

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

Priority Area 08: Functional Limitations and Disability

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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 A290-2010-00006-C). 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.

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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 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 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 150 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 five to 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 13 topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (This priority area included 107 topics that were being tracked in the system as of November 4, 2014.) We present summaries on 10 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. *Corneal collagen cross-linking (VibeX/KXL System) for treatment of progressive keratoconus	Moderately high
2. *Dimethyl fumarate (Tecfidera) for treatment of relapsing forms of multiple sclerosis	Lower end of the high-impact-potential range
3. *Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1	High
4. *Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome	Moderately high
5. *Idebenone (Catena) for treatment of Duchenne muscular dystrophy	Moderately high
6. *Intraoral tongue-drive computerized system to maneuver electric wheelchairs	Moderately high
7. Ocriplasmin (Jetrea) treatment for symptomatic vitreomacular adhesion including macular hole	Prior high impact topic (June 2014); archived 2 years after FDA approval
8. *Pediatric Vision Scanner screening for strabismus and amblyopia	Moderately high
9. *Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation	Moderately high
10. RenalGuard for prevention of contrast-induced nephropathy	Prior high Impact topic (June 2014); archived because company was sold and ongoing development status is uncertain
11. *Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	High

Topic	High-Impact Potential
12. Safinamide for adjunctive treatment of Parkinson's disease	No high impact potential at this time; archived on the basis of experts' comments
13. *Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder	Lower end of the high-impact-potential range

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).

Prior High-Impact Topics Archived Since June 2014 Report

Two potential high-impact topics from the June 2014 report have been archived.

- **Ocriplasmin (Jetrea) for Treatment of Symptomatic Vitreomacular Adhesion Including Macular Hole:** In the June 2104 report, this topic was deemed by expert comments to have high potential for high impact. Ocriplasmin (ThromboGenics NV, Heverlee, Belgium) is a truncated, recombinant form of plasmin that provides a nonsurgical option for vitreomacular adhesion. The U.S. Food and Drug Administration (FDA) approved ocriplasmin in October 2012, and we tracked the intervention for 2 years after approval and archived the topic in October 2014 on the basis of the horizon scanning protocol’s period for tracking FDA-approved interventions. Ocriplasmin addresses the significant unmet need for a minimally invasive vitreomacular adhesion treatment, as our experts commented.
- **RenalGuard for Prevention of Contrast-Induced Nephropathy:** In the earlier report, this topic was deemed by expert comments to have high potential for high impact. In patients with chronic kidney disease, contrast-induced nephropathy (CIN) is a common cause of acute renal dysfunction or failure when undergoing imaging exams that require use of contrast media. The RenalGuard System was under development by PLC Systems, Inc. (Milford, MA), as a preventive measure for such patients. RenalGuard purportedly reduces CIN risk by replacing fluid, actively synchronizing a patient’s urine output with sterile saline solution IV infusion, and maintaining renal blood flow. Two phase III trials have been completed, and study investigators reported positive data—about two to four times as many patients in the control groups developed CIN as in the RenalGuard groups. The company developing the technology encountered financing issues and in 2014, PLC Systems transferred RenalGuard System rights to its debt holder, GCP Capital Partners, LLC (New York, NY), in exchange for debt cancellation. Further development appears uncertain, and thus, we archived the topic in the horizon scanning system in September 2014. Should another company purchase the rights and continue development, we will resume tracking it in the system.

Eligible Topics Not Deemed High Impact

One eligible topic, discussed here, was deemed by experts to lack potential for high impact.

- **Safinamide for Adjunctive Treatment of Parkinson’s Disease:** Safinamide is a selective, reversible MAO-B inhibitor in late-stage development as an adjunct medication for treating motor symptoms associated with Parkinson’s disease. Purportedly, safinamide administration increases the treatment efficacy of levodopa and dopamine agonists. Safinamide’s manufacturer has completed multiple phase III clinical trials, and a new drug application (NDA) was submitted to FDA in early 2014. Experts evaluating this intervention acknowledged an unmet need for additional effective pharmacotherapies to treat Parkinson’s disease, but, overall, decided that that safinamide has little potential to address this need. Specifically, they noted safinamide’s modest reported treatment benefits and the availability of other MAO-B inhibitors for this indication. Thus, we have archived this topic.

Potential High-Impact Interventions

Below are 10 interventions that, according to experts’ comments, have high-impact potential. They are drugs and devices used in treating a number of conditions in this priority area. These conditions are grouped as central nervous system conditions, genetic disorders, sensory disorders, prosthetics, and spinal cord injury.

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

- **Key Facts:** Although several options are available for treating relapsing forms of multiple sclerosis (MS), approved medications do not universally alleviate patient symptoms and are intolerable for some patients. Dimethyl fumarate (Tecfidera, Biogen Idec International GmbH, Zug, Switzerland) is a homogenous fumaric acid ester formulation with purported immunomodulatory and neuroprotective properties. It is intended to treat relapsing forms of MS. Dimethyl fumarate’s mechanism of action for this indication is unknown, but its properties may reduce relapse rates and active brain lesions thought to contribute to disease progression. For treating relapsing MS, dimethyl fumarate is orally administered twice daily, 120 mg per dose, for 7 days, followed by twice-daily, 240 mg maintenance dosages. Two large completed clinical trials reported that annualized relapse rates and active lesions were significantly reduced in patients given twice- or thrice-daily dimethyl fumarate compared with placebo. Additional studies reported that the drug has comparable or superior efficacy to other, FDA-approved medications for relapsing MS. Ongoing trials are investigating the drug’s long-term safety and efficacy and also subgroup outcomes.
- FDA approved dimethyl fumarate in March 2013 for treating relapsing forms of MS in adults. Retail pharmacy pricing of a 30-day supply is between \$5,200 and \$5,700 and a year’s supply would cost about \$62,400 to \$68,400. The manufacturer also offers ActiveAccess™, a patient copayment assistance program. Many third-party payers include the drug in their formularies as a specialty pharmaceutical requiring prior authorization and imposing quantity limits. In 2014, investment analysts determined that dimethyl fumarate was the prescription-rate leader among oral medications for relapsing forms of MS, and the overall market share leader for second-line prescriptions for the same indication.
- **Key Expert Comments:** A significant need exists for effective alternative medications for patients with relapsing forms of MS, the experts concluded. They acknowledged that dimethyl fumarate is an effective, well-tolerated oral medication and will likely continue to

be widely accepted by clinicians and used by patients. Multiple competing oral and injectable medications are available for this indication, though, and experts thought that this crowded market could curtail dimethyl fumarate's overall impact on patient health outcomes.

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

Eliglustat Tartrate (Cerdelga) for Treatment of Gaucher's Disease Type 1

- **Key Facts:** Gaucher's disease, an orphan disease affecting an estimated 6,000 patients in the United States, has long been treated using intravenous (IV) enzyme replacement therapy (ERT); no oral therapy had been available until eliglustate tartrate was developed. ERT costs between \$300,000 and \$350,000 per patient per year (depending on the brand used) and is inconvenient for patients because it requires IV infusions every 2–3 weeks lifelong. Eliglustat tartrate purportedly partially inhibits the enzyme glucosylceramide synthase, resulting in reduced glucosylceramide. Three fully enrolled phase III trials of eliglustat tartrate are ongoing. The manufacturer reported positive interim-analysis data from two of these trials, showing significant reduction in spleen volume and noninferiority to one IV ERT comparator.

Eliglustat tartrate (Cerdelga™) was FDA approved in August 2014 as an orally administered alternative first-line treatment for Gaucher's disease type 1. The drug was developed by the Sanofi subsidiary Genzyme (which also markets IV ERT). The drug is administered as 84 mg tablets, once or twice daily depending on the patient's CYP2D6 metabolism rate. The drug costs about \$316,000 per patient per year, comparable to IV ERT. The manufacturer offers a copayment assistance program for patients with private insurance; several third-party payers cover the drug, but require prior authorization and quantity limits.

- **Key Expert Comments:** Patients need a more convenient treatment for Gaucher's disease, and experts suggested this oral compound could increase patient adherence to treatment recommendations, leading to improved health outcomes and better quality of life. Experts anticipated widespread adoption of eliglustat tartrate because of its convenience and favorable side effect profile thus far. Furthermore, experts suggested eliglustat tartrate adoption would reduce demand on IV infusion centers for this patient population and shift the care setting to home care. Experts noted these shifts would be contingent on eliglustat tartrate being proved to be as effective as the standard of care.
- **High-Impact Potential:** High

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

- **Key Facts:** Morquio A syndrome is a rare autosomal recessive inherited metabolic disorder caused by a deficiency of N-acetylgalactosamine-6-sulfatase, an enzyme that breaks down glycosaminoglycans, including keratan sulfate (KS). In affected patients, deficiencies in this enzyme are caused by mutations to the N-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) gene. The syndrome is progressive, and over time, KS accumulates in bone, tendons, connective tissue, cornea, urine, and synovial fluid. KS accumulation adversely affects movement, posture, and sensory and cardiovascular function, including systemic skeletal dysplasia (dwarfism), hydrocephalus, spinal cord compression, genu valgum ("knock knees"), heart valve abnormalities, and conductive or sensorineural hearing loss. Patients' life expectancy depends on symptom severity; severely affected pediatric patients may survive only to late childhood or adolescence.

The standard of care for Morquio A syndrome is palliative care, including corrective orthopedic surgeries, hearing and visual aids, and assisted mobility devices. BioMarin Pharmaceutical (Novato, CA), has developed elosulfase alfa (Vimizim™) as an enzyme replacement therapy that purportedly prevents or improves Morquio A syndrome symptoms by addressing patients' GALNS deficits. In completed clinical trials, pediatric patients administered weekly intravenous elosulfase alfa infusions demonstrated some improvement on two measures of locomotive function. The most common treatment-related adverse events included fever, headache, nausea and vomiting, and abdominal pain. Additional ongoing clinical trials are investigating elosulfase alfa's long-term treatment efficacy and safety among various patient subgroups.

FDA approved the therapy in February 2014. The product labeling indicates a treatment protocol of weekly 2 mg/kg infusions, infused over a minimum of 3.5–4.5 hours. The company notes that “life-threatening allergic reactions have occurred in some patients during VIMIZIM™ (elosulfase alfa) infusions and up to 3 hours after infusion. Patients with acute respiratory illness may be at increased risk and require additional monitoring.” The manufacturer has priced the drug at \$1,069 per 5 mL vial, which puts annual per-patient costs at about \$380,000 for pediatric patients weighing 22.5 kg (about 49 pounds). However, searches of online pharmaceutical wholesale prices found per vial costs as low as \$256. For the first 9 months of 2014, the manufacturer reported elosulfase alfa sales of \$40.4 million. Several third-party payers cover elosulfase alfa as a specialty pharmaceutical, requiring prior authorization.

- **Key Expert Comments:** Experts commenting on elosulfase alfa acknowledged that it is the only FDA-approved medication for treating Morquio A syndrome, and agreed that it may address an unmet need for some patients. Experts also noted that this intervention could provide a viable nonsurgical intervention for some patients' symptoms. However, experts stated that reported clinical trial data failed to demonstrate significant treatment efficacy, with multiple patients failing to respond to treatment. Additionally, experts thought that elosulfase alfa's high-impact potential clinically (as the only available treatment) would be affected by its high cost (inability of some patients to access it) and noncurative nature.
- **High-Impact Potential:** Moderately high

Idebenone (Catena) for Treatment of Duchenne Muscular Dystrophy

- **Key Facts:** Duchenne muscular dystrophy (DMD) is a rare, severe, muscle-wasting disorder caused by a mutation in the dystrophin gene, which encodes a protein necessary for muscle cell structural integrity. Dystrophin gene mutations lead to mitochondrial defects that broadly affect muscle cell tissue throughout the body. As the disorder progresses, affected patients experience symptoms including heart defects, general muscle weakness, fatigue, and respiratory and motor difficulties. Despite improved patient care and management processes, patients often survive only into their fourth decade.

The standard of care for DMD is palliative treatment, which emphasizes management of severe motor and respiratory symptoms. Many patients need wheelchairs for mobility, and various medications and assistive devices are used to address respiratory declines. Idebenone (Catena®) is an oral tablet short-chain benzoquinone with potent antioxidant and cytoprotective properties. The drug purportedly facilitates sustained intracellular energy transfer, through adenosine triphosphate (ATP) production. Researchers hypothesize that this mechanism of action sidesteps pathways affected by mitochondrial defects and can offset DMD's characteristic muscle-wasting symptoms. In phase II and phase III clinical

trials, patients received 450–900 mg idebenone daily and demonstrated improvements on several respiratory function assessments; idebenone was also well tolerated at both doses.

Idebenone is the first DMD medication to successfully complete a phase III trial. In early 2014, citing pending positive phase III trial data, the manufacturer announced intentions to pursue regulatory approval in North America and Europe. The company has not yet submitted an NDA. In late November 2014, the company announced a collaboration with Parent Project Muscular Dystrophy (PPMD), a patient advocacy organization, on a risk-benefit study focusing on patient and caregiver preferences regarding pulmonary therapies for the disease. The study used data from the recently completed phase III trial. The company plans to include data from the risk-benefit preference study with its NDA submission to FDA.

