risk and fewer adverse events than the standard of care and may improve patient health outcomes in that way.

Acceptance and adoption: Experts cited the relative ease of performing CXL procedures as an aid to acceptance and adoption; however, one expert noted the required training and knowledge base to perform the procedure could be a barrier to adoption. Because of the lack of available minimally invasive procedures for the condition, this technology would be readily accepted by clinicians, experts thought, citing the safety and efficacy profile thus far from both U.S. and European trials. As a minimally invasive option, experts suggested, CXL would be a welcomed alternative to contact lenses and more intensive surgery.

Health care delivery infrastructure and patient management: Experts did not anticipate CXL would significantly affect the current health care delivery infrastructure citing that CXL would supplant the outpatient procedure now used. Experts noted the minimally invasive nature of CXL could potentially reduce clinician and staff time now required for treating these patients.

Experts suggested the potential reduction in the number of corneal transplants resulting from CXL could reduce health care costs. One expert proposed that costs of CXL might lower over time, citing LASIK surgery as an example of decreasing in cost over time.⁹⁷ However, another expert with a health systems perspective expressed concern about possible overuse of CXL that could potentially result “in high costs for the overall management of keratoconus in the population. . . . CXL would be one more example of new, more expensive treatments taking the place of existing satisfactory approaches.”⁹³

Health disparities: Most of the experts thought CXL would have a negligible impact on health disparities. Some experts thought that costs of CXL might deter health disparate populations from accessing treatment; however other experts thought that, if covered by health insurance, costs would not limit access to the procedure because it would be supplanting other surgical options.

High-intensity Focused Ultrasound (EyeOP1 HIFU-system) for Treatment-Refractory Glaucoma

Unmet need: Glaucoma, if left untreated or inadequately treated, can lead to blindness, and the vision loss cannot be restored.⁹⁸ The main goal of glaucoma management is reducing intraocular pressure (IOP), which is frequently accomplished using medications. For patients with high IOP that does not respond to medication, several laser-based and surgical options exist; however, these treatments each have their shortcomings and may not adequately control IOP in all patients.^{99,100} High-intensity focused ultrasound (HIFU) would offer a novel option for patients with treatment-refractory glaucoma that could avoid side effects seen with thermal ablation procedures.

Intervention: The EyeOp1[®] HIFU system is a novel approach intended to reduce the production of aqueous humor. The rationale behind the EyeOp1 procedure is similar to currently employed ablative procedures that target the ciliary bodies, the eye tissues responsible for production of aqueous humor. The system uses miniaturized piezoelectric transducers to perform controlled HIFU thermocoagulation of ciliary processes without affecting surrounding ocular tissue. This stands in contrast to currently used laser ablation and cryoablation procedures, which both induce thermal damage to surrounding tissues. The EyeOp1 system's HIFU-generating transducers are placed in a ring to allow ablation of the full circumference of the eye in a single treatment session, which takes about 1 minute of ablation time.⁹⁹

EyeOP1 is a two-part system consisting of a command module and a sterile, single-use therapy device that is placed in direct contact with the patient's eye. The command module has a generator, pressure-reduction system, touch screen, command pedal, and control systems to generate power, set treatment parameters, and control the system. The generator in the command system delivers power to the ultrasound transducers while the pressure-reduction system applies suction to fixate the therapy device to the eyeball, guaranteeing it remains in place throughout the procedure.¹⁰¹ HIFU is delivered through six circular, miniaturized transducers arrayed at regular intervals on the upper and inferior circumference of the therapy device ring. The ring mirrors the anatomy of the ciliary body, allowing simultaneous ablation of multiple sites within the ciliary body, and the small size of the transducers generates small focal zones, potentially allowing highly selective ablation of small structures such as the ciliary processes.¹⁰² Treatment with the EyeOP1 system purportedly produces localized, reproducible, and sustainable histological damage to the ciliary processes without harming surrounding tissue.⁹⁹ The procedure can be performed in an examination room rather than an operating room.¹⁰¹

Clinical trials: Three registered clinical trials of the EyeOp1 system for treatment-refractory glaucoma are ongoing.¹⁰³⁻¹⁰⁵ Two trials of EyeOp1's ability to reduce IOP have been completed.^{102,106} Study investigators of a 39-patient trial compared 4-second and 6-second exposure times using the EyeOp1 and reported, "IOP was significantly reduced in both groups ($p < 0.05$), from a mean preoperative value of 28.9 ± 6.8 mmHg in group 1 and 29.2 ± 6.9 mmHg in group 2 to a mean value of 18.1 ± 4.4 mmHg in group 1 and 16.1 ± 8.5 mmHg in group 2 at last follow-up. Success (IOP reduction $> 20\%$) was achieved in 15 of 18 (83%) eyes of the group 1 with an average of IOP decrease of 42% and in 19 of 21 (90%) eyes of the group 2 with an average of IOP decrease of 49%."¹⁰⁶ An earlier pilot trial of the EyeOp1 in 12 patients also had statistically significant positive findings.¹⁰²

Safety data from this pilot study indicated that no major intraoperative or postoperative complications occurred. Superficial punctate keratitis corneal ulceration occurred in three patients (25.0%), and central superficial corneal ulceration occurred in one patient (8.3%); however, all four of these patients had previous corneal conditions. Investigators reported that postoperative examinations revealed little to no signs of intraocular inflammation.¹⁰²

Manufacturer and regulatory status: EyeOP1 is being developed by EyeTechCare, S.A. (Rillieux la Pape, France). The technology was based on joint research between EyeTechCare and the French National Institute of Health and Medical Research (INSERM).¹⁰⁷

