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. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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Financial Disclosure Statement

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

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Preface

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

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

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

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

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 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 21 topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Ninety-three topics in this priority area were being tracked in the system as of May 15, 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. Alemtuzumab (Lemtrada) for treatment of relapsing-remitting multiple sclerosis	No high-impact potential at this time
2. Amygdala retraining program for treatment of chronic fatigue syndrome	No high-impact potential; archived on basis of expert comments
3. Amygdala retraining program for treatment of fibromyalgia	No high-impact potential; archived on basis of expert comments
4. * Corneal collagen cross-linking (VibeX/KXL System) for treatment of progressive keratoconus	Moderately high
5. * Dimethyl fumarate (Tecfidera) for treatment of relapsing forms of multiple sclerosis	Lower end of the high-impact-potential range
6. Droxidopa (Northera) for treatment of symptomatic neurogenic orthostatic hypotension	No high-impact potential at this time
7. * Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type I	Moderately high
8. * Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome	Moderately high
9. High-intensity focused ultrasound (EyeOP1 HIFU-system) for treatment-refractory glaucoma	Prior high-impact topic (December 2013); archived because manufacturer no longer pursuing U.S. market
10. * Intraoral tongue-drive computerized system to maneuver electric wheelchairs	Moderately high

Topic	High-Impact Potential
11. Micro-bypass implant (iStent Trabecular Micro-Bypass Stent System) for treatment of glaucoma	No high-impact potential; archived 2 years after FDA approval
12. * Ocriplasmin (Jetrea) treatment for symptomatic vitreomacular adhesion including macular hole	High
13. Off-label mexiletine for treatment of nondystrophic myotonia	No further high-impact potential; archived; experts indicated intervention is already well diffused among most eligible patients
14. * Pediatric Vision Scanner screening for strabismus and amblyopia	Moderately high
15. Pimavanserin for treatment of Parkinson's disease psychosis	No high-impact potential; archived; experts saw little impact because of efficacy data
16. Pridopidine (Huntexil) for treatment of Huntington's disease	No high-impact potential; archived; FDA rejected phase III trial results; experts questioned lack of ideal dosage
17. Real-time MRI-guided laser interstitial thermal therapy for epilepsy	No high-impact potential at this time
18. * RenalGuard for prevention of contrast-induced nephropathy	High
19. * Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	High
20. * Tasimelteon (Hetlioz) for treatment of non–24-hour sleep-wake disorder	Lower end of the high-impact-potential range
21. Wearable battery-powered exoskeletons (ReWalk and Ekso systems) for rehabilitation after spinal cord injury	Prior high-impact topic (December 2013) archived April 2014 because of diffusion for rehabilitation indication

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 December 2013 Report

Two potential high-impact topics from the December 2013 report have been archived.

- **High-Intensity Focused Ultrasound (EyeOP1) for Treatment-Refractory Glaucoma:** In the December 2013 report, this topic was deemed by expert comments to have potential for high impact (on the lower end of the high-impact-potential scale) because the technology is a less-invasive, nonsurgical option for medication-resistant glaucoma. The EyeOP1 system uses high-intensity focused ultrasound to deliver concentrated energy to the eye's ciliary body, which purportedly reduces aqueous humor production leading to lower intraocular pressure. The manufacturer has not started U.S. investigational device exemption (IDE) trials despite previously stating intentions to submit regulatory documents to the U.S. Food and Drug Administration (FDA) by the end of 2013. Thus, we archived the topic in the horizon scanning system in April 2014.

- **Wearable Battery-Powered Exoskeletons (ReWalk and Ekso Systems) for Rehabilitation of Spinal Cord Injury:** Wearable battery-powered exoskeletons consist of a set of computer-controlled, motorized leg braces that allow patients with paraplegia to stand and walk with crutches. In the December 2013 report and earlier potential high impact reports, this topic was deemed by expert comments to have moderately high potential on the high-impact-potential scale because it might offer improved physical and mental health outcomes to patients who have few other options. Experts also thought it would substantially impact staffing models because of training and education required to use the device with patients during rehabilitation. Projected impact was also high because experts thought the cost was high to acquire and maintain the equipment in rehabilitation centers. The Ekso institutional system (Ekso Bionics, Richmond, CA) costs an estimated $130,000. Available since 2011, exoskeleton systems have diffused to at least 36 U.S. rehabilitation centers. Thus, we consider this technology to have passed a tipping point and in April 2014, we archived it in the system for the rehabilitation indication. The devices used exclusively in rehabilitation centers are not subject to FDA regulatory pathways; however, exoskeletons for home use are regulated and continue to be under development by several developers. Thus, for the personal at-home use indication, we are continuing to track the technology in the horizon scanning system and will solicit expert comments on this application of the system. The manufacturer of the ReWalk system (Argo Medical Technologies, Ltd., Yokneam Ilit, Israel) has submitted to FDA an application for a personal-use system for home and community settings; FDA cleared the system under the 510(k) de novo clearance process on June 26, 2014 for personal use. Ekso Bionics is also developing an exoskeleton for home use with anticipated costs of $50,000–$75,000.

Eligible Topics Not Deemed High Impact

Nine eligible topics discussed below in eight summaries were deemed by experts to lack potential for high impact. They include drugs, programs, devices, and a thermal-therapy technique.