- **Key Expert Comments:** Experts commenting on idebenone agreed that a significant unmet need exists for effective medications for treating DMD and concluded that idebenone could potentially address this need. These experts noted that no medication is approved for treating this disorder and that idebenone may reach market before other investigational medications. As a well-tolerated oral medication demonstrated to improve a key disease symptom, experts anticipated that, if approved, idebenone would be widely accepted and adopted by clinicians and patients. Although idebenone may improve health outcomes, experts noted that patients would likely continue to require palliative therapies, limiting idebenone to adjunct use and reducing its high-impact potential.
- **High-Impact Potential:** Moderately high

Corneal Collagen Cross-Linking (VibeX/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. Keratoconus 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 usually the first-line treatment. Most cases stabilize after several years, but in some cases, extreme corneal thinning and scarring 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 the photosensitizer 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 /KXL[®] System to perform accelerated CXL. Purported advantages of this system are increased UVA power leading to reduced exposure time, and a 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.

FDA granted orphan drug designation and priority review status for the system. The system is not yet FDA approved, but the company submitted an NDA to FDA in March

2012 that stated the proposed indications are for treating keratoconus and corneal ectasia after refractive surgery. Both indications are orphan drug indications. In trials supporting the NDA, patients who received CXL were reported to have significantly improved uncorrected and corrected distance visual acuity and maximum keratometry values 1 year after treatment. FDA sent a complete response letter to Avedro regarding the NDA in March 2014, and in September 2014, Avedro resubmitted its NDA addressing that complete response letter. Cost information for the U.S. market is not yet available. The system received the Conformité Européenne (CE) mark in Europe in 2010, allowing marketing there, and is available in other countries as well. According to The Straits Times of Singapore, the Avedro KXL machine costs approximately \$35,000 in markets outside the United States. Surgery at one Singapore location was listed at about \$3,500 per eye.

- **Key Expert Comments:** Experts thought the system could fill the unmet need for a progressive keratoconus treatment that is less invasive than standard treatment. The ease of performing CXL with the system was cited by experts as a main factor that would facilitate adoption and acceptance. 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.
- **High-Impact Potential:** Moderately 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 amblyopia detection by pediatricians and other primary care clinicians can be difficult because standard screening methods lack sufficient sensitivity and specificity and require children to sit still for several minutes, making them impractical for many infants and toddlers. Thus, current screening technologies miss detection in young children who should be referred to an ophthalmologist 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 and more accurate amblyopia or strabismus detection so that patients can be more appropriately referred to specialist care. The system uses proprietary technology called retinal birefringence scanning to screen for amblyopia and strabismus. The PVS simultaneously assesses both eyes during a 2- to 5-second scan to detect both binocular alignment and the eyes' ability to focus on a target. The system's software indicates (with a "pass" or passing grade) whether the patient's eyes accurately fixated on the target. If the eyes did not fixate, an ophthalmologist refers the patient for further evaluation. Five clinical trials evaluated the sensitivity and specificity of the PVS compared with other screening devices. Investigators from the largest and most recently reported PVS trial (Jost et al., 2014), in children aged 2–6 years, reported that, "The sensitivity of the PVS to detect strabismus and amblyopia (0.97; 95% CI [confidence interval], 0.94-1.00) was significantly higher than that of the SureSight Autorefractor (0.74; 95% CI, 0.66-0.83). Specificity... (0.87; 95% CI, 0.80-0.95) was significantly higher than that of the SureSight Autorefractor (0.62; 95% CI, 0.50-0.73)." FDA has determined the PVS to be a nonsignificant risk device. This means the PVS has abbreviated requirements for labeling; institutional review board approval is all that is needed to conduct trials (i.e., no prior FDA approval needed to conduct a trial); and reporting rules are streamlined for the regulatory approval pathway.

The device's cost is not yet available, but cost of its use is expected to be in line with costs of existing scanning vision screening equipment. Third-party reimbursement for pediatric vision screening has been long established and the payment is about \$30 per screening; the company indicated it expects its screening exam's cost to fall within the reimbursed amount. REBIScan is collaborating with VisionQuest 20/20, a nonprofit organization that addresses preventable vision loss in children, to establish a nationwide vision screening and tracking program in pediatric offices and preschools. The company has also established a crowd-funding site to raise funds to complete its development to meet regulatory requirements.

- **Key Expert Comments:** The PVS's use in younger populations is a significant factor in its potential to fulfill the unmet need for early diagnostic tools for amblyopia and strabismus, experts agreed. Experts thought that the early diagnostic capabilities of the PVS could 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, which may improve the accuracy of referrals to specialists.
- **High-Impact Potential:** 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 due to retinitis pigmentosa (RP), a debilitating genetic vision disorder that eventually results in blindness. The implantable Argus[®] II Retinal Prosthesis System, manufactured by Second Sight Medical Products, Inc. (Sylmar, CA), 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 learns to interpret as images. In clinical studies, patients receiving the 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 include 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.

In February 2013, FDA approved Argus II for marketing as the first implantable device for treating adult patients with advanced RP. Argus II reportedly costs about \$115,000 to \$145,000, which includes the device and surgical procedure.

- **Key Expert Comments:** A significant unmet need exists for RP treatment options because no therapies were available until approval of the device, experts noted. Most experts who commented thought this intervention potentially fulfills 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. Patient management is likely to be most affected because patients will need extensive device training and followup care not necessary without the implant.
- **High-Impact Potential:** High

Tasimelteon (Hetlioz) for Treatment of Non-24-Hour Sleep-Wake Disorder

- **Key Facts:** About half of blind people are believed to be affected by non-24-hour sleep-wake disorder (non-24) because of a lack of light receptors to reset the circadian rhythm. Patients with non-24 may experience reduced quality of life and debilitation due to poor sleep quality and excessive daytime sleepiness. Stimulants and sedatives may provide temporary or partial relief of symptoms, but patients need treatment that addresses the underlying cause of the disease. Tasimelteon is a dual melatonin receptor agonist that, according to the manufacturer, resets the circadian rhythm by acting in the hypothalamus. According to Lockley et al. (2013b), in a clinical trial of 20 patients, total nighttime sleep in the worst quartile of nights improved by 67.2 minutes and daytime sleep shortened by 59.4 minutes.

FDA granted orphan drug designation and priority review to Vanda Pharmaceuticals, Inc.'s (Washington, DC) NDA and approved the drug in January 2014; the brand name is Hetlioz™. According to a U.S.-based, online aggregator of prescription-drug prices, tasimelteon costs about \$86,000 per patient per year. Several third-party payers cover the drug as a specialty pharmaceutical requiring prior authorization and quantity limits.

- **Key Expert Comments:** Overall, tasimelteon's biggest impact on the health care system will likely be its cost, experts agreed. The manufacturer has aggressively marketed tasimelteon in direct-to-consumer advertising; thus, patients are likely to request prescriptions and influence private payers' coverage determinations, experts agreed. In terms of improving patient health or altering patient management, experts noted the small amount of data and modest improvements in sleep and waking times when suggesting the drug is likely to have a lesser impact.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Prosthetic Arm with Body-Machine Interface (DEKA Arm System) to Restore Natural Arm Function After Amputation

- **Key Facts:** Prosthetic arms that provide natural movements, intuitive control, and fine motor function are not available to patients who have had an arm amputated, leaving many with still limited function. The DEKA Arm System combines a body-machine interface with other inputs to control a prosthetic hand and arm with up to 10 powered degrees of freedom. According to Resnik et al. (2013), more than 90% of users in a clinical study (n=37) reported being able to perform functions with the DEKA Arm that could not be performed with their own prosthesis. Resnik and Borgia (2014) reported that about 80% of patients said they would want to or might want to receive the device.

DEKA Integrated Solutions (Manchester, NH), the developer, received FDA marketing clearance for the prosthetic arm in June 2014, but has not found a manufacturing partner for commercial distribution. Thus, the prosthesis is not yet commercially available. Cost is unclear but reportedly will be tens of thousands of dollars. Prosthetic arms are covered under Medicare Part B as durable medical equipment; coverage from private third-party payers is uncertain but may be similar to policies for other prostheses.

- **Key Expert Comments:** A significant unmet need exists for restoring natural arm function to patients with upper limb amputations, and this device provides functionality beyond any available prostheses, experts agreed. They thought that clinician and patient enthusiasm, likely to be high, might be tempered by high costs and complex training, potentially

increasing health disparities because of unequal access. Experts suggested that its overall impact would be mitigated by the small population likely to use the DEKA Arm.

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

Intraoral Tongue-Drive Computerized System to Maneuver Electric Wheelchairs

- **Key Facts:** Clinicians recommend conventional manual and powered-assisted devices to attempt to improve quality of life for individuals with quadriplegia, but efficacy and safety remain a primary concern. The Tongue Drive System (TDS, Georgia Institute of Technology, Atlanta) is a tongue-operated, assistive neurotechnology that consists of a lentil-sized magnetic tracer/stud that is embedded in a dental retainer worn in the mouth with the tracer affixed to the tongue, most commonly by piercing. This magnetic tracer communicates synergistically with a headset, magnetic sensors, and a smartphone device to increase patient mobility and allow patients to participate in daily activities. Using the system would represent a way to purportedly enhance patient mobility and allow patients to perform more daily tasks in a safer, less invasive, and more effective manner than afforded by existing devices. Patients must undergo computer training with TDS for the computer program to appropriately interpret and calibrate tongue movement, allowing for proper control of the patient wheelchair and computer device. TDS is in early phase clinical trials in two locations (Atlanta, GA, and Chicago, IL). The trial continues to recruit patients, with about 20 patients participating thus far. According to Kim et al. (2014), 11 patients with spinal cord injuries performed mobility and computer-based communication tasks up to three times faster with TDS than with the sip-and-puff system, despite using the sip-and-puff system for a substantially longer period of time. The National Science Foundation (Arlington, VA), the Christopher & Dana Reeve Foundation (Short Hills, NJ), and the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health (Bethesda, MD) are providing funding for system development.

The device is not yet FDA approved. According to the developers, TDS is probably 2 years away from receiving FDA approval. The developers anticipate the per-patient cost of the TDS system to be between \$6,000 and \$7,000.

- **Key Expert Comments:** Most experts commenting thought TDS could be a viable alternative to existing technologies, although they had diverse perspectives on its potential impact. Some thought the unmet need was not significant, but others who have worked directly with patients with spinal cord injuries in need of assistive devices to control powered wheelchairs saw this intervention as a significant improvement for patient health outcomes, independence, and quality of life, allowing patients to perform daily activities in a less strenuous manner than with sip-and-puff straws. Several experts thought safety concerns could be a barrier to clinician acceptance, because device malfunction might pose risks to this patient population. Overall, this device's perceived complex nature, the existence of alternatives, and limited safety and efficacy data thus far have made some experts question the device's true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and quality of life when compared with standard mobility devices.
- **High-Impact Potential:** Moderately high

Central Nervous System Disorder Intervention

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

Unmet need: Multiple sclerosis (MS) is an autoimmune demyelinating disease that is the most common disabling neurologic disease among young adult Americans. Researchers hypothesize that MS has an underlying autoimmune etiology.¹ Relapsing forms of MS are most frequently diagnosed, affecting about 85% of patients with MS.²

As the disease progresses, symptoms broadly affect cognitive, motor, sensory, and sexual functioning.^{3,4} Available first-line MS medications include injectable and orally administered immunomodulators that purportedly treat MS by dampening patients' autoimmune responses.⁵ However, many patients do not respond adequately to available treatments or find associated side effects intolerable. Additionally, no available treatments are demonstrated to halt long-term disease progression.^{1,6-8} An unmet need exists for alternative, effective, well-tolerated therapies for treating symptoms and minimizing disease progression and relapses in patients with relapsing forms of MS.