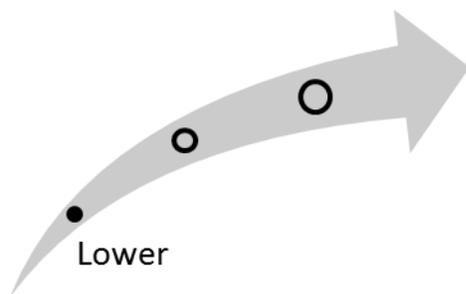
In May 2011, EyeOP1 received the CE mark enabling marketing in Europe.¹⁰⁸ EyeOP1 is not yet approved by the U.S. Food and Drug Administration (FDA). The company's EyeMUST 2 international trial is expected to publish results in early 2014, and the company intends to register with FDA by the end of 2013 to pursue regulatory approval for the U.S. market.¹⁰⁸

Diffusion: The EyeOP1 system and procedure costs, coverage, coding, and payment policies have not yet been established in the United States. If it gains FDA approval, EyeOP1 might be reimbursed by public and private third-party payers in a manner similar to that of other available surgical and laser-based therapies for glaucoma. Generally, established glaucoma treatments are covered by third-party payers; however, some more recently developed treatments (e.g., canaloplasty, viscocanalostomy) are covered by some, but not all payers.¹⁰⁹⁻¹¹³

Clinical Pathway at Point of This Intervention

The primary glaucoma-treatment goal is to reduce IOP. Glaucoma cannot be cured nor can the damage caused by increased IOP be reversed. First-line treatment options to slow disease progression include eye drops and oral medications;¹¹⁴ when these options fail, laser surgery or cryoablation may be considered.¹¹⁵ Eye drops are associated with discomfort from stinging and burning. First-line treatments are also associated with patient adherence issues because of inability to dispense the drops properly, adverse side effects, dissatisfaction with the discomfort, difficulty of use, or frequency of application required.⁹⁹ The EyeOP1 system is expected to compete with other options for treatment-refractory glaucoma (e.g., argon laser trabeculoplasty, selective laser trabeculoplasty, or cycloablation), traditional trabeculoplasty, drainage implant surgery, and nonpenetrating surgery.¹¹⁴

Figure 5. Overall high-impact potential: high-intensity focused ultrasound (EyeOP1 HIFU-system) for treatment-refractory glaucoma



Experts highlighted that the primary unmet need in glaucoma treatment lies in raising awareness about the disease and getting people screened; however, experts saw a need for less-invasive treatment options that would improve health outcomes and reduce side effects. They thought the EyeOP1 could potentially fill a need. Experts cited the minimally invasive nature of EyeOp1 as facilitating clinician and patient adoption. Experts indicated the potential for this intervention to have a significant impact on glaucoma treatment would be contingent on a parallel increase in awareness, screening, and early diagnosis and treatment. 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

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.¹¹⁶⁻¹²¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts' perspectives were mixed on the unmet need for treatment-refractory glaucoma options, citing availability of several options. They stated the primary unmet need in glaucoma treatment lies in raising awareness about the disease to promote screening, earlier diagnosis, treatment, and adherence to daily treatment regimens. However, experts also expressed a need for minimally invasive treatment options with fewer side effects and thought EyeOP1 could potentially fill this need. Experts suggested the less invasive nature of EyeOP1 relative to current surgical interventions, might benefit patient health outcomes and satisfaction. However, experts called for more data on safety and efficacy relative to other options, as well as long term data proving lasting effects on IOP and sustained visual acuity.

Acceptance and adoption: Experts suggested the minimally invasive nature of this intervention and ability to perform the procedure outside of the operating room could contribute to acceptance and adoption by both clinicians and patients. Experts further cited the technology's low reported risk of adverse events and patient adherence issues with the current standard of care as facilitating clinician adoption. However, some experts thought acceptance would be contingent on additional data supporting safety and efficacy.

Health care delivery infrastructure and patient management: Because EyeOP1 procedures could be performed in the examination room rather than an operating room, experts suggested this could decrease the amount of care and staffing resources needed for medically refractory glaucoma treatment, and thereby also might reduce costs of care. Furthermore, experts anticipated a small reduction in post-treatment monitoring time and treatment for adverse events, if this proves to be safer and more effective. Experts suggested that the procedure might reduce incidence of blindness from glaucoma and health care services and costs associated with blindness. Experts anticipated that the EyeOP1 system's costs would be borne by third-party payers if the system is approved and has sufficient supporting efficacy and long-term effects.

Health disparities: Experts were divided on the potential impact of the EyeOP1 system on health disparities: some thought it would have no impact on health disparities; others noted that because glaucoma is more prevalent in certain marginalized populations, the treatment option might reduce disparities if available to these populations. Experts noted that this impact would be contingent on a complimentary increase in screening, and early diagnosis and treatment of glaucoma.