- **Alemtuzumab (Lemtrada) for Treatment of Relapsing-Remitting Multiple Sclerosis:** Alemtuzumab (Genzyme Corp., a subsidiary Sanofi, Paris, France), a humanized monoclonal antibody that binds to CD52, previously received FDA approval for treating various lymphomas. Genzyme recently investigated it for treating relapsing-remitting multiple sclerosis, and rebranded it as Lemtrada™. Experts commenting on alemtuzumab concluded that it had no high-impact potential at this time based on results from two pivotal phase III trials. FDA issued a Complete Response Letter to the company in December 2013 based on its initial supplemental biologics license application; in May 2014, Sanofi announced that it had resubmitted a supplemental application for alemtuzumab; FDA accepted the resubmission in June and an FDA response is expected by late 2014.
- **Amygdala Retraining Program for Treatment of Chronic Fatigue Syndrome or Fibromyalgia:** The amygdala retraining program combines techniques from meditation, self-awareness, cognitive restructuring, and hypnosis to interrupt fearful, stress-based responses originating in the amygdala and to replace them with relaxation responses. Ashok Gupta is the program developer, and the program is based on his theory and is administered under his direction through DVDs, online webinars, and in-person seminars. Experts noted that data supporting Gupta's theory or the program's effectiveness are lacking and that clinicians are unlikely to recommend the program. Patients who seek it out would have to pay out-of-pocket and may have difficulty completing the program outside of traditional health care settings and support.

- **Droxidopa (Northera) for Treatment of Symptomatic Neurogenic Orthostatic Hypotension:** Droxidopa (Northera™, Chelsea Therapeutics, Inc., Charlotte, NC) is a norepinephrine precursor that stimulates vasoconstriction, providing symptomatic relief for patients with neurogenic orthostatic hypotension. Experts expressed skepticism of droxidopa's long-term efficacy because published data were based on only a 1-week followup. Experts noted that although acceptance may be high for a subset of patients who are not dissuaded by its side effects, droxidopa does not address the underlying cause, alternatives are available, and compliance may be an issue because droxidopa must be taken three times daily. An ongoing phase III trial with a primary completion date in September 2016 may provide data that alters droxidopa's potential impact.
- **Micro-Bypass Implant (iStent Trabecular Micro-Bypass Stent System) for Treatment of Glaucoma:** The iStent® Trabecular Micro-Bypass Stent System (Glaukos Corp., Laguna Hills, CA) is intended to increase aqueous outflow from the eye's anterior chamber through the Schlemm's canal to reduce intraocular pressure. FDA approved the iStent for marketing in June 2012 for treating mild to moderate open-angle glaucoma when implanted during cataract surgery. Since 2012, the iStent has widely diffused in the U.S. market, including use of multiple stents during one procedure. Experts noted diffusion was likely fueled by easy integration of the device with existing treatment options. However, multiple alternative treatments consisting of different materials or targeting different tissues potentially contributed to its lack of overall high-impact potential.
- **Off-Label Mexiletine for Treatment of Nondystrophic Myotonia:** Off-label use of mexiletine, a class Ib anti-arrhythmic medication, for treating myotonic symptoms in patients with various forms of nondystrophic myotonia (NDM), was considered to have no high-impact potential currently because, experts noted, many clinicians already accept mexiletine as a first-line treatment for many patients with NDM. Thus, it has passed its tipping point, and experts indicated that recent positive clinical trial data were not likely to further alter prescribing of off-label mexiletine for this indication.
- **Pimavanserin for Treatment of Parkinson's Disease Psychosis:** Pimavanserin is a selective serotonin 2A ($5\text{-}HT_{2A}$) receptor inverse agonist being developed to treat Parkinson's disease psychosis. Although pimavanserin's manufacturer stated that FDA agreed that its phase III clinical trial data were sufficient for a planned late-2014 new drug application, experts indicated that this intervention lacked high-impact potential because of the drug's inconsistent efficacy profile and lack of clear superiority to antipsychotic medications already commonly prescribed for this indication.
- **Pridopidine (Huntexil) for Treatment of Huntingdon's Disease:** Experts commenting on pridopidine (Huntexil®), a dopaminergic stabilizer for treating symptoms of Huntington's disease, considered this intervention to have no high-impact potential because in 2011, FDA rejected NeuroSearch's phase III trial results as insufficient and requested additional late-phase data. Development rights to pridopidine were subsequently sold by NeuroSearch a/s (Ballerup, Denmark) to Teva Pharmaceutical Industries, Ltd. (Petah-Tikva, Israel) in 2012. No new phase III trials investigating pridopidine for this indication have been planned.
- **Real-Time MRI-Guided Laser Interstitial Thermal Therapy for Epilepsy:** Real-time MRI-guided laser interstitial thermal therapy (MRgLITT) first received FDA approval in 2007; recently, neurosurgeons have utilized this technique to treat selected patients who have medically refractory epilepsy. Results from case studies and aggregated data from facilities that have performed the surgery in multiple patients have reported some evidence of MRgLITT superiority over traditional epileptic foci-resections in reducing seizure rates

and inpatient recovery time. However, experts evaluating this intervention concluded that it lacked high-impact potential, noting lack of coverage, high cost of the procedure for patients, significant infrastructure burden required to offer the procedure, low likelihood of diffusion, and lack of sufficient data from clinical trials.

Potential High-Impact Topics

Below are the 10 topics that, according to experts' comments, have high-impact potential. They are drugs and devices used in treating the wide range of conditions in this priority area. These conditions are grouped as central nervous system conditions, genetic disorders, renal disorders, sensory disorders, and spinal cord injury.