Intervention: Dimethyl fumarate is a homogenous fumaric acid ester formulation with purported immunomodulatory and neuroprotective properties. The drug's mechanism of action in treating MS is unclear, but converging evidence suggests that dimethyl fumarate's promotion of Nrf2 expression may mediate its activity.⁹ Nrf2 functions as a transcription factor that upregulates cellular antioxidant pathways; this upregulation, in turn, modulates the cellular redox system, raising reduced and intracellular glutathione levels. Researchers suggest that modulating the cellular redox system serves to protect neurons and astrocytes from oxidative stress during inflammatory episodes.^{10,11} Downstream, these modulations purportedly inhibit nuclear translocation of NF- κ B and prevent pro-inflammatory signaling in immune cells.¹² Dimethyl fumarate's anti-inflammatory and neuroprotective effects may reduce the number of active brain lesions believed to underlie disease progression.^{13,14}

Dimethyl fumarate is administered orally in tablet form. For relapsing forms of MS, the manufacturer's recommended chronic protocol is 120 mg tablets, taken twice daily for 7 days, followed by a twice-daily maintenance dose of 240 mg.¹⁴

Clinical trials: Two large phase III trials, DEFINE and CONFIRM, investigated dimethyl fumarate's safety and efficacy for treating relapsing forms of MS. In the DEFINE study (n=1,234), investigators reported lower relapse rates among patients administered twice-daily (BID) or thrice-daily (TID) dimethyl fumarate than among patients in the placebo group (BID, 27%; TID, 26%; placebo, 46%; p<0.001). Two-year annualized relapse rates were also significantly lower for patients administered dimethyl fumarate than for patients taking a placebo (BID: 17%; TID: 19%; placebo: 36%; p<0.001).¹³ Subgroup analyses also demonstrated that dimethyl fumarate administration reduced 2-year disability progression risk, compared with placebo; this finding was consistent in most subgroups of patients treated with twice-daily dimethyl fumarate, and in all subgroups treated with the thrice-daily dimethyl fumarate.¹⁵

The CONFIRM study (n=1,417) compared BID and TID dimethyl fumarate administration treatment efficacy to that of injectable glatiramer acetate (GA) and placebo. Two-year annualized relapse rates for patients administered BID and TID dimethyl fumarate and GA were significantly lower than those of the placebo group (BID: 22%; TID: 22%; GA: 29%; placebo: 40%).¹⁴ Treatment-related side effects were noted as mild and reversible, with flushing, gastrointestinal symptoms, and nausea as the most commonly reported adverse events.¹⁴

More than 65% of patients (n=1,738) from the DEFINE and CONFIRM studies are enrolled in ENDORSE, a long-term extension trial.¹⁶⁻¹⁸ Enrolled patients receive BID or TID dimethyl fumarate, after previously receiving BID dimethyl fumarate, TID dimethyl fumarate, 20 mg subcutaneously injected GA, or placebo.¹⁶ Investigators used magnetic resonance imaging (MRI)

lesion imaging to analyze treatment efficacy after the second year of this trial. After 2 years, 68% of patients continuing a BID dimethyl fumarate dosing regimen and 61% of patients continuing a TID dimethyl fumarate dosing regimen had no new or enlarging T2 lesions. Imaging analyses also demonstrated that significant percentages of these patients had no new T1-hypointense lesions (BID: 76%; TID: 70%) or gadolinium-enhancing lesions (BID: 88%; TID: 84%).¹⁶ Overall and severe treatment-related adverse event rates were similar across patients, regardless of previous or present treatment protocol; investigators also found no evidence of increased risk of renal or urinary events.¹⁸

No treatment-related deaths have been reported in dimethyl fumarate clinical trials. However, in October 2014, the manufacturer acknowledged the first treatment-related case of progressive multifocal leukoencephalopathy (PML).¹⁹ PML is a rare brain infection with a high mortality rate, and it has been associated with long-term MS medication administration. The reported case involved a patient in a clinical trial who took dimethyl fumarate for 4.5 years; the patient eventually died of pneumonia.¹⁹

Nearly 20 ongoing late-phase clinical trials—enrolling more than 7,000 patients—investigating dimethyl fumarate safety and efficacy for treating relapsing forms of MS in various patient populations are registered in the United States.²⁰⁻²⁸

Manufacturer and regulatory status: Biogen Idec International GmbH (Zug, Switzerland) develops and manufactures dimethyl fumarate for treating relapsing-remitting MS, marketing it in the United States as Tecfidera[®]. In March 2014, the U.S. Food and Drug Administration (FDA) granted marketing approval for dimethyl fumarate for treating adult patients who have relapsing forms of MS.²⁹

Diffusion: A recent query of GoodRx, a U.S.-based, online aggregator of prescription drug costs, found prices for 1 month's supply of dimethyl fumarate ranging from about \$5,200 to \$5,700.³⁰ For eligible patients, Biogen Idec's ActiveAccess[™] assistance program waives monthly dimethyl fumarate copayments.³¹

In November 2014, private health care analysis company Decision Resources Group (DRG) identified dimethyl fumarate as the market-share leader among prescribed oral medications for relapsing forms of MS, capturing 7% of first-line medication market share.³² Based on patient-level claims data, DRG also reported that dimethyl fumarate was the overall preferred second-line disease modifying therapy for the same indication, with nearly 50% of market share.³²

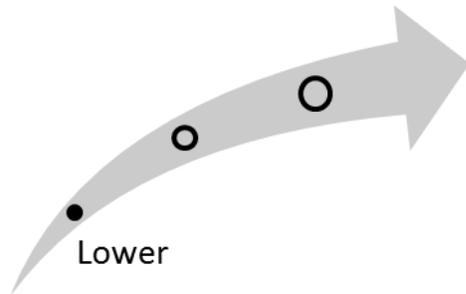
Clinical Pathway at Point of This Intervention

In MS, inflammation and demyelination of neurons affect nerve signaling and functioning. Resulting symptoms vary and can include dizziness, general fatigue, pain, peripheral numbness or weakness, slurred speech, tremor or unsteady gait, and visual deficits.^{33,34} The severity and location of neural damage at symptom onset determine which symptoms manifest; about half of patients in whom MS is diagnosed exhibit cognitive impairment.³⁵

Along with the primary-progressive form, three relapsing forms—progressive-relapsing, relapsing-remitting, and secondary-progressive—have been identified.³⁶⁻³⁸ Standard pharmacotherapies for these disorders attempt to treat inflammation frequency and reduce lesions, potentially minimizing functional limitations and delaying disease progression.³³ Presently, there is no cure for MS, and approved medications have inconsistent efficacy and severe to intolerable side effects in some patients.³⁵ As a first- and second-line MS medication, dimethyl fumarate primarily competes with two injectable pharmacotherapies, glatiramer acetate (Copaxone[®]) and natalizumab (Tysabri[®]), and two oral pharmacotherapies, fingolimod (Gilenya[®]) and teriflunomide (Aubagio[®]).^{6,39-41} In November 2014, FDA also granted marketing approval to a third injectable

pharmacotherapy, alemtuzumab (Lemtrada™), that could compete with dimethyl fumarate for treating some patients who have relapsing forms of MS.⁴² However, this medication is available only through a restricted access program and is recommended primarily as a third-line treatment because of its safety profile.⁴²

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



Experts commenting on this intervention agreed that a significant need exists for effective alternative treatments for relapsing forms of MS and thought that dimethyl fumarate could meet this need. As an oral medication with demonstrated efficacy and tolerability, dimethyl fumarate would continue to be widely accepted by both clinicians and patients, experts anticipated. However, with many approved medications for this indication, and none, including dimethyl fumarate, proved effective for all patients, experts concluded that this intervention would have limited impact on patient health outcomes. 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, and health systems backgrounds, provided perspectives on this intervention.⁴³⁻⁴⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: MS is a disorder that places a sizeable burden on patients, caregivers, and the national health care system, the experts acknowledged. Because no curative treatments are available, experts agreed that a significant unmet need exists for additional safe, effective treatments for relapsing forms of MS. Although they concluded that dimethyl fumarate provides a viable, comparatively safe and well-tolerated alternative treatment for patients, some experts noted that because other effective medications are available, dimethyl fumarate offers only an incremental overall benefit to patients with these indications.^{44,46}

Acceptance and adoption: The experts anticipated continued wide acceptance of dimethyl fumarate, particularly among patients unresponsive to other medications. These experts also noted dimethyl fumarate's oral administration route and favorable efficacy and adverse event profiles as factors promoting acceptance. Although experts noted dimethyl fumarate's relatively high retail price, they did not foresee financial burdens as a major deterrent to adoption among clinicians and patients.

Health care delivery infrastructure and patient management: Dimethyl fumarate is one of multiple approved oral medications for MS, and experts stated that, like available competitors, it would have little impact on health care delivery infrastructure. Aside from recommended monitoring for treatment response and adverse events, experts thought that this intervention would also have minimal impact on patient management.

Health disparities: In general, experts thought that dimethyl fumarate would have little impact on health disparities. Several experts noted that dimethyl fumarate’s manufacturer-sponsored copayment assistance program could address some patients’ potential financial hardships. However, two experts stated that this medication may still be prohibitively expensive for patients who might otherwise benefit from access.^{44,45} One expert with a research background noted that MS has differential prevalence rates based on ethnicity, gender, and genetic heritability, and that this intervention could positively impact health disparities for patients with increased MS risk factors.⁴⁷

Genetic Disorder Interventions

Eliglustat Tartrate (Cerdelga) for Treatment of Gaucher's Disease Type 1

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 because of glucosylceramide accumulation in these tissues. About 6,000 U.S. patients are affected by the disease, although not all of them experience symptoms.⁴⁹ The only oral drug approved for the disorder (miglustat; Zavesca[®]) is not available as first-line treatment; intravenous (IV) enzyme replacement therapy (ERT) is approved as first-line therapy and is the standard of care.⁵⁰ Eliglustat tartrate (Cerdelga[™]) is the first orally administered drug approved by FDA for first-line therapy.⁵¹ It is also intended to have fewer side effects than miglustat, which is known to cause diarrhea, abdominal swelling, tremor, and weight loss. Approaches to Gaucher's disease treatment have taken two routes:

- 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.⁵² A temporary break from ERT because of personal issues or changes in lifestyle can lead to disease progression.

Intervention: Eliglustat tartrate, a self-administered oral compound, is FDA-approved as first-line treatment for Gaucher's disease. The drug purportedly partially inhibits the enzyme glucosylceramide synthase to reduce glucosylceramide production.^{53,54} Dosing depends on a patient's rate of CYP2D6 metabolism as determined by an approved genotype test. Patients who are extensive or intermediate metabolizers take 84 mg, twice daily. Patients who are poor metabolizers take 84 mg, once daily. Patients who are ultra-rapid metabolizers cannot use eliglustat tartrate because they may not achieve adequate concentrations for therapeutic effect. A specific dose cannot be recommended for patients who are indeterminate metabolizers.⁵¹

Clinical trials: Three phase III trials are ongoing;⁵⁵⁻⁵⁷ positive interim-analyses have been reported from two of them.⁵³ One of these is the ENCORE trial (n=160), which is evaluating the percentage of patients whose disease remains stable during eliglustat tartrate treatment. In interim results derived from the first 52 weeks of the study, a manufacturer press release reported the following:⁵⁸

Eliglustat tartrate met the pre-specified criteria for non-inferiority to Cerezyme [miglustat], 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.

Another of these phase III trials is the ENGAGE trial (n=40), which is evaluating improvement (i.e., reduction) in spleen size. A manufacturer press release reported the following:⁵⁸

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).

Manufacturer and regulatory status: Genzyme Corp. (Cambridge, MA), a subsidiary of Sanofi (Paris, France), developed eliglustat tartrate for treating type 1 Gaucher's disease.⁵⁴ FDA

approved eliglustat tartrate in August 2014 “...for the long-term treatment of adult patients with Gaucher[‘s] disease type 1 who are CYP2D6 extensive metabolizers (EM), intermediate metabolizer (IM), or poor metabolizers (PM) as detected by an FDA-cleared test.”⁵¹ Eliglustat tartrate is available through specialty pharmacies.⁵⁹

As conditions of FDA approval, FDA is requiring Genzyme to complete two postmarketing clinical trials to evaluate the effects of renal and hepatic impairment on eliglustat tartrate pharmacokinetics, to be completed in 2017. Genzyme has further committed to developing 21 mg and 42 mg dosage strengths to accommodate dosage adjustments.⁵¹

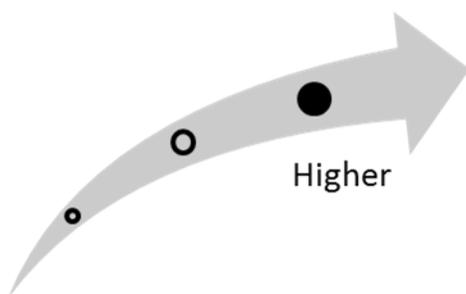
Diffusion and cost: Diffusion among the intended patient population is expected to be brisk, because it is the first oral treatment available; however, cost might affect access for patients without prescription drug insurance. According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, eliglustat tartrate costs about \$316,000 per patient per year (when taken twice daily, based on costs for 56 capsules of 84 mg each),⁶⁰ compared with \$300,000 to \$350,000 per patient per year for IV ERT.⁶¹⁻⁶³ Genzyme offers a copayment assistance program for U.S. patients who have commercial insurance, prescription drug coverage, and are prescribed eliglustat tartrate. The program covers 100% of out-of-pocket expenses including copayments, co-insurance, and deductibles up to the program maximum, regardless of financial status. Patients are ineligible if they have insurance or prescription coverage in part or in full from any State or Federal health care program (e.g., Medicare, Medicaid, Medigap, Veterans Affairs).⁶⁴

ECRI Institute routinely searches 11 representative, private, third-party payers that publish their policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark). Our searches found two formularies listing eliglustat tartrate,^{65,66} four payers have policies that may cover eliglustat tartrate with prior approval.⁶⁷⁻⁷⁰

Clinical Pathway at Point of This Intervention

ERT (e.g., imiglucerase, taliglucerase alfa) is the standard first-line treatment for Gaucher’s disease.⁷¹ Eliglustat tartrate is expected to compete with ERT as first-line treatment. Oral miglustat therapy for type 1 Gaucher’s disease is approved for use only by patients who are ineligible for ERT.⁷² Miglustat frequently causes side effects, such as diarrhea, abdominal swelling, tremor, and weight loss, that affect patient acceptance. Further, the associated clinical improvements of miglustat are reported to be less effective and slower than that of ERT.⁷¹