Ocriplasmin (Jetrea) Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole

Unmet need: The efficacy of traditional vitreoretinal surgery for symptomatic vitreomacular adhesion (VMA) is limited by the potential for incomplete vitreoretinal separation and/or removal, complications (e.g., cataract development), and high costs.¹²² Therefore, nonsurgical methods are needed that could replace or complement surgery for VMA.¹²³ Ocriplasmin (Jetrea®) is intended as a medical option for VMA

Intervention: Ocriplasmin is a truncated form of plasmin produced using recombinant methods in a yeast (*Pichia pastoris*) expression system.¹²⁴ Recombinant ocriplasmin retains the catalytic characteristics of human plasmin and is purported to have several advantages as a therapeutic agent, including its sterility, its increased stability over plasmin, and its smaller molecular size, allowing for greater penetration of epiretinal tissues.^{122,125} Ocriplasmin is provided in a single-use, glass vial at a concentration of 2.5 mg/mL. The recommended dose is a single injection of 0.1 mL of solution at a concentration of 1.25 mg/mL.¹²⁶ Clinicians must dilute the solution with sterile sodium chloride before use.¹²⁷ Intravitreal injections require a local anesthetic (eye drops) to minimize discomfort to the patient and an antiseptic solution to prevent contamination when injecting the solution into the eye.¹²⁸

Clinical trials: Completed trials of ocriplasmin have reported positive findings. One phase III trial investigated the resolution of symptomatic VMA 28 days after injection of 1.25 mg/mL or placebo in 652 different eyes (ocriplasmin=464, placebo=188). Study investigators found that “[VMA] resolved in 26.5% of ocriplasmin-injected eyes and in 10.1% of placebo-injected eyes (P<0.001). Total posterior vitreous detachment was more prevalent among the eyes treated with ocriplasmin than among those injected with placebo (13.4% vs. 3.7%, P<0.001). Nonsurgical closure of macular holes was achieved in 40.6% of ocriplasmin-injected eyes, as compared with 10.6% of placebo-injected eyes (P<0.001). The best-corrected visual acuity was more likely to improve by a gain of at least three lines on the eye chart with ocriplasmin than with placebo.”¹²⁹

In both completed phase III trials of ocriplasmin, treatment was generally safe and well tolerated. In particular, no increased risk of retinal tear or detachment was associated with ocriplasmin treatment.¹³⁰ The prescribing information for ocriplasmin provided by the manufacturer states that the most commonly reported adverse reactions, with incidence of 5% or more, include vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.¹²⁷

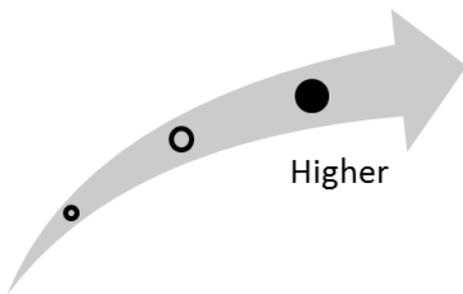
Manufacturer and regulatory status: Ocriplasmin was developed by ThromboGenics NV (Heverlee, Belgium).¹³¹ In October 2012, FDA approved ocriplasmin for treating symptomatic VMA.¹³² Ocriplasmin became available in the United States in January 2013.¹³¹

Diffusion: According to the manufacturer at the time of ocriplasmin’s launch, the price of the single-use vial of ocriplasmin had been set at \$3,950.¹³¹ Based on a September 2013 query of a U.S. based, online aggregator of prescription drug prices, a 0.2 mL vial of ocriplasmin 2.5 mg/mL (1 single-use vial) costs about \$4,250.¹³³ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified 4 payers with policies that provide coverage for ocriplasmin use in treating VMA.¹³⁴⁻¹³⁷ No specific policies were identified for the other payers.

Clinical Pathway at Point of This Intervention

Patients with asymptomatic or mildly symptomatic VMA typically undergo watchful waiting, and some cases spontaneously resolve. Patients with significant visual impairment caused by VMA typically undergo vitrectomy (i.e., vitreous removal), an invasive surgery that is the standard of care for symptomatic VMA.¹³⁸ Enzymatic vitreolysis with ocriplasmin has the potential to obviate the need for surgery in some patients if it induces a therapeutic PVD. Additionally, intravitreal ocriplasmin injection has the potential to be used in combination with surgical intervention; ocriplasmin given in the days leading up to surgery could make difficult vitreoretinal surgical procedures easier to perform by essentially priming regions of vitreoretinal adherence for detachment.¹³⁹

Figure 6. Overall high-impact potential: ocriplasmin (Jetrea) treatment for symptomatic vitreomacular adhesion including macular hole



Experts commenting on this intervention suggested ocriplasmin has potential to fulfill the significant unmet need for minimally invasive treatment for VMA. Furthermore, experts anticipated ocriplasmin could reduce the need for invasive surgery, reducing associated risks of surgery. The minimally invasive nature of ocriplasmin, experts agreed, would facilitate clinician and patient acceptance and adoption. If adopted, experts thought, ocriplasmin could shift the care setting for VMA from the surgical center to outpatient care. 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, health systems, and health administration backgrounds, provided perspectives on this intervention.¹⁴⁰⁻¹⁴⁵ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need exists for a less-invasive treatment for VMA, the experts agreed, concluding that ocriplasmin has the potential to address this need. Furthermore, one expert with a health systems perspective indicated that this need will continue to grow as the aging U.S. population continues to expand.¹⁴³ Experts also wanted to see long-term efficacy data for this intervention as well comparator studies between ocriplasmin and the current standard of care, surgery. Available data from randomized controlled trials suggest that the underlying mechanism of action of is sound, and these data serve as quantitative proof of the intervention's potential impact, experts noted.