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

- **Key Facts:** For many patients with relapsing forms of multiple sclerosis (MS), available treatments do not appreciably relieve symptoms or are intolerable. No effective treatments are available to halt long-term disease progression. Biogen Idec International GmbH (Zug, Switzerland), has developed dimethyl fumarate (Tecfidera®), a homogenous fumaric acid ester formulation purported to have immunomodulatory and neuroprotective properties, for treating relapsing forms of MS. Dimethyl fumarate's mechanism of action in treating MS is not known, but its properties may act to minimize relapse rates and reduce active brain lesions hypothesized to contribute to disease progression. For treating MS, the drug is orally administered, twice daily, at a dosage of 120 mg for 7 days, followed by 240 mg maintenance dosages twice daily. In two completed clinical trials, about half as many patients administered dimethyl fumarate experienced relapses as patients administered placebo. Long-term safety and efficacy studies are ongoing.

  Dimethyl fumarate received FDA approval in March 2013 for treating adult patients with relapsing forms of MS. A U.S.-based, online aggregator of prescription-drug prices indicates that a 30-day supply costs approximately $5,200–$5,400. The manufacturer offers an assistance program, ActiveAccess™, waiving the drug's co-payment for patients who meet eligibility criteria. Many third-party payers include the drug in their formularies as a specialty pharmaceutical requiring prior authorization and the presence of certain conditions (such as treatment failure with interferon therapies) and imposing quantity limits. By March 2014, just 1 year after dimethyl fumarate's approval, market analysts determined that the drug led market share among oral medications for relapsing forms of MS.
- **Key Expert Comments:** Experts agreed a significant need exists for safer, effective treatments for this indication and concluded that dimethyl fumarate could address this need for patients who failed to adequately respond to other treatment options. Experts also noted that reported data for dimethyl fumarate demonstrate improved adverse-event profiles compared with other treatment options but suggested that dimethyl fumarate's side effects might limit acceptance and use somewhat. As an orally administered treatment, dimethyl fumarate would be widely accepted by both clinicians and patients, experts thought. They thought the drug could potentially both reduce reliance on infusion centers and lessen or delay overall care burdens and need for long-term care facilities by slowing disease progression. However, experts cited a need for long-term comparative efficacy and safety data on the drug; these issues may be addressed by ongoing long-term clinical trials.
- **Potential for High Impact:** Lower end of the high-impact potential range

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

- **Key Facts:** FDA-approved oral drugs are not available as first-line treatment of Gaucher's disease, an orphan disease affecting an estimated 6,000 patients in the United States. The current treatment option is intravenous (IV) enzyme replacement therapy (ERT). ERT costs between $200,000 and $500,000 per patient per year (depending on the brand used and patient weight) and is inconvenient for patients because it requires IV infusions every 2–3 weeks lifelong. If approved, eliglustat tartrate (Cerdelga™) may provide an orally administered alternative. The drug, developed by the Sanofi subsidiary Genzyme (which also markets IV ERT), is under study as a first-line treatment for Gaucher's disease type I. Eliglustat tartrate purportedly partially inhibits the enzyme glucosylceramide synthase, resulting in reduced glucosylceramide. Three fully enrolled phase III trials of eliglustat tartrate are ongoing. In these trials, the drug has been administered in 50, 100, or 150 mg doses, twice daily. Positive interim-analysis data have been reported from two of these trials. In December 2013, FDA granted priority review to the manufacturer's new drug application and a decision is expected in mid-2014. Pricing for the drug is not known, but is anticipated to be comparable to IV ERT.
- **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 delaying disease progression. Experts anticipated widespread adoption of eliglustat tartrate, if approved, because of its convenience and favorable side effect profile thus far. Furthermore, experts suggested eliglustat tartrate adoption would reduce the need for 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. Experts commented before FDA's decision.
- **Potential for High Impact:** Moderately high

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

- **Key Facts:** Morquio A syndrome is a very 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 children, deficiencies in this enzyme are caused by mutations to the N-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) gene. A progressive syndrome, it leads to accumulation of KS in bone, tendons, connective tissue, cornea, urine, and synovial fluid. KS accumulation causes symptoms affecting 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 neurosensitive hearing loss. The life expectancy of affected children depends on symptom severity; the most severely affected children may survive only until 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. As a GALNS ERT, elosulfase alfa purportedly provides a pharmaceutical intervention to prevent or alleviate symptoms of Morquio A syndrome. In completed clinical trials, pediatric patients who were given weekly IV infusions demonstrated some improvement on two measures of locomotive function. The most commonly reported adverse events included fever, vomiting, headache, nausea, and abdominal pain. Additional clinical trials are ongoing, investigating elosulfase alfa's long-term treatment efficacy among patient subgroups.

FDA approved the drug in February 2014. The approved dose protocol is for weekly infusions of 2 mg/kg, 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). Through the first quarter of 2014, the manufacturer reported that 50 patients were receiving elosulfase alfa, and the company has had about $900,000 in sales. The company also has stated that many third-party payers are including the drug on their specialty pharmaceutical formularies and require prior authorization.