Figure 2. Overall high-impact potential: eliglustat tartrate (Cerdelga) for treatment of Gaucher’s disease type 1



Patients need a more convenient treatment for Gaucher’s disease, experts suggested, and the oral compound eliglustat tartrate might increase patient adherence to treatment recommendations. In doing so, they thought, it could lead to improved health outcomes and quality of life. Experts anticipated widespread adoption, because of its convenience as an oral drug. Furthermore, experts

suggested adoption of eliglustat tartrate could reduce demand on infusion centers and shift the care setting to home care. The experts noted that the drug's impact potential is contingent on eliglustat tartrate being proved as effective as or more effective than the standard of 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.⁷³⁻⁷⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for a treatment with easier administration than IV ERT, experts agreed. An oral drug may potentially improve outcomes by increasing patient compliance with treatment and improving quality of life, experts also agreed. Two experts with research perspectives called for more trials comparing eliglustat tartrate to standard treatment and studying its long-term efficacy.^{77,78}

Acceptance and adoption: Acceptance from clinicians is likely to be high, experts agreed. Clinicians are likely to prefer the oral drug if it increases patient compliance with treatment and therefore improves patient health, one expert with a health systems and administration perspective said.⁷⁶ Patients are likely to prefer oral administration over IV ERT, experts concurred. For patients for whom cost is not a barrier, acceptance will be high, experts said.^{74,77}

Health care delivery infrastructure and patient management: Health care delivery infrastructure is unlikely to experience a large disruption, experts agreed. Although infusion centers that serve patients with Gaucher's disease might see a decrease in demand, the patient population is small enough to temper the disruption, experts explained. Although experts agreed eliglustat tartrate is expensive and is a lifelong cost, they also noted it will replace the cost of IV ERT instead of adding to overall health care spending.

Health disparities: The high cost of the drug might prevent some patients from accessing it, especially those who are insured through State or Federal agencies (because they are ineligible for the manufacturer's assistance program) or those without insurance, several experts noted. Conversely, ease of administration might reduce access issues for patients who find it difficult to get IV infusions once every 2–3 weeks, one expert with a research perspective thought.⁷³ A clinical expert pointed out that populations that are disproportionately affected by Gaucher's disease (e.g., Ashkenazi Jews) would benefit from this treatment option.⁷⁵

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

Unmet need: Mucopolysaccharidosis type IV A, more commonly called Morquio A syndrome, is a rare, autosomal recessive inherited metabolic disorder caused by N-acetylgalactosamine-6-sulfatase deficiencies. N-acetylgalactosamine-6-sulfate is an enzyme responsible for degrading various glycosaminoglycans, including keratan sulfate (KS).^{79,80} Mutations to the N-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) gene trigger N-acetylgalactosamine-6-sulfatase deficiencies; these deficiencies result in abnormal KS accumulation in bone, connective tissue, cornea, and synovial fluid, tendons, and urine.⁸⁰⁻⁸² Accumulated KS can lead to debilitating cardiovascular, locomotor, postural, and sensory symptoms such as hydrocephalus, systemic skeletal dysplasia (dwarfism), spinal cord compression, and conductive or sensorineural hearing loss.^{81,83}

The standard of care for Morquio A syndrome is palliative treatments, including orthopedic surgeries and assistive devices to address sensory and motor symptoms.^{81,84,85} As Morquio A syndrome progresses, advanced symptoms may necessitate multiple surgeries, particularly when disease progression affects patients' respiratory function. Pediatric patients with severe symptoms may survive only to late adolescence. An unmet need exists for disease-modifying interventions for treating Morquio A syndrome.

Intervention: Elosulfase alfa is a purified human form of GALNS, composed to mediate cellular uptake to lysosomes and hydrolyze sulfate from nonreducing ends of glycosaminoglycans.^{86,87} This functionality replaces missing or defective GALNS genes by stimulating catabolism of excess KS.^{83,86,88} As an exogenous source of GALNS, elosulfase alfa is purported to prevent or treat reversible functional symptoms of Morquio A syndrome and is the first enzyme replacement therapy approved for this indication.

Clinical trials: An ongoing phase III trial (n=176) provides the most extensive clinical data for this intervention. In this trial, patients with Morquio A syndrome are administered placebo, 2 mg/kg elosulfase alfa either weekly or biweekly. After 24 weeks, weekly elosulfase alfa administration improved patient ambulation compared with placebo, measured on the 6-minute walk (estimated mean effect, 22.5 m (74 feet); 95% confidence interval [CI], 4.0 to 40.9; p=0.017) but this was not the case with biweekly administration. The 3-minute stair climbing test did not improve in either group. Weekly and biweekly elosulfase alfa treatments reduced normalized urine KS levels compared with placebo.⁸⁹ For adverse events, 22.4% of patients (representing 1.3% of all infusions) receiving weekly elosulfase alfa treatments reported infusion-related adverse events; no adverse events forced patients to discontinue treatments.⁸⁹ These results were similar to reports from other completed trials enrolling smaller patient populations.^{90,91}

Recently, investigators reported additional secondary analyses from this trial. Investigators found that weekly elosulfase alfa infusions are also associated with improved development (growth rate and height), respiratory function, and general functional status; no statistically significant differences were found between biweekly elosulfase alfa treatment and placebo.⁹²

A small ongoing phase II clinical trial also reported preliminary efficacy results for elosulfase alfa in treating pediatric patients younger than 5 years of age. At 26 weeks, eight patients receiving weekly 2 mg/kg elosulfase alfa infusions demonstrated statistically significant reductions in urine KS levels (35.2% reduction; standard deviation, 15.57%).⁹³

Additional ongoing clinical trials are examining elosulfase alfa's treatment efficacy in American and international patients in whom Morquio A syndrome has been diagnosed.^{20,94-97}

Manufacturer and regulatory status: Elosulfase alfa is manufactured by BioMarin Pharmaceutical (Novato, CA), and marketed as Vimizim™.⁸⁶ FDA approved elosulfase alfa in February 2014 for treating Morquio A syndrome.⁹⁸

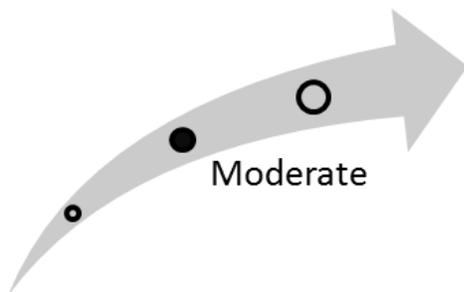
Diffusion and cost: Elosulfase alfa’s February 2104 FDA approval made it the first medication for treating Morquio A syndrome. BioMarin Pharmaceutical initially priced elosulfase alfa at \$1,069 per 5 mL vial;⁹⁹ however, a recent search of online retailers found one wholesaler listing the drug for about \$256 per vial.¹⁰⁰ BioMarin originally estimated annual per-patient treatment costs of \$380,000, assuming a pediatric patient weighing approximately 22.5 kg.⁹⁹ Because elosulfase alfa dosing recommendations are body weight–dependent and pricing appears to vary widely, actual annual per-patient costs could be higher or lower.⁸⁶

BioMarin’s 2014 third-quarter financial reported stated \$40.4 million in net revenue in sales for elosulfase alfa for the 9 months ended September 30, 2014.¹⁰¹ Based on the manufacturer’s initial pricing, these figures represent more than 37,000 vials of elosulfase alfa sold.

Clinical Pathway at Point of This Intervention

Palliative treatments—including surgeries to alleviate patients’ associated cardiovascular, respiratory, and sensory symptoms—are the standard of care for Morquio A syndrome.^{85,102} Upper cervical spinal fusion is among the most common palliative surgeries for this disorder, and it is performed during childhood to prevent further spinal damage, compression, or paralysis.^{83,102} Elosulfase alfa is the only ERT for treating Morquio A syndrome and is the only FDA-approved medication for this indication.

Figure 3. Overall high-impact potential: elosulfase alfa (Vimizim) for treatment of Morquio A syndrome



As the only approved medication for treating Morquio A syndrome, elosulfase alfa could address an unmet need for some patients, the experts stated. Although multiple experts advocated this position, they also thought that reported clinical trial data failed to sufficiently demonstrate significant efficacy across patients. Additionally, experts noted elosulfase alfa’s high retail price and potentially limited third-party payer coverage as factors that could reduce its impact. Based on this input, our overall assessment is that this intervention in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, health devices, and research backgrounds, provided perspectives on this intervention.¹⁰³⁻¹⁰⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts’ consensus was that, as the only approved non-palliative intervention for treating Morquio A syndrome, elosulfase alfa has significant potential to

address an unmet need. These experts, however, thought that elosulfase alfa has only moderate potential to improve patient health outcomes. Two experts with research backgrounds explicitly cited weaknesses in reported clinical trial data, which showed that elosulfase alfa treatments resulted in little to no improvement in patients' functional ability.^{103,108} Another expert opined elosulfase alfa is unlikely to significantly improve overall patient health outcomes and lacks long-term efficacy data to support potential long-term improvements.¹⁰⁷

Acceptance and adoption: All consulted experts concluded that as the first nonsurgical intervention for Morquio A syndrome, elosulfase alfa would be widely adopted by clinicians and patients.

Health care delivery infrastructure and patient management: As an infusion treatment, elosulfase alfa use will present little impact on health care delivery infrastructure, the experts agreed. Although experts noted that elosulfase alfa's weekly IV infusion protocol creates a significant patient management burden, they also favorably compared this intervention to the standard of care for this disorder.

Health disparities: Experts believe that elosulfase alfa would have little effect on health disparities.

Idebenone (Catena) for Treatment of Duchenne Muscular Dystrophy

Unmet need: Duchenne muscular dystrophy (DMD) is a rare, X-linked recessive form of muscular dystrophy, caused by a mutation in the dystrophin gene.^{109,110} The dystrophin gene normally encodes dystrophin protein, a key component in muscle tissue. Patients with dystrophin gene mutations exhibit a resulting lack of dystrophin protein, compromising their muscle cells' structural integrity and increasing those cells' vulnerability to damage.¹¹⁰ These muscle deficiencies result in fatigue, heart defects, general muscle weakness, and problems with motor skills and respiratory function.^{111,112}

Presently, there is no cure for DMD;¹⁰⁹ symptoms often manifest by age 6 years and may be apparent during infancy.^{113,114} Palliative care is the standard treatment for DMD, concentrated on managing patients' most prominent symptoms.¹⁰⁹ Muscle weakness forces many patients to use wheelchairs in early adolescence, and respiratory and cardiac symptoms can begin around age 20.^{109,110} Although progress in cardiac and respiratory care has extended DMD patients' average life expectancy, the disease is still fatal for most patients by age 40.^{110,115} An unmet need exists for effective treatments that improve debilitating symptoms and enhance patients' quality of life and daily functioning.

Intervention: Idebenone is a short-chain benzoquinone demonstrated to have potent antioxidant and cytoprotective properties.¹¹⁶ Structurally, idebenone contains the same functional quinone group as coenzyme Q₁₀ but has significantly higher therapeutic potential.^{116,117}

Biochemical studies of patients with DMD and animal models found that the disorder is marked by excessive oxidative cell damage, due to underlying mitochondrial defects.¹¹⁶ Purportedly, idebenone acts as a transporter molecule, moving electrons directly from the cytoplasm to complex III of the mitochondrial respiratory chain.^{116,118} This direct transit bypasses pathways affected by mitochondrial defects, supporting sustained adenosine triphosphate (ATP) production that can offset characteristic muscle wasting symptoms in patients with DMD.^{116,119}

In clinical trials, idebenone is administered as a 150 mg oral tablet. Daily dosages between 450 mg and 900 mg (3–6 tablets) have been tested and are well tolerated by patients with DMD.^{120,121}

Clinical trials: In an earlier small phase II trial, investigators administered 450 mg idebenone or placebo, daily, to a randomized group of adolescent patients with DMD (n=21). After 12 months, idebenone administration was associated with improved cardiovascular and respiratory functioning.^{120,122}

Idebenone's manufacturer also presented positive results in October 2014 from the DELOS study, a randomized phase III clinical trial investigating idebenone's efficacy in treating adolescent patients who have DMD (n=64). Patients in the treatment group received 900 mg idebenone daily; investigators administered placebo tablets to the control group. Compared with the placebo group at 52 weeks, patients administered idebenone showed improvements on eight different measures of respiratory function, including peak expiratory flow and forced vital capacity. Additionally, patients administered idebenone had fewer respiratory tract infection–related adverse events.¹²¹

In late November 2014, the company announced that it had begun a collaboration with Parent Project Muscular Dystrophy (PPMD), a patient advocacy organization, on a risk-benefit study that will focus on patient and caregiver preferences regarding pulmonary therapies for the disease and will be based on data from the recently completed phase III trial. The company plans to include data from that study with the new drug application (NDA) it intends to submit to FDA.¹²³

Manufacturer and regulatory status: Santhera Pharmaceuticals Holding AG (Liestal, Switzerland) is developing and manufacturing idebenone for treating DMD (and is also

investigating the drug for treating primary progressive multiple sclerosis); it was granted FDA orphan drug designation for this indication in February 2007.¹²⁴ In an early 2014 financial report, Santhera indicated that successful phase III clinical trial outcomes would be followed by regulatory approval submissions for idebenone in both American and European markets, branded as Catena[®] and Raxone[®], respectively.¹²⁵ The company has not yet announced having prepared its NDA submission to FDA.