With regard to ocriplasmin's impact on patient health outcomes, experts anticipated that the intervention has the potential to reduce the need for surgery and its associated adverse events in the affected population. A clinical expert noted that although ocriplasmin injection has some side effects, they are not as serious as those associated with surgery.¹⁴² Another expert, with a research

perspective, stated, “if this technology helps patients retain their visual acuity, it could make a large difference in their health. Loss of visual acuity can lead to other health problems.”¹⁴⁴

Acceptance and adoption: Experts unanimously agreed that both clinicians and patients would readily accept ocriplasmin injections for VMA as a less-invasive and safer treatment option. An expert with a clinical perspective thought that clinicians would be eager to make a change from a surgical intervention to a medical one and further noted that the techniques used in the administration of ocriplasmin injections are in the realm of the ophthalmologist skills set.¹⁴² This low training barrier would promote clinician acceptance, some experts indicated.

Health care delivery infrastructure and patient management: Experts agreed that ocriplasmin injection could shift the treatment paradigm for VMA from an outpatient surgical center to outpatient physician’s office. Most notably, an expert with a health systems perspective indicated that, “it is anticipated that care would shift from a surgical setting to a non-surgical outpatient setting making care more readily available, more cost effective, and possibly making care more available to patients in outlying areas.”¹⁴⁴ This paradigm shift may result in patients accessing treatment earlier. Furthermore, experts suggested this change in care delivery could present a cost savings opportunity for clinicians, patients, and payers.

Health Disparities: Experts did not think this intervention would impact health disparities or access to care.

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

Unmet need: The leading cause of preventable monocular vision loss in children is amblyopia, which is most often caused by strabismus.¹⁴⁶ Early detection of amblyopia can be difficult because standard screening methods lack sufficient sensitivity and specificity, missing cases of children who should be referred for further evaluation and possible treatment. They also cannot be effectively used on children younger than about age 4 years. If found early, amblyopia and strabismus are fully treatable; however, as many as half of affected children are not identified until school age, when treatment may not be as effective. A need exists for improved screening for these conditions to identify children who should be referred to a specialist for further evaluation.

Intervention: The Pediatric Vision Scanner (PVS) is intended for use as a screening tool for early detection of amblyopia or strabismus so that patients can be more appropriately referred to specialist care. The device can be either used as a portable, handheld device or mounted on a table.¹⁴⁷

According to the manufacturer, the device uses proprietary technology called retinal birefringence scanning. Retinal birefringence scanning measures the reflection of polarized light by the retina and can distinguish between light reflected by the fovea and light reflected by the paracentral retina. Based on this technology, the PVS simultaneously assesses both eyes to detect both binocular alignment and whether the eyes are focused on a target.¹⁴⁸ The PVS performs a 2.5-second scan of the eyes to automatically detect the presence of amblyopia, strabismus, or other serious eye conditions.¹⁴⁷ Testing with the PVS requires minimal cooperation and no verbal response from the individual being screened. During the scan, the patient looks at a fixed target within the device as a focal point. The device is designed to determine when the patient looks away from the target during the scan, which allows for these measurements to be discarded and for measurements to continue until a requisite minimum of five scans has been obtained. The software then provides a result as to whether the patient's eyes were accurately fixating on the target, indicating a "pass" or passing grade, or if one or both eyes were not properly fixating, indicating the need to refer the patient to a specialist for further testing.¹⁴⁷

The PVS is designed for use in a pediatric office as an early detection screening tool to promote preventative care and reduce false referrals for ophthalmic specialist care.¹⁴⁷

Clinical trials: The PVS is under investigation in independent clinical trials.¹⁴⁷ Three registered trials evaluated the sensitivity and specificity of PVS with positive results (sensitivity 98%; specificity 74% to 88%).¹⁴⁹⁻¹⁵¹ The most recent trial of the PVS (compared to SureSight Vision Screener and Randot Preschool Stereoacuity test) enrolled 250 patients 2–6 years of age. Study investigators reported, "The PVS correctly identified 144 of 147 children with strabismus and/or amblyopia; sensitivity=98% (95%CI [confidence interval]: 95-100%). The PVS correctly identified 89 of 102 control children; specificity=87% (95% CI, 79%-96%)."¹⁴⁹

A 2011 study investigated the degree of binocularity of the PVS and reported, "With the pass/refer threshold set at binocularity score (BIN) 60%, sensitivity and specificity were 96% for the detection of amblyopia or strabismus. Assuming a 5% prevalence of amblyopia or strabismus, the inferred positive and negative predictive values of the PVS were 56% and 100%, respectively. Fixation accuracy was significantly reduced in amblyopic eyes. In anisometric amblyopia patients treated successfully, the BIN improved to 100%."¹⁵²

As with any screening tool, the potential for false-positive or false-negative tests results exists with the PVS. False-negative results could lead to a delay in care for amblyopia or strabismus; false-positive results could lead to unnecessary specialty referrals. However, the PVS purportedly will reduce the rate of false-positive results associated with current screening methods.¹⁴⁷

Manufacturer and regulatory status: The PVS is under development by REBIScan, Inc. (Cambridge, MA). FDA has determined the PVS to be a nonsignificant risk investigational device,¹⁴⁷ meaning it has abbreviated requirements for labeling, institutional review board (IRB) approval for trials, and streamlined trial and reporting rules. The IRB serves as FDA’s surrogate for review, approval, and ongoing review of nonsignificant-risk device studies.¹⁵³

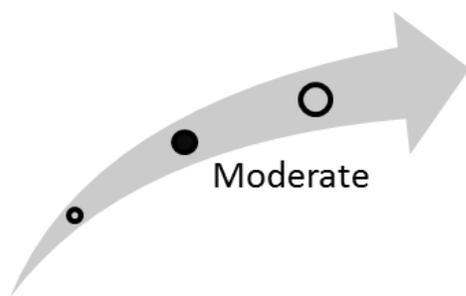
Diffusion: The PVS is not yet commercially available in the United States, and its cost, coverage, coding, and payment policies have not yet been established. If it gains FDA approval, PVS testing may be reimbursed covered by public and private third-party payers in a manner similar to that of other vision screening tests.