- **Key Expert Comments:** Experts commenting on elosulfase alfa noted that it is the only approved medication for treating Morquio A syndrome and may address an unmet need for some patients by providing nonsurgical intervention for some symptoms. Experts also remarked that data from completed clinical trials did not demonstrate significant and consistent efficacy across all patients, with many patients failing to respond to the therapy. Additionally, experts stated that the ERT's high-impact potential on health outcomes may be limited by its very high cost and that fact that this intervention does not cure the syndrome. Based on this input, our overall assessment is that this intervention has moderate high-impact potential.
- **Potential for High Impact:** Moderately high

RenalGuard for Prevention of Contrast-Induced Nephropathy

- **Key Facts:** In patients with chronic kidney disease, contrast-induced nephropathy (CIN) that occurs from undergoing an imaging procedure is a common cause of acute renal dysfunction or failure. CIN can occur after contrast media is administered during an imaging procedure such as computed tomography. Many CIN cases are not identified until 48–72 hours after contrast media exposure. When CIN occurs, the only treatment available is hydration and avoidance of additional nephrotoxic agents. The RenalGuard System is under development by PLC Systems, Inc. (Milford, MA), as a preventive measure for patients at risk of developing CIN while undergoing an imaging procedure that uses contrast media. RenalGuard purportedly reduces CIN risk by reducing contrast-media effects on the kidneys. The system replaces fluid, actively synchronizing a patient's urine output with sterile saline solution IV infusion. Inducing high urine-flow rates purportedly limits contrast exposure time and maintains renal blood flow, thereby limiting hypoxia from endothelin-mediated vasoconstriction. High urine flow also accelerates duct flow via reduced sludging and reduced contrast material precipitation in renal tubular cells. Two phase III trials and one phase IV trial are ongoing. Two additional 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 RenalGuard System is not yet FDA approved; a phase III pivotal trial is ongoing to support the planned premarket approval application filing. The manufacturer received Conformité Européene (CE) mark for the system in December 2007 allowing marketing in Europe. Costs of using the system are not available, but would include the cost of the RenalGuard equipment used during an imaging procedure.
- **Key Expert Comments:** Experts unanimously agreed on the importance of preventing CIN, because no effective treatment is available. Overall, experts thought RenalGuard represents

a viable option for clinicians to reduce the risk of CIN in patients at high risk of developing chronic kidney disease or who already have it. The intervention would also increase access to imaging procedures using contrast media among patients at high risk of developing CIN. Experts thought RenalGuard would face very few barriers to adoption and could be easily implemented into the existing infrastructure.

- **Potential for High Impact:** 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 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, 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. The system is not yet FDA approved, but received the CE mark in Europe in 2010. FDA granted orphan drug designation and priority review status for the system. The company stated that the proposed indications in the new drug application are for treating keratoconus and corneal ectasia after refractive surgery, both of which are orphan drug indications. In trials supporting the application, patients who received CXL had significantly improved uncorrected and corrected distance visual acuity and maximum keratometry values 1 year after treatment. In March 2014, FDA sent a complete response letter to the manufacturer requesting more information. The manufacturer stated it would work with FDA to submit the requested information and continue to pursue approval. Cost information for the U.S. market is not yet available; however, 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.

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

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

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

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

- **Key Facts:** The leading cause of preventable monocular vision loss in children is amblyopia, which is most often caused by strabismus. Early amblyopia detection can be difficult because standard screening methods lack sufficient sensitivity and specificity, thereby missing children who should be referred for further evaluation and possible

treatment. The Pediatric Vision Scanner (PVS) is under development by REBIScan, Inc. (Cambridge, MA), and is intended for use as a screening tool to enable earlier 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. 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. Three clinical trials evaluated the sensitivity and specificity of PVS. Investigators from the largest and most recently reported PVS trial (2013), in children aged 2–6 years, reported that "PVS correctly identified 144 of 147 children with strabismus and/or amblyopia; sensitivity=98% (95% CI [confidence interval]: 95-100%)… [and] correctly identified 89 of 102 control children; specificity=87% (95% CI, 79%-96%)." FDA has determined PVS to be a nonsignificant risk device. This means 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 cost of device use is not available, but its use is not expected to be costly.

- **Key Expert Comments:** 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 early diagnostic capabilities of 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. They also suggested that use would be fueled by parent and caregiver awareness and demand for the screening tool.
- **Potential for High Impact:** Moderately high

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

- **Key Facts:** Medications or devices have not been available to restore lost vision 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. FDA approved for marketing Argus II in February 2013 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.
- **Potential for High Impact:** 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 non-24. 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. (2013), 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, D.C.) new drug application. FDA approved the drug for marketing in January 2014; the brand name is Hetlioz™. According to a U.S.-based, online aggregator of prescription-drug prices, tasimelteon costs about $60,000 per patient per year. Several third-party payers have listed the drug in their formularies as a specialty pharmaceutical requiring prior authorization and quantity limits.
- **Key Expert Comments:** Overall, tasimelteon's cost will likely make the drug's biggest impact on the health care system, experts agreed. The manufacturer has aggressively marketed tasimelteon in direct-to-consumer advertising, and 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 thought the effects are likely to have much less impact because of the small amount of data and modest improvements in sleep and waking times.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Spinal Cord Injury Intervention

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. (2013), 11 patients with spinal cord injuries performed mobility and computer-based communication tasks up to three times faster with TDS compared to 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 to support system development. 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 expert commenters 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 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.
- **Potential for High Impact:** Moderately high

Central Nervous System Disorder Intervention

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

Unmet need: Multiple sclerosis (MS) is a demyelinating disorder ranked as the most common disabling neurologic disease among young adult Americans. Researchers hypothesize that MS has an underlying autoimmune etiology.[1] The relapsing form of MS is the most frequently diagnosed form, affecting about 85% of patients with an MS diagnosis.[2]

As MS progresses, symptoms broadly affect motor, sensory, cognitive, and sexual functioning.[3,4] Available first-line MS treatments act as immunomodulators that attempt to treat the disease by dampening autoimmune responses against patients' central nervous systems.[5] However, many patients do not respond adequately to available therapies (e.g., interferons), or are unable to tolerate their side effects. Additionally, no available treatments have been shown to stop long-term disease progression.[1,6-8] An unmet need exists for safe, effective therapies for treating symptoms and minimizing disease progression and relapses in patients with relapsing forms of MS.