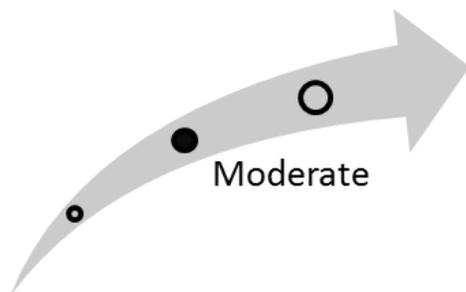
Diffusion: If approved by FDA, idebenone’s earliest likely commercial availability would be very late 2015 or 2016.

Clinical Pathway at Point of This Intervention

Standard DMD treatments focus on palliative interventions addressing one or more pronounced symptoms. Orthopedic devices—including wheelchairs and braces—can compensate for lost mobility; steroids treat declining cardiac and general muscle function; medications and assisted breathing devices address respiratory issues; and educational interventions mediate any associated learning disabilities.^{109,126,127} Idebenone is the first experimental DMD medication to successfully complete a phase III trial and has shown efficacy for improving respiratory function. As a non-disease-modifying medication, if approved, idebenone will likely be positioned as an adjunct to palliative interventions, either to delay or prevent disease symptoms.

Two additional drugs, eteplirsen and drisapersen, are in late-phase clinical trials for this indication.¹²⁸ Both medications are designed to splice certain sections of the errant dystrophin gene that causes DMD. These “exon-skipping” mechanisms purportedly enable mutated dystrophin genes to encode shorter, functional dystrophin proteins, relieving patients’ primary DMD symptoms.^{128,129} Eteplirsen is a subcutaneous injectable, while drisapersen is infused intravenously.¹²⁸ If these drugs are approved, they would be direct competitors to idebenone.

Figure 4. Overall high-impact potential: idebenone (Catena) for treatment of Duchenne muscular dystrophy



Experts acknowledged that a significant unmet need exists for approved DMD medications and thought that idebenone could potentially address this need. As a well-tolerated oral therapy with some demonstrated treatment efficacy, idebenone would be widely adopted by patients and clinicians, the experts also anticipated. They also noted that this intervention would minimally impact health care delivery infrastructure and patient management. Based on this input, our overall assessment is that this intervention in the moderate high-impact-potential range.

Results and Discussion of Comments

Five experts, with clinical, research, and health devices backgrounds, provided perspectives on this intervention.¹³⁰⁻¹³⁴ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: DMD has substantial disease burden and a lack of approved nonpalliative treatments, and all experts acknowledged a significant unmet need for interventions that effectively treat severe disease symptoms. Although available clinical data is limited, multiple experts noted that idebenone has demonstrated effectiveness in improving patients' respiratory function and has moderate to high potential to positively impact patient health outcomes.¹³¹⁻¹³³

Acceptance and adoption: Citing its oral administration route, relatively minimal adverse effect profile, and potential to improve patients' quality of life, experts agreed that idebenone is likely to be broadly accepted by clinicians and patients. The experts also thought that, with no other approved DMD medications, clinicians and patients might quickly adopt this intervention.

Health care delivery infrastructure and patient management: As an orally administered medication that does not completely replace palliative care, this intervention would not significantly affect health care delivery infrastructure and patient management, the experts thought. Some experts thought that idebenone adoption could eventually ease patient management burdens, but they appeared hesitant to strongly endorse this projection without long-term treatment efficacy data.^{131,132,134}

Health disparities: Experts anticipated that idebenone, if granted marketing approval, would have minimal impact on health disparities, particularly because its potential treatment population is so small. Although the experts acknowledged that idebenone could have a prohibitively high retail price, they anticipated that patient assistance programs and third-party payer coverage would alleviate some financial burdens.

Sensory Disorder Interventions

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

Unmet need: 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. Keratoconus 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.

Patients with progressive keratoconus or corneal ectasia face treatments that involve invasive procedures (e.g., corneal transplant, corneal ring insertion). Without treatment, blindness eventually occurs. These invasive interventions are associated with complications, such as graft rejection, risk of permanent vision loss, and prolonged recovery after surgery. Minimally invasive treatments are needed that can stabilize or slow keratoconus or corneal ectasia progression. The VibeX/KXL[®] System purportedly 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.

Intervention: CXL is intended to strengthen 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 corneal ectasia progression, including keratoconus.¹³⁵ 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.^{135,136} The procedure is performed in the outpatient setting with the patient awake. Topical anesthesia is used for pain management.¹³⁶ 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.¹³⁷ However, CXL surgery has also been performed in clinical trials without removing the corneal epithelium.^{137,138}

The VibeX/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.^{139,140}

Clinical trials: Four registered phase III trials of the system are ongoing in the United States, and data have been reported from two completed trials, UVX-002 and UVX-003.¹⁴¹⁻¹⁴⁶ These data are from trials performed only in the United States and use the KXL system. Many manufacturers of CXL systems distribute in Europe, but only one manufacturer (Avedro) appears to be pursuing regulatory approval in the United States.¹⁴⁷ Additional data and a large body of literature have been published on using CXL in treatment performed outside the United States using the cross-linking systems of multiple manufacturers. From the U.S. trials, patients subjectively reported that visual symptoms (e.g., night driving problems, difficulty reading, diplopia, glare, halo, starbursts, and halo-body sensations) improved 1 year after CXL treatment; however, no associations between symptoms and changes in corrected distance visual acuity (CDVA) were found; however, a weak association with maximum keratometry values and some symptoms were found.¹⁴² Another report stated, "after CXL, HOAs [higher order aberrations] were significantly improved compared with the

control group. Changes in HOAs were not statistically associated with an improvement in visual acuity or most subjective visual symptoms, however.”¹⁴³

Study investigators further reported on uncorrected distance visual acuity (UDVA), CDVA, and keratometry values at 1 year of 76 patients who underwent CXL treatment (patients were divided into 3 groups based on maximum keratometry location: central cone group, paracentral cone group, and peripheral cone group). Study investigators reported as follows:¹⁴⁴

In the combined cohort, maximum keratometry (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 logMAR ($p < 0.001$), 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).

These differences were not significant between the groups for UDVA and CDVA outcomes.¹⁴⁴

For a trial of 71 eyes of patients who had 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 $p < 0.001$).”¹⁴⁵ 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.¹⁴⁸

Manufacturer and regulatory status: Avedro, Inc. (Waltham, MA), is developing the system for the U.S. market.¹³⁹ The system received a Conformité Européene (CE) mark in 2010, allowing marketing in Europe.¹³⁹ In December 2011, the manufacturer announced that FDA had granted orphan drug designation for the system for treating keratoconus and corneal ectasia after refractive surgery.¹⁴⁰ In September 2014, Avedro resubmitted an NDA addressing questions and requests from a complete response letter received in March 2014.¹⁴⁹ The original NDA was submitted in 2012.¹⁴⁰ 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.¹⁵⁰

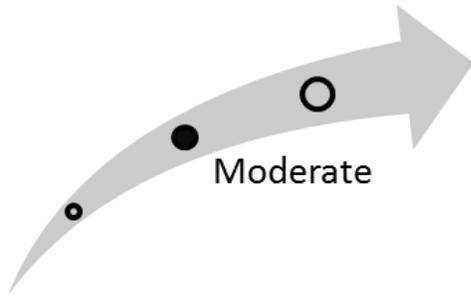
Diffusion and cost: The system is in an innovative phase of diffusion in the United States (i.e., under development); no coverage, coding, or payment information is available at this time. Cost information for the U.S. market is also not yet available. However, the cost of surgery at one Singapore location was listed in 2012 at about \$3,500 per eye.¹⁵¹ Although not available in the United States, the Avedro KXL machine reportedly costs about \$35,000 in markets outside the United States.¹⁵¹

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. Intracorneal ring segments can be implanted to enhance the effectiveness of contact lenses, but a corneal transplant may still be required.¹³⁵ 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 5. 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. Health care delivery infrastructure would be slightly affected when acquiring the machine, the experts thought, but they noted that the short, minimally invasive procedure would integrate smoothly into existing patient management systems. Experts suggested that costs associated with CXL procedures could negatively affect health disparate populations and might limit access except for patients with third-party payer coverage. 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.¹⁵²⁻¹⁵⁷ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: CXL would fulfill the need for a minimally invasive option for progressive keratoconus that is not satisfied by the standard of care, experts agreed. They highlighted the time-intensive nature of available treatment options and noted the potential for CXL to reduce treatment time and associated risks. One expert with a research perspective called for more data to prove CXL's long-term efficacy and outcomes sustainability.¹⁵³ CXL is associated with less risk and fewer adverse events than the standard of care and may improve patient health outcomes in that way, experts indicated.

Acceptance and adoption: Adoption would be high among clinicians, most experts thought, citing improved patient vision outcomes, relative ease of performing CXL procedures, and its limited invasiveness. One expert with a research perspective noted that some clinicians might require more evidence of its efficacy before adopting CXL.¹⁵³ Experts agreed that patients might be more skeptical, because of adverse events or cost but would still widely accept it as a welcomed alternative to contact lenses and more invasive surgery.

Health care delivery infrastructure and patient management: CXL would not significantly affect health care delivery infrastructure except for the cost of acquiring the machine, thought the experts. They noted that the minimally invasive nature of CXL could potentially reduce clinician and staff time now required for treating these patients.

Initial capital costs may be high, some experts noted. But in the long term, the potential reduction in the number of corneal transplants or corneal ring implants resulting from CXL could reduce health care costs, experts suggested.

Health disparities: CXL would have a negligible impact on health disparities, thought most of the experts, but some thought that costs of CXL might deter health disparate populations from accessing treatment. The others thought that if covered by health insurance, cost would not limit access to the procedure because it would supplant other surgical options.

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

Unmet need: The leading cause of preventable monocular vision loss in children is amblyopia (lazy eye), which is most often caused by strabismus (misaligned eyes).¹⁵⁸ Early amblyopia detection can be difficult because standard screening methods only identify risk factors for amblyopia and lack sufficient sensitivity and specificity. They either miss cases that should be referred for further evaluation and possible treatment or over-refer cases.¹⁵⁹ Standard screening methods also cannot be effectively used on children younger than about 4 years old. 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 amblyopia or strabismus detection 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.¹⁶⁰

According to the manufacturer, the device uses proprietary technology called retinal birefringence scanning. Retinal birefringence scanning measures polarized light reflection 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.¹⁶¹ The PVS performs a 2.5-second scan of the eyes to automatically detect the presence of amblyopia, strabismus, or other serious eye conditions.¹⁶⁰ 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.¹⁶⁰

The PVS is designed for use in a pediatric office as an early detection screening tool to promote preventive care and reduce false referrals for ophthalmic specialist care.¹⁶⁰

Clinical trials: Five registered trials evaluated the sensitivity and specificity of the PVS with positive results (sensitivity 94% to 98%; specificity 74% to 88%).¹⁶²⁻¹⁶⁶ The most recent trial of the PVS (compared with the SureSight Vision Screener test) enrolled 300 patients 2–6 years of age. Study investigators reported the following:¹⁶⁵

The sensitivity of the PVS to detect strabismus and amblyopia (0.97; 95% CI, 0.94-1.00) was significantly higher than that of the SureSight Autorefractor (0.74; 95% CI, 0.66-0.83). Specificity of the PVS for strabismus and amblyopia (0.87; 95% CI, 0.80-0.95) was significantly higher than that of the SureSight Autorefractor (0.62; 95% CI, 0.50-0.73).