Clinical Pathway at Point of This Intervention

Amblyopia-associated refractive error is treated with consistent use of corrective lenses.¹⁵⁴ Additionally, any eye condition causing vision problems, such as cataracts, needs to be corrected.¹⁴⁶ Patches and eye-drop treatments are used to force the child to use the nondominant eye, allowing the weak eye to get stronger.¹⁵⁴ Children younger than the age of 5 years who receive treatment typically recover to almost complete normal vision; however, delaying treatment can result in permanent vision problems and, after the age of 10 years, only partial vision recovery can be expected.¹⁴⁶

The REBIScan PVS is intended for use as a screening tool for amblyopia and strabismus to allow referral of young children to an ophthalmologist for further evaluation so that treatment can start when the disorder is at a more correctable stage.¹⁴⁷ Current detection methods include annual visual acuity testing at a well-child checkups; however, such screening cannot be performed until a child is 4–5 years old (i.e., can follow directions and respond). Automated photoscreening devices are also used.¹⁴⁶ Both visual acuity testing and photoscreening devices lead to missed diagnoses and false positives leading to unnecessary referrals.¹⁴⁷ The manufacturer has indicated that the PVS, if used during annual well-child visits, can reduce expenditures by detecting amblyopia and strabismus in earlier stages and reducing false referrals to specialist care.

Figure 7. Overall high-impact potential: Pediatric Vision Scanner screening for strabismus and amblyopia



Overall, experts thought the ability of PVS to be used in very young children was a significant factor in its potential for fulfilling the unmet need for early diagnostic tools for amblyopia and improving patient outcomes for affect patients. The quick, noninvasive screening procedure, low associated risks, and minimal training requirements to use the device could aid in wide acceptance and adoption, experts anticipated. They suggested widespread use would be fueled by parent awareness and demand for screening. 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, health systems, and health administration backgrounds, provided perspectives on this intervention.¹⁵⁵⁻¹⁶⁰ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A need exists for effective early screening tools to identify children needing referral to an ophthalmologist for amblyopia evaluation, the experts agreed. They cited the REBIScan device's applicability to populations younger than age 4 as an important factor in fulfilling this unmet need. Furthermore, experts remarked that the device could meet this need because of its good specificity and sensitivity to guide referral to ophthalmologists that, if followed, allowing earlier treatment. Conversely, one expert with a research perspective suggested PVS does not address an unmet need because it does not address the underlying issue of access to care stating: "Adding this to a physician office might improve screening accuracy, but it would not help children who don't get pediatric well visits, for whatever reason."¹⁵⁶

Experts viewed the purported ability of the PVS to aid in early diagnosis of vision problems as important for improving patient health. One expert noted that "after the age of 6 or 8, the vision loss [associated with strabismus or amblyopia] is largely permanent, even with surgery, patching therapy, and/or powerful glasses. The sooner the problem can be detected, the proportionally greater chance there is to correct the problem."¹⁶⁰ Overall, the majority of experts agreed the PVS could fulfill a gap in preventative eye screenings and affect the rate at which these issues are fully addressed with earlier diagnosis and treatment.

Acceptance and adoption: Experts suggested the REBIScan PVS device would be widely accepted and adopted because of its ease of use especially in young children, and its noninvasiveness. One expert with a research perspective specifically noted that because current screening methods are associated with low rates of patient cooperation (because of age), the PVS, which requires minimal patient cooperation, would be widely utilized. Another expert with a health systems perspective indicated that "with the low overhead (pending information on device cost) and great benefit of early detection and treatment, this [PVS] would be a must-have for physician/pediatrician offices."¹⁵⁹

Experts anticipated PVS acceptance and adoption would be fueled by parent demand for the screening. One expert with a health systems perspective proposed that as testing and potential outcomes data becomes more widely publicized, parents and guardians of young children may actively seek out providers who offer the screening.¹⁵⁹

Health care delivery infrastructure and patient management: The potential reduction in false referrals, experts agreed, could substantially affect health care delivery and patient management. The majority of experts noted use of the PVS could also possibly extend the length of a pediatric care visit, though not by more than a few minutes. They also cited a potential reduction in long-term health care costs for strabismus and amblyopia treatment by enabling earlier intervention.

Health disparities: Overall, experts did not think PVS use had significant potential to affect health disparities. However, one expert with a research perspective thought increased disparity might occur, noting that individuals in health disparate populations that do not have access to regular well-child pediatric visits might not have access to the screening tool.

Retinal Prosthesis System (Argus II) for Treatment of Retinitis Pigmentosa

Unmet need: Medications or devices had not been available to restore lost vision or halt progression of vision loss that occurs because of retinitis pigmentosa (RP) prior to the implantable Argus[®] II Retinal Prosthesis System. This system purportedly restores a level of vision that allows patients greater independent functioning, although it does not restore ability to see details such as facial features. Argus II is the first FDA-approved, implanted device for treating adults with advanced RP.