Intervention: Dimethyl fumarate (Tecfidera®) is a homogenous fumaric acid ester formulation purported to have immunomodulatory and neuroprotective properties. The drug's mechanism of action in treating MS is unclear, but evidence from multiple lines of research presents a possible pharmacologic pathway.[9] In humans, dimethyl fumarate increases expression of Nrf2, a transcription factor shown to upregulate cellular antioxidant pathways. Nrf2 upregulation modulates the cellular redox system, leading to an increase in both reduced and intracellular glutathione. Researchers suggest that this modulation could, in turn, protect neurons and astrocytes from oxidative stress during inflammatory processes.[10,11] These changes purportedly inhibit nuclear translocation of the proinflammatory transcription factor nuclear factor kappaB (NF-κB), potentially inhibiting downstream proinflammatory signaling in immune cells.[12] These anti-inflammatory and neuroprotective effects may reduce the number of active brain lesions thought to promote MS progression.[13,14]

For treating MS, dimethyl fumarate is orally administered at a dose of 120 mg, twice daily for 7 days, followed by a maintenance dose of 240 mg, twice daily.[14]

Clinical trials: Two large clinical trials, the DEFINE and CONFIRM studies, are investigating the effects of dimethyl fumarate on relapsing forms of MS. In the DEFINE study (n=1,234), the estimated proportion of patients with relapsing-remitting MS who experienced a relapse was significantly lower among patients receiving twice- or thrice-daily dimethyl fumarate compared with patients in the placebo group (27%, 26% and 46%, respectively, $p<0.001$). Annualized relapse rates after 2 years were significantly lower among patients receiving twice- or thrice-daily dimethyl fumarate than with patients given a placebo (0.17, 0.19, 0.36, respectively, $p<0.001$).[13] Subsequent subgroup analyses also revealed that dimethyl fumarate administration reduced the risk of disability progression at 2 years compared with placebo in most subgroups of patients treated with the twice-daily protocol and in all subgroups treated with the thrice-daily protocol.[15]

In the CONFIRM study (n=1,417), researchers compared twice- and thrice-daily dimethyl fumarate administration with glatiramer acetate and placebo in patients with relapsing-remitting MS. After 2 years, annualized relapse rates of twice-daily and thrice-daily dimethyl fumarate and glatiramer acetate groups were significantly lower than those of the placebo group (0.22, 0.22, 0.29, 0.40 respectively).[14] Subgroup analyses also found annualized relapse rate reductions of 34% to 53% for twice-daily dimethyl fumarate, and 13% to 67% reductions for thrice-daily dimethyl fumarate.[16] Side effects were noted as mild and reversible, with flushing, gastrointestinal symptoms, and nausea as the most commonly reported side effects.[14]

As of June 2014, 12 U.S.-based clinical trials were ongoing on dimethyl fumarate's safety and efficacy.[17-28]

Manufacturer and regulatory status: Biogen Idec International GmbH (Zug, Switzerland) developed and manufactures dimethyl fumarate. In March 2014, FDA approved the drug for treating adult patients with relapsing forms of MS.[9,29]

Diffusion and cost: A June 2014 query of a U.S.-based, online aggregator of prescription-drug prices found costs for a 30-day supply of dimethyl fumarate ranging from about $5,200 to $5,400.[30] However, for qualifying patients with prescription drug insurance, a manufacturer-sponsored program, ActiveAccess,™ waives monthly copayments.[31] Third-party payers generally list the drug on their specialty pharmaceutical formularies and require prior authorization that typically includes conditions, such as documented diagnosis of relapsing-remitting MS and discontinuation of other MS therapies while on dimethyl fumarate. Other conditions of coverage also may include documented contraindication or intolerance or allergy or failure of older MS therapies, such as interferon.

In March 2014, Decision Resources Group, a private health care analysis company, reported that for oral MS medications, dimethyl fumarate was the market leader for relapsing forms of MS, with a 42% higher weighted market share than fingolimod, its closest competitor (10% vs. 7% of overall share, including infusion medications); additionally, a clinician survey also rated dimethyl fumarate as the preferred second-line disease-modifying therapy for the same indication.[32]

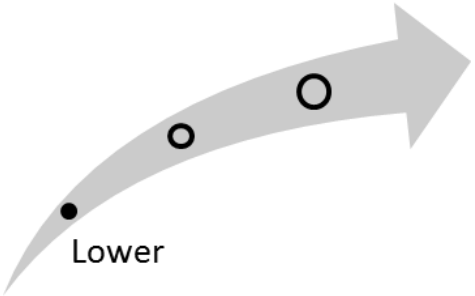
Clinical Pathway at Point of This Intervention

In MS, demyelination, caused by inflammation or scarring, reduces nerve signaling and functioning throughout the body. Symptoms vary and can include numbness or weakness in the limbs; partial or complete central vision loss, optic neuritis, and double or blurred vision; pain; electric-shock sensations that occur with specific head movements; tremor or unsteady gait; slurred speech; fatigue; and dizziness.[33,34] The severity and location of nerve damage at the time of symptom onset determine which symptoms manifest; about half of patients with MS experience some degree of cognitive impairment.[35]