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 other screening methods.¹⁶⁰

Manufacturer and regulatory status: The PVS has been developed by REBIScan, Inc. (Cambridge, MA). FDA has determined the PVS to be a nonsignificant risk investigational

device,¹⁶⁰ 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.¹⁶⁷ Some in the ophthalmology field expected the device to be on the market before the end of 2014.¹⁵⁹

Diffusion and cost: Reimbursement for pediatric vision screening has been long established; the company indicated it expects its screening exam cost to fall within the reimbursed amount. Thus, PVS testing may be reimbursed by public and private third-party payers in a manner similar to that of other instrumented pediatric vision screening tests that use photoscreening devices, which insurance companies cover under the current procedural terminology code (CPT; published by the American Medical Association) for “ocular photoscreening with interpretation and report, bilateral.”¹⁵⁹ The reported reimbursement rate is about \$25 to \$30 per screening. Reported prices for photoscreening devices range from about \$4,200 to \$7,500.¹⁵⁹

REBIScan is collaborating with VisionQuest 20/20, a nonprofit organization that addresses preventable vision loss in children, to establish a nationwide vision screening program. Pediatric offices and preschools are expected to use the PVS to screen for amblyopia and strabismus. A tracking system will monitor children referred to specialists to ensure they receive proper followup care.¹⁶⁸

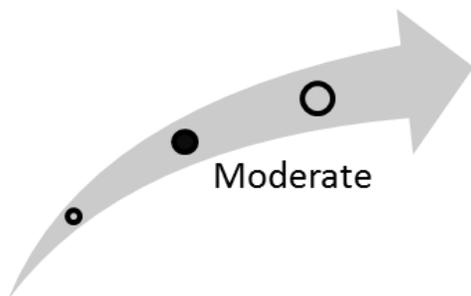
The company has also established a crowd-funding site to raise funds to complete its development to meet regulatory requirements.¹⁶⁹

Clinical Pathway at Point of This Intervention

Amblyopia-associated refractive error is treated with corrective lenses. Patches and eye drops are used to force the child to use the nondominant eye, allowing the weaker eye to become stronger.¹⁷⁰ Children younger than 5 years of age who receive treatment typically recover to almost completely 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.¹⁵⁸

The REBIScan PVS is intended to enable more appropriate referrals and referrals of children at younger ages to an ophthalmologist for further evaluation so that treatment can start when the disorder is at a more correctable stage.¹⁶⁰ Detection methods include annual visual acuity testing at 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.¹⁵⁸ Visual acuity testing and photoscreening devices lead to both missed diagnoses and false positives that lead to unnecessary referrals.¹⁶⁰ The REBIScan manufacturer has indicated that the PVS, if used during annual well-child visits, can reduce health care expenditures by detecting amblyopia and strabismus at earlier stages and reducing false-positive referrals to specialist care.

Figure 6. Overall high-impact potential: Pediatric Vision Scanner screening for strabismus and amblyopia



Overall, experts commenting on this intervention thought use of the PVS in very young children was a significant factor in its potential for fulfilling the unmet need for early screening tools for amblyopia and improving patient outcomes for affected 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 improve the accuracy of referrals to specialists. 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 devices, health systems, and health administration backgrounds, provided perspectives on this intervention.¹⁷¹⁻¹⁷⁶ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for earlier screening, diagnosis and treatment of amblyopia and strabismus, most experts agreed. Experts speculated that patients would achieve better outcomes with earlier treatment and clinicians would make more accurate referrals to specialists. However, one expert with a health systems and administration perspective expressed skepticism for the unmet need and was “...not compelled to believe that earlier scanning actually saves the patient any time, money, pain, or quality of life.”¹⁷²

Acceptance and adoption: Acceptance among clinicians, young patients, and their parents is likely to be high, experts agreed. The PVS is easy to use, noninvasive, and allows earlier diagnosis of amblyopia and strabismus, experts said, which will contribute to clinician adoption. If used in schools, “...one could [imagine] the holy grail of childhood vision screening. That is, all children screened cheaply and effectively without having to see an eye doctor,” one clinical expert suggested.¹⁷¹ Several experts thought patients and parents would not distinguish the novel screening from any other testing conducted as part of a well-child visit.

Health care delivery infrastructure and patient management: Providers who replace their current screening modalities with the PVS, necessitating purchase of the device and training of staff, will experience an initial small disruption in care delivery, experts agreed. Any disruptions in patient management will likely be related to specialist referrals—improved screening accuracy could increase referrals if more cases are detected earlier while some false positives are avoided—the experts thought.

Initial costs may increase as providers purchase the PVS and train staff. However, if minimally trained staff could perform the screening instead of pediatricians or specialists, costs would decrease, one clinical expert said.¹⁷¹ Lifetime vision care costs may decrease if children receive earlier and more effective treatment, experts noted. Likewise, overall health care system costs might decrease if fewer false positive referrals are made to specialists, one expert with a research perspective pointed out.¹⁷⁵

Health disparities: If the PVS is used in low-cost clinics or preschools, health disparities might decrease for children who do not have insurance, experts said. However, as one research expert noted, disparities will not be affected unless early screening is followed by corrective vision care for those who have the condition.¹⁷⁵ If the PVS is primarily used in pediatrician offices, disparities are unlikely to be affected, other experts thought.

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

Unmet need: Retinitis pigmentosa (RP) is relatively rare, occurring in an estimated 1 in 4,000 people in the United States.¹⁷⁷ Medications or devices to restore lost vision due to RP were not available before the development of 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 who have advanced RP.

Intervention: 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.”¹⁷⁸ 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.¹⁷⁹ According to the manufacturer, the steps required to use Argus II 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.¹⁸⁰

Argus II purportedly restores some shape recognition and shade distinction 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.¹⁸¹ Patients using the commercial version of Argus II can perceive only black, gray, and white.¹⁸²

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.¹⁸¹

Clinical trials: In clinical trials, investigators studied patients performing tasks such as object location, following a street crosswalk, and locating bus stops. Patients also performed tasks to detect light and variations of color.^{183,184} 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, as follows:¹⁸⁵

The mean±SD percentage correct letter identifications for 21 subjects tested were 72.3±24.6% with the system on when testing letters L, T, E, J, F, H, I, U versus 17.7±12.9% with the system off. The result was 55.0±27.4% with the system on when testing letters A, Z, Q, V, N, W, O, C, D, M, versus 11.8%±10.7% with the system off. Correct letter identifications were 51.7±28.9% with the system on when testing letters K, R, G, X, B, Y, S, P, versus 15.3±7.4% with the system off. The result was statistically significant ($p<0.001$) for all groups. A subgroup of six study participants consistently read letters of reduced size, the smallest measuring 0.9 cm (1.7°) at 30 cm. Four of these participants correctly identified, unrehearsed, two-, three- and four-letter words. Average implant duration was 19.9 months.

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) procedures 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 in whom the device is implanted 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).¹⁷⁸

Manufacturer and regulatory status: Second Sight Medical Products, Inc. (Sylmar, CA), manufactures the Argus II Retinal Prosthesis System. In February 2013, FDA approved Argus II for marketing for treating adults with advanced RP.¹⁷⁹ In January 2014, the first patient with RP received the Argus II implant.¹⁸⁶ Twelve hospitals are offering consultations for patients with RP and are starting Argus II implantation programs.¹⁸⁷

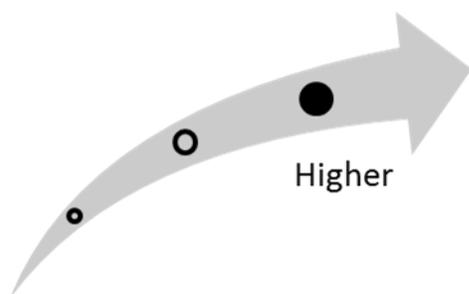
In March 2011, the Argus II received the CE mark, allowing marketing in Europe.¹⁸⁸

Diffusion and cost: According to the manufacturer, the system costs about \$115,000 to \$145,000, which includes the device and the surgical procedure.^{182,189} ECRI Institute routinely searches 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). Our searches found four policies that were developed after FDA approval of the device. Those payers—Aetna, Anthem, Blue Cross/Blue Shield Massachusetts, and Regence—consider use of artificial retinal devices to be experimental and do not cover them.¹⁹⁰⁻¹⁹³ CIGNA also denies coverage for artificial retinal devices, but its policy on artificial retina devices from 2006 had not been updated since FDA approved the Argus II.¹⁹⁴

Clinical Pathway at Point of This Intervention

RP can be familial, inherited as an autosomal dominant, autosomal recessive, or X-linked defect. The disease has been linked to defects in more than 40 genes.¹⁹⁵ 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.¹⁷⁷ No cure exists; however, some treatment options, such as limiting light exposure, are thought to help preserve vision,¹⁹⁶ and other treatments under study include high doses of vitamin A palmitate and omega-3 fatty acid DHA.¹⁷⁷

Figure 7. 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 for patients with RP, although Argus II's ability to restore independence or improve quality of life is unknown. Experts noted the number of adverse events reported in studies and opined that clinical acceptance may be affected by that, 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 because of patients' desire or hope to be more independent. Most experts agreed that this intervention might significantly affect patient management because patients would need training on using the device, followup care, and vision rehabilitation. Health disparities related to costs and use of a complex device in this patient population might increase, experts thought. 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 devices, and health systems backgrounds, provided perspectives on this intervention.¹⁹⁷⁻²⁰² We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for treatment options to restore some level of vision for patients with RP, the experts agreed. The technology addresses the unmet need for a small patient population by providing some visual function, although the degree to which the vision improvement restores independence or quality of life is unknown, experts stated. One expert with a health devices perspective noted that the device does not halt or reverse RP progression. Electronic interference from nearby objects (e.g., cell phones, televisions) might render the device unusable in many places, the same expert said.²⁰¹

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 surgery difficulty could limit clinician adoption. Additionally, one health systems expert stated that unknown long-term effects of electrical stimulation on the retina might limit clinician acceptance.¹⁹⁷ Limited improvement in vision and high risk of adverse events might also slow adoption, according to several experts.

The potential for patient acceptance would be high, most experts agreed, but patients would need to be active partners in their treatment. Some patients who would accept this intervention might not be able to afford the device, surgery, and followup treatment, most experts noted.

Health care delivery infrastructure and patient management: Several experts thought that this intervention would not disrupt health care delivery infrastructure because implantation could be performed in centers already offering ophthalmologic surgery. Experts thought that this intervention has the potential to greatly disrupt patient management because patients would need extensive training and followup after surgery, instead of yearly monitoring of RP progression as is the

standard. The small number of patients expected to receive this device would limit the disruption to specialists providing this option, experts thought. However, surgeons, therapists, and other providers would need extensive training.

Health disparities: Experts generally agreed that the cost of this intervention could significantly affect health disparities because its cost is reported to be \$115,000 or more. The complexity of the rehabilitation needed to correctly interpret the visual signals might also limit this technology to highly literate patients, noted two experts, one with a research perspective and the other with a clinical perspective.^{198,202}

Tasimelteon (Hetlioz) for Treatment of Non-24-Hour Sleep-Wake Disorder

Unmet need: The National Sleep Disorders Foundation estimates that, of people who are totally blind in the United States, 65,000–95,000 experience a disorder called non-24-hour sleep-wake disorder (non-24). The disorder arises from a lack of light receptors to reset the circadian rhythm.²⁰³ Besides difficulties associated with blindness, patients with non-24 often experience reduced quality of life and debilitation due to poor sleep quality and excessive daytime sleepiness. Patients may attempt to relieve symptoms of non-24 using sleep aids such as melatonin and stimulants during the day, but these do not address the underlying cause. In January 2014, FDA approved tasimelteon (Hetlioz™) as the first drug approved for treating non-24.²⁰⁴

Intervention: Tasimelteon is a dual melatonin-receptor agonist with selective activity mediated through receptors MT1 and MT2. It reportedly resets the circadian rhythm by acting on the suprachiasmatic nucleus of the hypothalamus to synchronize melatonin and cortisol release with the 24-hour, day-night cycle.²⁰⁵ Tasimelteon is intended to improve nighttime sleep and reduce daytime sleep by maintaining a 24-hour sleep-wake cycle.

According to the manufacturer, tasimelteon is taken orally at a dose of 20 mg, 1 hour before bedtime, at the same time every night. Tasimelteon may cause drowsiness or affect mental alertness, so patients are advised to limit activity after taking it.²⁰⁶ Patients might not notice its effects for weeks to months after initiating treatment, according to a discussion held between FDA and the manufacturer.²⁰⁷

Clinical trials: A clinical trial (n=84) assessed circadian rhythm by measuring urinary 6-sulphatoxymelatonin (aMT6s) and cortisol. Clinical responders were defined as patients whose circadian rhythm was entrained (adjusted) by tasimelteon who scored 3 or higher on the Non-24 Clinical Response Scale. In results of this study, Lockley et al. reported that the proportion of patients entrained by tasimelteon was greater than placebo, as measured by urinary aMT6s and cortisol timing (p=0.0171 and p=0.0313, respectively). They also reported that the number of clinical responders was greater for tasimelteon than placebo, and greater improvement was seen in the Clinical Global Impression of Change and measures of total nighttime sleep, daytime nap duration, and mid-point of sleep timing (MoST) than in the placebo group (p<0.05).²⁰⁸ In an extension of the clinical trial (n=20), Lockley et al. reported that patients receiving the drug maintained their circadian rhythms (as measured by aMT6s and cortisol levels) better than those taking placebo (aMT6s: tasimelteon, 90%; placebo, 20%; p=0.0026; cortisol: tasimelteon, 80%; placebo, 20%; p=0.0118). Total nighttime sleep was 67.2 minutes longer in the worst quartile of nights and total daytime sleep duration was 59.4 minutes shorter in tasimelteon-treated patients (p<0.05). The MoST from both nighttime and daytime sleep increased 36 minutes in tasimelteon-treated patients (p=0.0108).²⁰⁹ In both trials, tasimelteon was reported to be safe and well tolerated.