Intervention: The Argus II is intended to provide “electrical stimulation of the retina to induce visual perception in blind patients with severe to profound retinitis pigmentosa and bare light or no light perception in both eyes.”¹⁶¹ It comprises both implanted parts and external equipment. The implanted device is an epiretinal prosthesis that is surgically attached to one of the patient’s eyes. It contains an antenna, electronics case, and electrode array. The external equipment includes a pair of glasses that is used not for sight but to carry a digital video camera, another antenna, and a video processing unit (VPU). The VPU also houses the battery that runs the entire system. The VPU connects to the glasses via a cable worn by the patient with an over-the-shoulder harness.¹⁶² According to the manufacturer, the steps required to use the Argus II System include device implantation, postoperative clinical followup, device fitting and training, and vision rehabilitation. An ophthalmologic surgeon performs the procedure in the outpatient setting while the patient is under general anesthesia.¹⁶³

The Argus II purportedly restores some degree of shape and color recognition by taking advantage of functioning photoreceptors and bypassing damaged photoreceptors, using electrical pulses. When the digital camera registers video, the cable sends the digital information to the VPU, where it is processed and transmitted to the antenna mounted on the glasses. The processed visual information is then transmitted wirelessly from the glasses to the antenna in the implant. When the implant receives the information, an electrode ray emits pulses of electricity to stimulate functioning photoreceptors in the retina. Visual information then travels from the stimulated photoreceptors via the optic nerve to the brain.¹⁶⁴

The visual information creates patterns of light that the patient can learn to interpret. For example, during use, the patient may be able to interpret the frame of a doorway via the perceived patterns of light the device generates.¹⁶⁴

Clinical trials: In clinical trials, investigators studied patients performing tasks such as object location, following a crosswalk across a street, and locating bus stops. Patients also performed tasks to detect light and variations of color.^{165,166} In February 2013, da Cruz and colleagues published results from a trial of 28 patients with light perception vision to determine letter and word reading and long-term function in patients with profound vision loss. “The mean \pm SD percentage correct letter identification for 21 subjects tested were: letters L, T, E, J, F, H, I, U, 72.3 \pm 24.6% system on and 17.7 \pm 12.9% system off; letters A, Z, Q, V, N, W, O, C, D, M, 55.0 \pm 27.4% system on and 11.8 \pm 10.7% system off, and letters K, R, G, X, B, Y, S, P, 51.7 \pm 28.9% system on and 15.3 \pm 7.4% system off. (p<0.001 for all groups). A subgroup of six subjects was able to consistently read letters of reduced size, the smallest measuring 0.9 cm (1.7 $^\circ$) at 30 cm, and four subjects correctly [identified] unrehearsed two-, three- and four-letter words. Average implant duration was 19.9 months.”¹⁶⁷ Multiple trials are ongoing in the United States and Europe.

Contraindications listed by the manufacturer include optic nerve disease, central artery or vein occlusion, history of retinal detachment or trauma, severe strabismus, thin conjunctiva, and corneal opacity not including cataracts. Device implantation is also contraindicated in patients who are unable to tolerate general anesthesia, antibiotics, or steroids. The manufacturer warns against

undergoing short wave or microwave diathermy, electroconvulsive therapy, or magnetic resonance imaging (MRI) procedure with equipment other than a 1.5 or 3.0 Tesla MRI System. If lithotripsy or high output ultrasound must be used, the treatment beam should not be focused near the Argus II Implant. The manufacturer has issued warnings against interference from medical monitoring, diagnostic, or life support equipment: Patients implanted with the device should not use it within 3 feet of this type of equipment. The manufacturer also warns against the use of monopolar electrosurgical equipment in patients who have received the implanted device. The most common adverse events reported in clinical studies included conjunctival dehiscence, conjunctival erosion, retinal detachment, inflammation, and hypotony (low intraocular pressure).¹⁶¹

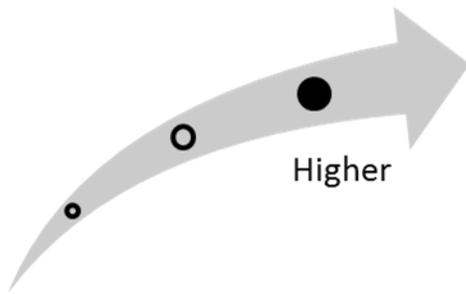
Manufacturer and regulatory status: Second Sight Medical Products, Inc., of Sylmar, CA, makes the Argus II Retinal Prosthesis System. In February 2013, FDA granted Argus II humanitarian device exemption to “treat adult patients with advanced retinitis pigmentosa (RP).”¹⁶² The manufacturer earlier announced that Argus II had received the CE mark in March 2011, allowing marketing in Europe.¹⁶⁸

Diffusion: According to manufacturer, the system costs about \$115,000, which includes the device and the surgical procedure.¹⁶⁹ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark,) found 5 policies, all of which were developed before FDA’s approval of the device. Those payers were Aetna, Anthem, Blue Cross/Blue Shield Massachusetts, CIGNA, and Regence, and all considered the use of artificial retinal devices to be “investigational.” and so denied coverage. Four of the five policies were formulated before the FDA decision to grant the system a humanitarian device exemption; however, the Regency policy was reviewed September 2013 and maintained its listing of the device as “investigational.”¹⁷⁰⁻¹⁷⁴ We did not identify any updated policies as of this writing.