Four types of MS have been identified, including three relapsing forms: relapsing-remitting; secondary-progressive; progressive-relapsing; and the non-relapsing form, primary-progressive.[36-38]

Typical treatments focus on strategies to reduce attack frequency and functional limitations and to delay disease progression.[33] Although several medications are available to treat MS, none offer a cure or consistently demonstrate effectiveness in slowing or halting disease progression, and many have serious side effects.[35] Dimethyl fumarate competes with injectable natalizumab (Tysabri®) and glatiramer acetate (Copaxone®) and two other oral medications, fingolimod (Gilenya®) and teriflunomide (Aubagio®).[6,39-41]

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



Experts agreed a significant need exists for safe treatments for relapsing forms of MS, and thought dimethyl fumarate could meet this need for patients unsuccessfully treated with other

interventions. Although side effects appear to be less severe than other available treatments, experts noted that dimethyl fumarate's observed side effects could limit its use. Because it is an oral medication, dimethyl fumarate would be widely accepted by both clinicians and patients, experts thought, anticipating that adoption could reduce the need for infusion centers. Experts also repeatedly noted a need for long-term and comparative safety and efficacy data for this drug to accurately compare it with other treatments that have a longer-term safety profile. 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.[42-47] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need exists for additional safe, effective treatments for relapsing forms of MS, experts agreed. Although dimethyl fumarate offers an additional option for patients whose MS is unresponsive to other treatments, some experts noted that, as one of many options, the drug would provide an incremental benefit overall. Experts also agreed that dimethyl fumarate has substantial potential to improve health outcomes in some patients with relapsing forms of MS, particularly those in need of treatment options after previous ineffective treatments. However, the drug's reported gastrointestinal adverse events divided experts' opinions on the true impact on health outcomes. Some experts considered these adverse events to be insignificant, while others anticipated that they would deter use. Multiple experts recommended additional studies comparing dimethyl fumarate with other drugs used to treat relapsing forms of MS.

Acceptance and adoption: Dimethyl fumarate would be widely adopted by both clinicians and patients, thought experts, citing its oral administration and reduced need for clinician monitoring as factors increasing its potential for acceptance. However, the intervention's reported gastrointestinal side effects and lack of comparative-effectiveness studies might be potential hindrances to adoption, thought some experts. Also, one expert with a research perspective cautioned that dimethyl fumarate's simplified treatment protocols may lead to overprescription, relative to other MS treatments.[45]

Health care delivery infrastructure and patient management: As an oral medication, experts commented, adoption could reduce infrastructure needed and patient management associated with infusion centers and shift care from that setting to home care.

Health disparities: Overall, dimethyl fumarate would have little impact on health disparities, concluded experts. One expert with a research perspective noted that the higher MS prevalence among women might lead to women benefitting most from the drug's availability.[45]

Genetic Disorder Interventions

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

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. 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 standard of care.[48] Eliglustat tartrate is being developed as a first-line oral therapy and is also intended to have fewer side effects than miglustat, which is known to cause 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.[49] A temporary break from ERT due to personal issues or changes in lifestyle can lead to disease progression.

Intervention: Eliglustat tartrate (Cerdelga™), a self-administered oral compound, is under investigation as first-line treatment for Gaucher's disease. The drug purportedly partially inhibits the enzyme glucosylceramide synthase to reduce glucosylceramide production.[50,51] Various dosage regimens are being compared in trials as follows: 50, 100, or 150 mg doses, twice daily (ENGAGE, ENCORE trials)[52,53] and 50 or 100 mg twice-daily doses (EDGE trial).[54]

Clinical trials: Three phase III trials are ongoing;[52-54] positive interim-analyses have been reported from two of them.[50] One of these is from the ENCORE trial (n=160), which is evaluating the percentage of patients who remain stable while taking eliglustat tartrate. Reported interim results derive from the first 52 weeks of the study. A manufacturer press release reported the following:[55]

> Eliglustat tartrate met the pre-specified criteria for non-inferiority to Cerezyme [imiglucerase], with the majority of patients in both groups remaining stable one year after randomization (84 percent of eliglustat tartrate patients and 94 percent of Cerezyme patients). In an additional, pre-specified, efficacy analysis of the percent change in spleen volume from baseline, a mean change of minus six percent was observed in the eliglustat tartrate arm compared with minus three percent in the Cerezyme arm. This analysis also met the criteria for non-inferiority.

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:[55]

> 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: Eliglustat tartrate is under development by Genzyme Corp., a U.S.-based subsidiary of Sanofi (Paris, France), for treating type 1 Gaucher's disease.[51] FDA granted priority review to the manufacturer's new drug application (NDA) and set a decision date for June 11, 2014, but no decision or further information was released on that date.

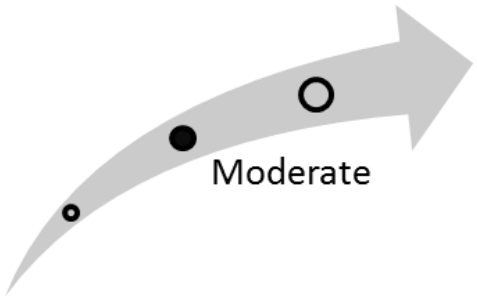
Diffusion and cost: If approved, diffusion among the intended patient population is expected to be brisk, because it would be the first oral treatment available; however, cost might affect access for patients without prescription drug insurance or with high copayments. As the first orally

administered, long-term therapy, eliglustat tartrate is anticipated to have high cost, and formulary coverage as a specialty pharmaceutical requiring preauthorization and quantity limits is expected. However, because eliglustat tartrate is not yet FDA approved, no actual cost, coverage, coding, or payment information is available.