Manufacturer and regulatory status: Vanda Pharmaceuticals, Inc. (Washington, DC), manufactures tasimelteon under the brand name Hetlioz.²¹⁰ FDA approved tasimelteon in January 2014 as an orphan drug²⁰⁴ that is indicated for treating non-24. It is contraindicated in women of child-bearing potential and individuals with severe liver impairment.²⁰⁶ The manufacturer's label warns that tasimelteon may impair mental alertness and thus, should be taken only before bedtime. Patients taking strong CYP1A2 inhibitors (e.g., fluvoxamine) or strong CYP3A4 inducers (e.g., rifampin) should not use tasimelteon. Two phase III trials are ongoing.

According to a medical review from FDA, common adverse events associated with tasimelteon included headache, increased alanine aminotransferase levels, abnormal dreams/nightmares, cardiac conduction disorder, sleep disorder, upper respiratory tract infection, somnolence, and urinary tract infection. The most common serious adverse event was gastroenteritis.²¹¹

Diffusion and cost: Tasimelteon is a specialty pharmaceutical that is available through a small network of pharmacies.²¹² As an orally administered pharmaceutical used in an outpatient setting, tasimelteon is not expected to require significant changes to health care staffing or infrastructure.

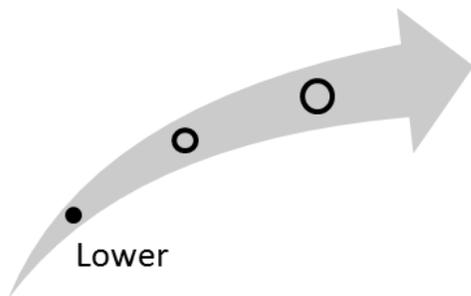
According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, tasimelteon costs about \$86,000 per patient per year.²¹³ If half (about 35,000 patients) the estimated population with non-24 opted to take the drug, the cost to the health system would be about \$3 billion annually.

ECRI Institute routinely searches 11 representative, private, third-party payers that publish their policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark). Our searches found 10 policies for tasimelteon that require prior authorization;²¹⁴⁻²²³ several policies list tasimelteon as a nonpreferred drug,^{215,217-219,223} subject to quantity limits,^{214,215,220,223} and approved only after failure of over-the-counter melatonin therapy.^{214,217,222}

Clinical Pathway at Point of This Intervention

Other drugs that may have an effect on regulating the circadian rhythm are melatonin and ramelteon, although neither is FDA approved for non-24. Benzodiazepines or nonbenzodiazepine hypnotics have also been prescribed to improve night-time sleep quality; to limit daytime sleep, patients have been prescribed caffeine in various forms.^{224,225} Nonpharmacologic treatments include chronotherapy and lifestyle changes.²²⁴ Tasimelteon is likely to be used in place of other drugs, but potentially in combination with nonpharmacologic treatments.

Figure 8. Overall high-impact potential: tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder



Overall, tasimelteon's cost will likely have the biggest impact on the health care system, experts agreed. The manufacturer aggressively marketed tasimelteon in direct-to-consumer advertising for several months after initial launch, and thus, patients and their physicians are likely to request prescriptions and influence private payers' coverage determinations, experts agreed. In terms of improving patient health or altering patient management, experts noted the small amount of data and modest improvements in sleep and waking times when suggesting the drug is likely to have a lesser impact. 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.²²⁶⁻²³¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for effective treatments for patients with non-24, experts agreed, but they were skeptical that tasimelteon improves efficacy compared with other drug options and good sleep hygiene (e.g., going to bed at the same time each night).

Non-24 significantly reduces quality of life, some experts thought, and tasimelteon could reduce some of the disease burden.

Acceptance and adoption: Two experts noted heavy marketing from the manufacturer through radio and television advertisements would likely increase patient demand for tasimelteon.^{226,227}

Among patients with third-party payer coverage and few side effects, adoption is likely to be significant if patients can afford their copayments. Clinicians may also readily accept tasimelteon because it is the only FDA-approved treatment for non-24, experts thought. One research expert pointed out that the drug is not prone to abuse, unlike comparators such as benzodiazepines, which would positively affect clinician acceptance.²²⁷ But several experts said some clinicians and patients will likely hesitate to use tasimelteon because of its high cost.

Health care delivery infrastructure and patient management: Because it is an oral pharmaceutical, tasimelteon is unlikely to affect infrastructure and patient management, experts agreed. The high cost of the drug is likely to have the largest impact on the health care system and third-party payers, experts noted.

Health disparities: If third-party payers do not reimburse for the drug or if they require high copayments, health disparities among the affected population would substantially increase, all experts agreed. One clinical expert thought coverage might not be forthcoming, saying, "...[with] cheaper alternatives such as melatonin available, it is hard to imagine third-party payers listing this medication as a primary therapy on formularies."²²⁶ A research expert and a health systems expert speculated that tasimelteon could improve psychosocial wellbeing, quality of life, and overall health status, which would reduce some disparities generally seen between patients who are blind and the general population.^{228,231}

Prosthetic Intervention

Prosthetic Arm with Body-Machine Interface (DEKA Arm System) to Restore Natural Arm Function After Amputation

Unmet need: Patients in whom an upper limb has been amputated have multiple prosthetic options available, but prosthesis function is generally limited to sequential movements that require deliberate effort to control. Patients do not have options that provide natural movement, intuitive controls, or tactile sensations.²³² As a result, many patients with an arm prosthesis are still functionally limited. Advances incorporating miniaturized computer components, lightweight but strong materials, and body-machine interfaces combined into a prosthetic hand and arm have resulted in the DEKA Arm System, a device that has up to 10 powered degrees of freedom and multiple unique features.²³³

Intervention: The following information is based on descriptions of the Gen 3 DEKA Arm used in clinical studies. Whether the features of this arm will be available in the commercially produced prosthesis is unclear.^{233,234} DEKA Arm features include movable joints, a wrist, and independently movable fingers. The device has a metallic external structure with no exposed mechanics, does not require a fabric sleeve, and is dust and water resistant. The entire arm is resistant to light rain, and the fingers up to the base can be immersed in water.²³⁴

An embedded LED wrist display alerts the user to grip, mode, power, battery charge, and system faults. An audible vibration indicates when the mode changes between hand and arm, when it moves in or out of standby, and when grip mode or grip pressure is changed.²³³

The Arm is designed for three configurations: shoulder, humeral, and radial.²³³ It can be used only by patients who have limb loss at the shoulder joint, mid-upper arm, or mid-lower arm. The DEKA Arm is not intended to be used in patients with limb loss at the elbow or wrist.²³⁵ The humeral and shoulder configurations can accommodate an internal battery while all configurations can use an external battery worn on a belt or harness.^{233,234} The internal battery has a run time of about 1 hour and the external battery, about 6 hours.²³⁴ The shoulder configuration weighs 9.8 lb, the humeral configuration weighs 6.8 lb, and the radial configuration weighs 2.8 lb.²³⁴

The shoulder configuration has 10 powered degrees of freedom and additional passive degrees of freedom that allow for simultaneous, coordinated movement at the shoulder, humeral rotator, elbow, forearm, wrist, thumb, index finger, or fingers three to five.²³³ Although several movements can be performed at once by combining foot controls, myoelectrodes, pneumatic bladders, manual switches, and other common input devices, the DEKA Arm must switch between hand and arm modes to accomplish many tasks.^{233,234} A limited number of hand movements can be performed when in arm mode.²³⁴ The hand mode has six programmed grips that the user employs to grasp various sizes and shapes.²³⁴ The detent feature allows users to manipulate an object in the hand without losing the grip on it (e.g., holding and using a spray bottle).²³⁴ The wrist has four powered movements.²³⁴ The shoulder configuration has an endpoint control system that uses software to coordinate joint movements to bring the end of the prosthesis into a desired position from one command instead of a series of commands.²³⁴ A dynamic socket controller regulates inflatable bladders inside transhumeral sockets to stabilize the device and provide pressure relief. Patients control this function using buttons.²³³

Patients using the DEKA Arm can perform several tasks that are reportedly too complex for other prosthetic devices, including using keys and zippers.²³⁵ Several features have been incorporated into the DEKA Arm to prevent accidents and user errors. For example, the device is able to recognize when it is moving toward the head and reduce its speed to avoid a collision. It can also distinguish between intentional foot controls and walking, trips, or stumbles.²³⁴

Clinical trials: In one study of 37 patients using second- and third-generation DEKA Arms, researchers reported that 79% of Gen 2 and 85% of Gen 3 users indicated they wanted to receive or

might want to receive a DEKA Arm; 95% of Gen 2 and 91% of Gen 3 prior prosthesis users reported that they had been able to perform new activities that were unable to perform with their own prosthetic devices.²³⁶ Researchers further reported that patients rated satisfaction and usability higher for the third-generation device than the second-generation device.²³⁷ A prospective, observational cohort study with 75 patients is ongoing to evaluate the change in quality of life while using the device at home for 13 weeks.

Manufacturer and regulatory status: The DEKA Arm System was developed by DEKA Integrated Solutions (Manchester, NH) in conjunction with prosthetic engineers from Next Step Bionics and Prosthetics, Inc. (Manchester, NH) and Biodesigns, Inc. (Westlake Village, CA).^{238,239} The U.S. Defense Advanced Research Projects Agency’s “Revolutionizing Prosthetics” program provided funding to DEKA with the goal of developing a prosthetic arm with natural control.²³⁹ In May 2014, FDA cleared the DEKA Arm System for marketing through its de novo classification process.^{235,240} The system is not yet commercially available because the developer is seeking a partner to manufacture and commercialize the prosthesis.

Diffusion and cost: DEKA Integrated Solutions does not yet have a manufacturing partner, so no cost information is available.²³⁵ In an interview with the Boston Business Journal, the developer said the cost will depend on the number made, but would ideally be in the range of tens of thousands of dollars.²⁴¹

Medicare Part B covers artificial limbs as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a durable medical equipment supplier does not accept direct Medicare reimbursement, Medicare cannot limit the amount a supplier can charge. In certain geographic areas, Medicare’s competitive bidding program may be in effect, which means that Medicare pays for the equipment and related supplies only if they are obtained from contracted suppliers. These suppliers cannot charge patients more than 20% coinsurance and any unmet yearly deductible for any equipment or supplies included in the competitive bidding program.²⁴²

To identify coverage policies, ECRI Institute routinely searches 11 representative, private, third-party payers that publish their policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark). Our searches found no policies that mention the DEKA Arm System, probably because it has only recently been FDA cleared and is not yet commercially available. Third-party payers generally cover prostheses needed (when physician prescribed) to enable the patient to perform activities of daily living. Thus, the DEKA Arm would likely be considered as another prosthetic option that could be eligible for coverage.

Clinical Pathway at Point of This Intervention

After a patient’s amputation site has completed primary healing, long-term care is often provided by physical medicine and rehabilitation physicians, who focus on pain management, medications, and occupational and physical therapy.²⁴³ They coordinate care for emotional health, prosthetic treatment, occupational and physical therapy, social services, and return-to-work issues.²⁴³ Occupational therapists also address pain control, self-care strategies, work needs, and prosthetic training.²⁴⁴

Patients who choose to use a prosthetic limb have multiple options that depend on the degree of amputation and remaining function. Amputations on the limb closer to the trunk require prostheses that have more functions to control more joints. Four types of prostheses are commonly available, as follows:^{244,245}

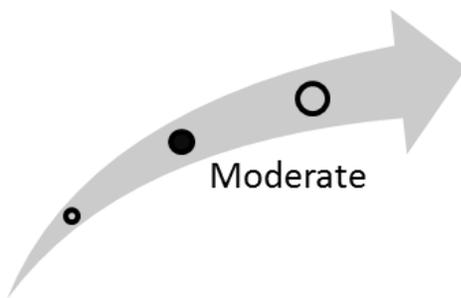
- Passive: requires use of another limb to reposition it; may be functional or cosmetic

- Body-powered: operated by moving a cable often connected to opposite shoulder or by a switch often controlled by the chin
- Myoelectric: composed of an external battery, electric motor, and microprocessing unit that responds to transcutaneous electric signals sent by remaining muscles
- Hybrid: combines body-powered and myoelectric mechanisms for controlling prosthesis

Tasks using a prosthesis are performed in sequential steps. Some myoelectric devices use pattern recognition to improve response speed and decrease operation burdens.²³²

Patients choose a prosthesis based on multiple factors including function, weight, aesthetics, and ease of use. Not all prostheses can be configured for all degrees of amputation. Although prostheses are designed to restore some function to a patient with an upper limb amputation, many prostheses have no fine motor control and cannot use multiple joints at once. They may look unnatural, can be heavy or uncomfortable, may not be waterproof, and have no tactile sensation.²⁴⁶ Patients commonly use prostheses for only a portion of the day or specific tasks because of these disadvantages.²⁴⁵

Figure 9. Overall high-impact potential: prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm function after amputation



Overall, experts commenting on this intervention thought a significant unmet need exists for restoring natural arm function to patients with upper limb amputations, and this device provides functionality well beyond any available prostheses. Experts thought that clinician and patient enthusiasm might be tempered by high costs and complex training, potentially increasing health disparities due to unequal access. Experts suggested that the prosthesis' overall impact would be mitigated by the small population likely to use the DEKA Arm. 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.²⁴⁷⁻²⁵² We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for a prosthetic arm that restores natural arm functions to patients who have had an amputation, experts agreed. The DEKA Arm System has more degrees of freedom, better coordinated gross and fine motor functions, and greater potential to improve quality of life than available prostheses, experts concurred. Some experts tempered their enthusiasm by noting that this device lacks sensory perception and is not suitable for all patients who have had an arm amputated.