Clinical Pathway at Point of This Intervention

RP can be familial, inherited as an inherited autosomal dominant, autosomal recessive, or X-linked defect. The disease has been linked to defects in more than 40 genes.¹⁷⁵ It can also arise in patients with no family history of the disease. RP signs and symptoms typically manifest in early childhood and progress through early adulthood as more rods and cones in the retina of the eye break down. Patients experience decreasing night and low-light vision and lose peripheral vision. In advanced cases, patients can lose central vision. To diagnose RP, physicians evaluate the retina using tests for refraction, color vision, visual field, visual acuity, and pupil-reflex response; retina ophthalmoscopy; fluorescein angiography; electroretinography; retina photography; and slit-lamp examination.¹⁷⁶ No cure exists; however, some treatment options, such as limiting light exposure, are thought to help preserve vision,¹⁷⁷ and other treatments under study include high doses of vitamin A palmitate and omega-3 fatty acid DHA.¹⁷⁶

Figure 8. Overall high-impact potential: retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa



Overall, experts commenting on this intervention thought that a significant unmet need exists for treatment options that restore some level of vision and provide greater patient independent functioning. Some experts opined that Argus II has potential to become the standard of care for vision loss due to RP because no other interventions are available. However, other experts noted the number of adverse events reported in studies and opined that clinical acceptance may be affected by that and by the difficulty of the surgery and the amount of training needed to perform the procedure. Experts generally agreed that patient adoption would be high if the technology was affordable by the patient because of patients' desire to be more independent. Most experts agreed that this intervention has the potential to fulfill the unmet need because of the lack of existing therapies and the potential to restore some vision in patients who have this disease. 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 intervention.¹⁷⁸⁻¹⁸³ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need: An unmet need exists for treatment options to restore some level of vision for patients with RP, the experts agreed. One research expert commented that the technology addressed a large unmet need, because RP leads to blindness and no other treatment is available, even though the affected patient population is small in number.¹⁷⁸ Although most experts agreed on the importance of visual restoration, one health systems expert commented on the limitations of the intervention, particularly that it does not enable facial recognition, which that expert deemed to be important.¹⁸⁰

Acceptance and adoption: Experts' comments varied regarding the degree to which Argus II would be adopted by clinicians and patients. Several experts noted that the required training and difficulty of surgery could limit clinician adoption. One research expert commented, "Surgeons, clinical staff, technicians, and therapists would all need intensive, product-specific training. The surgery learning curve would be high, and the surgery would be invasive."¹⁸¹

The potential for patient acceptance would be high, most experts commenting on this intervention agreed. But patients would need to be active partners in their treatment. One research expert noted, "Patients should be willing to fully participate in recommended postoperative clinical followup, visual rehabilitation, and device fitting or training."¹⁸² Some experts commented that some patients might not adhere to the time commitment for followup training and rehabilitation.

Health care delivery infrastructure and patient management: Several experts with research perspectives thought that this intervention would not disrupt the current health care delivery infrastructure. One research expert noted, "This is an operation plus training and followup whereas

before no treatment was available. So there will be increased contact with medical professionals for these patients. But, since it is an uncommon disorder the disruption will not be too large.”¹⁷⁹ However, some experts thought that this intervention has the potential to greatly disrupt current health care delivery infrastructure for retina specialists. One expert with a clinical background commented, “For surgeons placing this device, I imagine that it could considerably affect patient flow especially in the OR. Additionally because of the additional patient learning, the surgeon may have to spend time educating the patients. Also, I imagine a whole group of trainers/technical people needed for this.”¹⁸³

Health disparities: Experts generally agreed the cost of this intervention could significantly affect health disparities. The estimated cost of the device and surgical procedure is about \$115,000.¹⁶⁹ One expert with a clinical perspective commented, “It could potentially increase health disparities in the sense that for those who could not afford (or perhaps don't qualify) for the device would not benefit from the device. Of course this represents an obvious disparity.”¹⁸³

Spinal Cord Injury Intervention

Wearable Battery-powered Exoskeletons (ReWalk and Ekso Systems) To Enable Walking After Spinal Cord Injury

Unmet need: Conventional manual and powered wheelchairs are the primary assistive devices used to restore some degree of mobility in people with paraplegia after a spinal cord injury (SCI). However, these devices do not help users walk, climb stairs independently, or interact face-to-face with standing adults. Reciprocating gait orthosis systems in development by separate manufacturers, the ReWalk™ and Ekso™ systems, may provide greater mobility and freedom to people with paraplegia from SCI in the home setting. These two systems are being used now in rehabilitative settings for post-SCI rehabilitation, and personal use versions for use outside a rehabilitation setting are being developed.

Intervention: The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders for walking with crutches and who have good bone density and cardiovascular health. The wearable support system uses an array of sensors and proprietary computer algorithms to analyze body movements and manipulate the motorized leg braces to help users maintain proper gait using crutches for walking, climbing stairs, and other movements. The onboard computer, sensor array, and rechargeable batteries that power the wearable exoskeleton are contained in a backpack that users wear in addition to the leg braces. The ReWalk system weighs about 35 lb.¹⁸⁴

The Ekso system is another powered exoskeleton device for patients with paraplegia or lower-extremity paresis due to neurologic conditions, including SCIs, multiple sclerosis, amyotrophic lateral sclerosis, or Guillain-Barré syndrome. It incorporates technology similar to that of the ReWalk system. The 45 lb Ekso system is based on the U.S. military's Human Universal Load Carrier, a motorized exoskeleton designed to allow users to carry up to 200 lb continuously for several hours over any terrain. The manufacturer states that transfer to and from a patient's wheelchair and the powered exoskeleton device takes less than 5 minutes and that the user requires little to no assistance. The company estimates the battery life for this device to be 3 hours.¹⁸⁵