Clinical Pathway at Point of This Intervention

ERT (e.g., imiglucerase, taliglucerase alfa) is the standard first-line treatment for Gaucher's disease.[56] 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.[57] Miglustat frequently causes side effects, such as diarrhea, abdominal swelling, tremor, and weight loss, that affect patient acceptance. The associated clinical improvements are reported to be less effective and slower than that of ERT.[56]

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



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 slowed disease progression. Experts anticipated widespread adoption if approved, because of its convenience as an oral drug with possibility of once-daily dosing. Furthermore, experts suggested adoption of eliglustat tartrate could reduce the need for 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 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.[58-63] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Patients need a more convenient and well-tolerated treatment for Gaucher's disease, experts suggested. The convenience of eliglustat tartrate, experts noted, could increase patient adherence with treatment, leading to better health outcomes and lessening the risk of disease progression. The ease of incorporating an oral therapy, rather than using standard bi-weekly IV infusion of ERT, could positively impact quality of life, experts thought. However, experts also called for more comparative-effectiveness data to compare eliglustat tartrate with IV ERT. One expert with a health systems perspective questioned the potential overall benefit of the oral therapy, stating, "it is unclear whether there is any advantage to eliglustat [tartrate] over ERT in terms of safety, efficacy, and cost."[62] This expert proposed that these

parameters would be important factors influencing the ability of eliglustat tartrate to fulfill the unmet need in Gaucher's disease treatment.[62]

Acceptance and adoption: Clinicians would readily accept a more convenient treatment for patients with Gaucher's disease, experts unanimously agreed. Potential for increased compliance is an important factor contributing to clinician acceptance, experts noted. However, acceptance and adoption is likely contingent on eliglustat tartrate being proved at least as effective as the standard of care, experts remarked. Experts anticipated patients would also welcome an oral treatment over bi-weekly IV infusions if efficacy and safety were similar.

Health care delivery infrastructure and patient management: If adopted, eliglustat tartrate could reduce the demand for and burden on infusion centers, experts noted. Experts suggested eliglustat tartrate could shift the care setting from infusion centers to home care. One clinical expert noted that treatment convenience might also allow for a shift in some of the aspects of patient management and monitoring from specialist care to primary care.[61]

Experts were unclear on the cost impact of eliglustat tartrate. One expert with a research perspective noted that widespread adoption of a first-line oral therapy could reduce costs over time if a generic version became available.[59] Another clinical expert suggested potential for cost savings exists because of increased patient adherence with treatment, which could lead to fewer complications and emergencies and could reduce infusion-center staffing demands.[61]

Health disparities: Eliglustat tartrate would have only a small effect on health disparities overall because of the rarity of the disorder, concluded experts, although its cost might limit access for some patients, and thereby create a disparity.

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

Unmet need: Mucopolysaccharidosis type IV A, more commonly called Morquio A syndrome, is a very 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).[64,65] Deficiencies in this enzyme are caused by mutations to the N-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) gene. Diagnosis usually occurs early in childhood. The syndrome is progressive and affects mainly the skeletal system; it leads to accumulation of KS in bone, tendons, connective tissue, cornea, synovial fluid, and urine.[65-67] Accumulated KS causes symptoms affecting 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.[66,68] The life expectancy of affected children depends on the severity of symptoms; the most severely affected children may survive only until late childhood or adolescence.

The standard of care for Morquio A syndrome is palliation of symptoms, including corrective orthopedic surgeries, hearing and visual aids, and assisted mobility devices.[66,69] Disease progression can create the need for multiple surgeries, particularly when symptoms severely affect respiratory function. As a GALNS enzyme replacement therapy (ERT), elosulfase alfa purportedly provides a pharmaceutical intervention to prevent or alleviate symptoms of Morquio A syndrome.

Intervention: Elosulfase alfa (Vimizim™) is a purified human form of GALNS created to mediate cellular uptake of lysosomes and subsequently hydrolyze sulfate from nonreducing ends of glycosaminoglycans.[70,71] This functionality replaces the missing or defective *GALNS* gene.[70,72] As an exogenous source of GALNS, elosulfase alfa is intended to prevent or treat functional symptoms by stimulating catabolism of accumulated KS products.[68,70]

Clinical trials: In an ongoing phase III, randomized controlled extension trial (n=176), patients with Morquio A syndrome were administered 2.0 mg/kg elosulfase alfa weekly, 2.0 mg/kg elosulfase alfa every 2 weeks, or placebo. At 24 weeks, only weekly elosulfase alfa administration met the primary endpoint of improving patient ambulation compared with placebo, measured by 6-minute walk (estimated mean effect, 22.5 meters; 95% confidence interval [CI], 4.0 to 40.9; p=0.017) and 3-minute stair climb tests (estimated mean effect, 0.5 meters; 95% CI, -17.8 to 18.9; p=0.954). Normalized urine KS levels were reduced in both treatment groups compared with placebo. Among patients receiving weekly elosulfase alfa doses, 22.4% reported infusion-related adverse events, representing 1.3% of infusions received; no adverse events led to patients discontinuing treatments.[73] These results were similar to two reports from other completed trials enrolling smaller patient populations.[74,75]

An ongoing phase II randomized controlled trial (n=15) also reported preliminary efficacy results in pediatric 5 years of age or younger. After 26 weeks, study authors reported that eight patients receiving weekly 2.0 mg/kg elosulfase alfa infusions decreased normalized urine KS levels by 35.2% (standard deviation, 15.57%).[76]