Acceptance and adoption: Acceptance among clinicians may vary greatly as indicated by contrasting expert comments. Clinicians focusing on the improvement in quality of life and function for patients will readily accept the device. Other clinicians may be reluctant because of the cost and complexity of the prosthesis. One expert with a health systems and administration perspective

suggested that doctors might not want to invest time and effort in training themselves on the device if only a limited number of their patients would benefit.²⁴⁸

Patient adoption is linked to clinicians' viewpoints, one clinical expert noted.²⁴⁷ Cost and complexity may be barriers to patient adoption, experts agreed. Highly motivated patients who desire the increased function of the device will overcome these barriers, some experts said. One clinical expert suggested the device may be best suited for use in the Veterans Affairs system where clinician training may be more consistent.²⁴⁷

Health care delivery infrastructure and patient management: No infrastructure changes are necessary because the DEKA Arm will be offered in the same setting as other limb prostheses, experts noted. Increased staffing and training will be necessary for providing initial and ongoing care to patients who use the device, experts said. Patients will need device-specific surgery to use the device and extensive device maintenance provided by biomedical engineers, experts thought. However, the overall impact of these changes will be limited because of the small number of individuals expected to use the device, two experts said.^{247,251}

Initial costs for the device, surgery, and complex training will be high, experts agreed. Ongoing maintenance will also be expensive because of the complexity of the prosthesis, experts said. One research expert suggested that improved quality of life and function will reduce depression and other psychological issues, potentially reducing associated costs.²⁵⁰

Health disparities: Health disparities may be increased because of the high cost and complexity of the device, the experts agreed. Patients without any insurance or inadequate insurance may have difficulty paying for the device; even patients who have 80% of the cost covered by Medicare Part B as durable medical equipment might not be able to afford the remainder, two experts noted.^{248,252} The complexity of the device means patients will need access to maintenance and technical support experts, which may be a barrier for rural patients, two other experts pointed out.^{247,249} Experts also commented that patients with low literacy or mental capacity may be unable to learn how to use the device.

Spinal Cord Injury Intervention

Intraoral Tongue-Drive Computerized System to Maneuver Electric Wheelchairs

Unmet need: For individuals with quadriplegia from spinal cord injury (SCI), powered wheelchairs are the only self-mobility option for routine movement. Power-assisted devices enable these individuals to maneuver their electric wheelchairs independently and help improve quality of life; however, the safety and efficacy of devices available to maneuver the electric wheelchairs are suboptimal and remain a primary concern. For example, neuroassistive devices are surgically invasive and pose risk of adverse events; sip-and-puff technology, another commonly used modality to drive a wheelchair, can be exhausting for many individuals. The sip-and-puff technology is used by the patient to send signals to a device. The patient uses air pressure to “sip” (inhale) and “puff” (exhale) on a straw, tube, or wand, and the amount of air pressure exerted directs the wheelchair to perform the desired task. A new device has been developed that may overcome some of the limitations of existing technology for people with spinal cord paralysis and no arm function. A magnetic tracer/stud that is pierced through the individual’s tongue is a novel wireless computerized assistive device that might enhance mobility and allow patients to perform more daily tasks in a safer and more effective manner with less-invasive technology.

Intervention: The Tongue Drive System (TDS) is a computerized, assistive neurotechnology integrated with a powered wheelchair. It consists of a titanium, barbell-shaped, magnetic tracer/stud that is affixed to the tongue, most commonly by piercing, and a headset with magnetic field sensors located near the cheeks. The sensors detect when movement is made by the tongue. The output signals are then transmitted wirelessly to a device, such as a smartphone, which communicates with the powered wheelchair. TDS attaches to standard powered wheelchairs and is capable of housing and charging both the smartphone and headset when they are not in use.²⁵³ The smartphone transmits information to a computer, commanding it to perform daily tasks (e.g., email). A standby mechanism allows patients to perform activities such as eating, sleeping, and talking without unnecessary TDS use.²⁵⁴

According to a registered clinical trial protocol description, TDS requires that the patient’s teeth are brushed, the oral surface sterilized with chlorhexidine mouthwash, and local anesthetics are applied on the tongue before clinicians pierce it with a titanium magnetic stud.²⁵⁵ Patients must undergo computer training with the TDS for the software to appropriately interpret and calibrate tongue movement.

Clinical trials: The most recent published TDS study enrolled 21 individuals with tetraplegia from SCI at two centers (Shepherd Center in Atlanta, GA, and Northwestern University, Chicago, IL) for a 6-week evaluation of TDS usability. Ten participants dropped out during the trial because of disqualification during screening, loss of interest, noncompliance with scheduled study visits, loss of the tongue barbell, transportation difficulties, and medical issues unrelated to the study. The remaining 11 participants (9 male; 2 female) ages 38.6±9.8 years (range: 27–56 years), completed the study and the quality-of-life questionnaires. All participants had been driving their powered wheelchairs on a daily basis using either a sip-and-puff (54.5%) or a modified joystick (45.5%) tool. Of the participants, 36.4% did not use computers on a regular basis, 36.4% (with C5 and C6 level SCI) had some limited hand motion, and 36.4% used other technologies, such as a mouth stick, head controller, or speech recognition software. Participants were given a 75-question post-study system-usability questionnaire that included factors related to the piercing experience, TDS accessibility, usability, satisfaction, and comparison with other technologies they had used. The majority of questions were designed on a five-point Likert-type scale; two yes/no questions and four open-ended questions were included. Study authors reported that overall, participants “had no major

issues with the tongue piercing, and more than 70% would have been willing to keep a tongue barbell for ongoing use of the system. More than 60% of participants had no concerns about the appearance of the headgear, and ~50% of participants said that the TDS was easy to access.” Participants rated TDS performance as satisfactory at the end of the study, with half of users assessing the TDS as more effective than sip-and-puff or their current assistive technology despite the brief experience with the TDS.²⁵⁶

Another study enrolled both able-bodied subjects and individuals with high-level SCIs (level C3 to C5); researchers combined TDS with speech recognition software and reported preliminary results. They tested the technology in 14 able-bodied subjects and 3 individuals with high-level spinal cord injuries at level C3-C5. Authors reported that the (dual) TDS headset, combined with commercially available speech recognition software, provided users with significantly higher performance than either unimodal forms based on the tongue motion or speech alone, particularly in completing tasks that require both pointing and text entry.²⁵⁷

The developers have not published information regarding patient safety or adverse events yet. With computerized devices, a potential safety issue could be computer or device malfunctions that might place the patient at risk of harm in certain situations (e.g., device failure while crossing a street, going up or down a ramp, or in crowds).

Manufacturer and regulatory status: TDS is manufactured by Bionic Sciences (Atlanta, GA) and the Georgia Institute of Technology (Atlanta) in collaboration with the Shepherd Center (Atlanta, GA), Northwestern University (Evanston, IL), the Rehabilitation Institute of Chicago (IL), and the University of Arizona (Tucson). TDS developers estimated in November 2013 that the technology was about 2 years from receiving FDA clearance.²⁵⁸

Diffusion and cost: The developers anticipated the per-patient cost of the TDS system to be between \$6,000 and \$7,000.²⁵⁸ This cost would be in addition to that of the powered wheelchair. Costs may potentially be lower than for other brain-computer interface devices, because TDS does not require invasive brain surgery.

Medicare Part B covers power-operated wheelchairs as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a durable medical equipment supplier doesn't accept being paid the Medicare rate directly from Medicare, Medicare does not limit the amount a supplier can charge. In certain geographic areas, Medicare's Competitive Bidding Program may be in effect, which means that Medicare pays for the equipment and related supplies only if they are obtained from contracted suppliers. These suppliers cannot charge patients more than 20% coinsurance and any unmet yearly deductible for any equipment or supplies included in the Competitive Bidding Program.²⁵⁹ Third-party payers generally cover the interfaces needed (when physician prescribed) to enable the patient to maneuver and perform activities of daily living. Items typically covered include joystick handles, chin cups, sip-and-puff interfaces and their breathing-tube kits, and interfaces for mechanical, electronic, contact-switch, or proximity-switch head control and speech-generating devices. Thus, the TDS technology, if FDA-cleared, would likely be considered as another interface option that could be eligible for coverage.

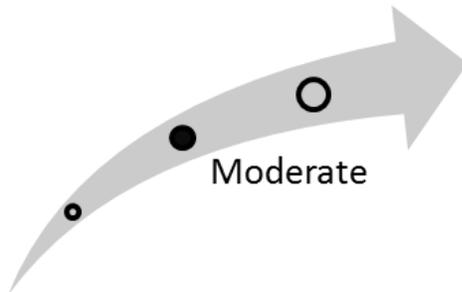
Clinical Pathway at Point of This Intervention

SCI requires immediate medical attention. A clinician completes a physical exam, including neurologic exam, to identify the likely injury location. Computerized tomography, myelogram, somatosensory evoked potential testing, or spine radiography may be ordered.²⁶⁰

Emergency SCI treatment involves immobilizing the spine as gently and quickly as possible. Acute stages of treatment include maintaining breathing, preventing shock, immobilizing the neck,

and avoiding possible complications. Medications, prolonged immobilization, or surgery may be required.²⁶¹ Ongoing treatment such as physical therapy, occupational therapy, or other rehabilitation therapies, as well as muscle spasticity medications, may be needed.²⁶⁰ For patients who become quadriplegic, assistive technology is required for mobility and performing activities of daily living. Patients need durable medical equipment, which is prescribed by the physician.

Figure 10. Overall high-impact potential: intraoral tongue-drive computerized system to maneuver electric wheelchairs



Overall, experts commenting on this intervention thought a significant unmet need exists for restoring more mobility and independence to patients with SCI who are quadriplegic. Experts' opinions differed on whether this intervention could accomplish that better than existing options already do. Acceptance would likely be high among clinicians and patients, experts thought, because the device appears to provide a more intuitive, less invasive, and less strenuous option for mobility than existing technology such as the sip-and-puff method. Although additional training of patients is needed to use TDS, providers and technical support are already in place to mitigate that impact, experts agreed. Some experts believe TDS might increase disparities if cost and coverage differed among third-party payers. 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.²⁶²⁻²⁶⁷ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant need exists for improved assistive technology to restore mobility in patients with SCI, experts opined, but they were split on whether TDS would fill that gap. Several experts thought this device might not significantly improve this patient population's ability to improve mobility because of alternatives already available, including sip-and-puff and scalp electrode-based control systems. However, several other experts reported that TDS could become a preferred and viable technology for this patient population by improving independence, psychological well-being, and quality of life. The technology could also be less strenuous to use than sip-and-puff and pose less risk than neurotechnology that requires invasive surgery, thought experts.

This intervention does not have clear potential to improve patient health outcomes because it does not repair or regenerate the spinal cord, several experts thought. One expert with a health systems perspective had concerns about potential malfunctions that may place the patient in a precarious situation.²⁶⁶ Still, this intervention could allow patients to perform daily activities with a greater degree of ease than with available comparators, another expert with a health devices perspective stated.²⁶⁵

Acceptance and adoption: Experts offered varied viewpoints on potential acceptance of TDS by both clinicians and patients. Some experts speculated TDS acceptance by clinicians and patients would be high because of its intuitive control, minimally invasive implementation, and improvements in quality of life. Acceptance by clinicians might be tempered by the small body of evidence available thus far indicating improved patient independence and by the ongoing maintenance of the hardware and software, which might require specialized staff, other experts thought. One expert with a health devices perspective stated that the device would pose minimal health risks to this patient population while increasing patients' accessibility and communication with society, significantly improving patient outcomes.²⁶⁵ Patient acceptance would likely depend on personal cost and feelings about the tongue piercing, a health systems expert noted.²⁶⁶

Health care delivery infrastructure and patient management: This device would not significantly disrupt health care delivery infrastructure or patient management, most experts thought, stating that a system is in place for this device's implementation and adoption. Its adoption might require increased hiring and training of rehabilitation specialists, computer specialists, and biomedical hardware specialists to train patients and ensure proper functioning of the device, several experts noted. One expert with a health systems perspective believes that the anticipated increase in specialists for managing the device in combination with the device's potential complexities may increase time in patient management.²⁶⁶ Another expert with a research perspective noted that patients will likely still need extensive daily care even if they gain some independence with this device.²⁶²

Health disparities: Experts generally agreed costs to acquire the device might affect health disparities, although several experts thought those disparities already are present between patients who have access to powered wheelchairs and those who do not. A health systems expert opining on the role of insurance said, "Insurance coverage is generally for base models in terms of power wheel chairs, and this ad[d-]on I would see a potential for insurance carriers to deny coverage for less expensive options."²⁶⁶

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