Clinical trials: ReWalk completed at least one pilot study on 12 patients and has registered two ongoing trials enrolling a total of 70 patients and expects to complete the trials in 2014. The company is testing the systems for standing, walking, and ascending and descending stairs at 4-, 12-, and 16-week followup.¹⁸⁶ The ReWalk pilot study results were reported at the meeting of the Association of Academic Physiatrists¹⁸⁷ and published in November 2012. The authors reported, "After training, all [12] subjects were able to independently transfer and walk, without human assistance while using the ReWalk, for at least 50 to 100 m continuously, for a period of at least 5 to 10 mins continuously and with velocities ranging from 0.03 to 0.45 m/sec (mean, 0.25 m/sec)."¹⁸⁸

Ekso's manufacturer reported that it carried out clinical testing of its system in 12 U.S. rehabilitation hospitals in 2011 and early 2012, but no published study results were available at the time of expert comment.¹⁸⁹ The Ekso system is undergoing testing in a registered trial sponsored by the Rehabilitation Institute of Chicago, of Chicago, IL; it is recruiting participants.¹⁹⁰

Manufacturer and regulatory status: The ReWalk-I system (Argo Medical Technologies, Ltd., of Yokneam Ilit, Israel) is used for institutional use and, according to a published report, the company expects to soon register the ReWalk-P for personal use in the community or home setting for those who qualify upon medical examination and rehabilitation training.¹⁹¹ The Ekso system (Ekso Bionics, Richmond, CA) available to the Craig Hospital in Denver, CO, in February 2012, the company's first commercial health care participant, for institutional use.¹⁸⁹

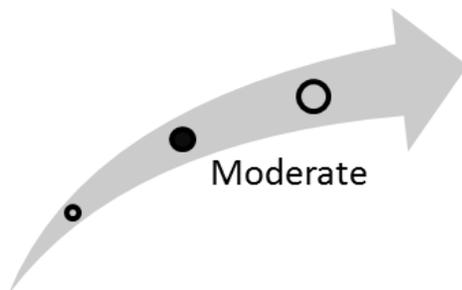
FDA classifies these reciprocating gait orthosis systems as powered exercise equipment (product code BXB) used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification or premarketing approval application procedures.¹⁹² Such products require only FDA device registration and listing. However, the companies have indicated they may seek 510(k) clearance for the personal use versions of the devices.

Diffusion: The ReWalk-I system is listed by FDA for institutional use only and reportedly costs about \$105,000 per system. The ReWalk-P reportedly will cost about \$20,000, although the manufacturer has not confirmed this pricing.¹⁹¹ The Ekso institutional system costs about \$130,000, with anticipated costs for personalized Ekso exoskeletons to be \$50,000–\$75,000.¹⁹³

Clinical Pathway at Point of This Intervention

Occupational and physical therapists work with patients after acute treatment of spinal cord injury to evaluate the patients' functional abilities, determine what type of rehabilitation is appropriate, implement specific exercises and routines, and determine the type of assistive devices that could help them become more independent with daily living skills.¹⁹⁴ Conventional manual and powered wheelchairs are the primary assistive devices used to restore mobility to people with paraplegia. The ReWalk and Ekso reciprocating gait orthosis systems would be used to help patients with paraplegia stand and move, potentially improving their quality of life by increasing their mobility and independence.

Figure 9. Overall high-impact potential: wearable powered exoskeletons (ReWalk and Ekso Systems) to enable walking after spinal cord injury



Experts indicated that patients with paraplegia from SCI have very limited mobility options, and stated that these systems may have great potential to benefit quality of life for these patients. However, they thought the high cost and technology complexity could limit its diffusion into the mainstream of rehabilitative services for patients with SCIs who are paraplegic. Staffing models would be affected by the need for technicians to maintain and adjust the equipment, the experts thought (although the companies supply the needed expertise). Further, they thought that the equipment would likely be appropriate only for patients with robust health, as indicated by the health requirements (height, weight, cardiovascular and upper body strength) specified by manufacturers. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.¹⁹⁵⁻²⁰¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Acceptance and adoption: This intervention has significant potential to provide patients with improved overall quality of life, the experts agreed, especially considering the lack of available mobility options that can enable such individuals to stand and walk on their own. A main benefit of this intervention would be psychological, the experts generally agreed, saying it would allow patients to have improved self-image, reduced depression, and increased ability to participate in social interactions. However, one expert with a research perspective commented that patients would probably prefer to use a wheelchair, even after trying a computerized walking system. Experts from both research and clinical perspectives thought that this technology has the potential to spur further technological innovations for treating this patient population.

Health care delivery infrastructure and patient management: Several experts with research perspectives thought that this type of device could greatly disrupt the current health care delivery infrastructure. One expert noted: “Physical therapists, medical professionals, and biomedical engineers would need to be trained on the risks, control, and maintenance of this device.”²⁰¹ In terms of patient management, several experts thought that besides providing psychological benefits, this intervention might improve pressure ulcer incidence as well. One expert with a clinical perspective noted, “These decubiti can be very detrimental and have significant morbidities. These skin issues can get infected and often require surgical intervention.”¹⁹⁶

Health disparities: Cost was a limiting factor mentioned by experts in terms of access and diffusion, especially to populations affected by health disparities and with limited access to rehabilitative services. The devices’ estimated costs range between \$105,000 and \$130,000 for institutional use and between \$20,000 and \$75,000 for personal use, plus the cost of software programing and adjustments. One expert with a research perspective commented, “Cost will be substantial and this will definitely limit diffusion and adoption.”¹⁹⁵

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