Six clinical trials, including two extension studies, are ongoing, further evaluating the ERT's efficacy in reducing KS accumulation and increasing ambulation for these patients.[17,77-81]

Manufacturer and regulatory status: Elosulfase alfa is manufactured by BioMarin Pharmaceutical (Novato, CA). In February 2014, elosulfase alfa received FDA marketing approval for treating Morquio A syndrome.[82] The company notes on its Web site and in its prescribing information, "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."[83]

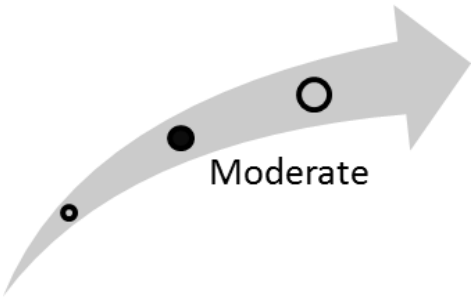
Diffusion and cost: BioMarin Pharmaceutical announced that elosulfase alfa would be priced at $1,069 per 5 mL vial. The annual per-patient cost for this treatment is about $380,000, assuming a pediatric patient weight of approximately 22.5 kg (49 pounds).[84] Dosage recommendations for elosulfase alfa depend on body weight, however, so per-patient costs could be higher.[70]

The manufacturer's 2014 first-quarter financial report listed $900,000 in sales for elosulfase alfa through March 31.[85] BioMarin chief executive officer, Jean-Jacques Bienaimé, noted that during that quarter, 50 patients were already receiving commercial elosulfase alfa, with 120 patients referred to the company's physician and patient services channel. Bienaimé also remarked that this diffusion rate was greater than that of galsulfase, the company's mucopolysaccharidosis type VI drug, which has been commercially available for 9 years.[85] The company has stated that many third-party payers are including the drug on their specialty pharmaceutical formularies and require prior authorization.[85]

Clinical Pathway at Point of This Intervention

Palliative care, including surgeries to alleviate patient's associated musculoskeletal, cardiovascular, respiratory, visual, oral, and auditory symptoms, is the standard treatment for Morquio A syndrome.[86,87] Upper cervical spine fusion is among the most commonly used palliative surgical procedures, employed in childhood to prevent further spinal damage, compression, and paralysis.[68,86] Elosulfase alfa is the only medication with FDA approval 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, experts thought that elosulfase alfa might effectively address an unmet need for some patients. Several experts also noted that clinical trial results thus far did not adequately demonstrate significant efficacy across all patients. They also noted this medication's high cost and thought that some third-party payers might not cover it and that cost could limit patient access. 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 and research backgrounds, provided perspectives on this intervention.[88-93] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Elosulfase alfa, as the only approved nonpalliative intervention for treating Morquio A syndrome, has significant potential to address an unmet need, experts thought. However, they were less enthusiastic regarding elosulfase alfa's potential to

improve patient health outcomes, given the data thus far. Two experts with a research perspective noted shortcomings in the reported clinical trial data, which showed no or modest improvement in patients' functional ability after treatment with elosulfase alfa.[88,93] Another expert stated that long-term efficacy data were needed to consider this intervention as significantly improving patient health outcomes.[92] Overall, expert consensus was that elosulfase alfa had moderate potential to improve health outcomes in some patients.

Acceptance and adoption: As the first nonsurgical intervention for Morquio A syndrome, elosulfase alfa would be widely adopted by clinicians and by patients who could afford the drug, the experts unanimously agreed.

Health care delivery infrastructure and patient management: As an infusion treatment, the experts' consensus is that elosulfase alfa use would have little impact on health care delivery infrastructure. Weekly infusion protocols would replace physical therapy sessions, and possibly reduce the need for surgeries and other palliative care measures.

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

Renal-Protection Intervention

RenalGuard for Prevention of Contrast-Induced Nephropathy

Unmet need: Contrast-induced nephropathy (CIN) is a common cause of acute renal dysfunction that occurs (in the absence of other causes) after contrast media is administered to patients with chronic kidney disease (CKD) or who have a risk of CIN or acute kidney injury (AKI) during a surgical procedure.[94] Many cases are not identified until 48–72 hours after contrast media exposure, and the only treatment available is hydration and future avoidance of nephrotoxic agents.[95] Because no treatment for CIN exists, the primary goal is prevention in patients known to be at risk.[96]

Intervention: The RenalGuard® System consists of a console and a single-use set for infusion of a sterile solution and urine collection. The infusion set connects to a standard IV catheter, and the urine-collection set connects to a patient's Foley catheter. According to the manufacturer, the console measures the urine volume in the collection set and infuses a volume of hydration fluid to match the patient's urine output. Proprietary, patented software and electronic weight measurements control the rate at which fluid is infused as urine output is monitored. The RenalGuard System is under investigation to reduce the risk of CIN in patients with CKD, in patients who have known risk factors for CIN and need to undergo imaging with contrast media, or in patients at risk of AKI while undergoing a procedure such as transcatheter aortic valve implantation. The system is intended to minimize the risk of over- or under-hydration, both of which can increase a patient's CIN risk during imaging procedures.[97] Inducing high urine-flow rates purportedly limits contrast exposure time, maintains renal blood flow, limits hypoxia from endothelin-mediated vasoconstriction, and accelerates duct flow through reduced sludging and contrast material precipitation in renal tubular cells.[98] RenalGuard is intended for temporary use (up to 14 days) to maintain intravascular fluid volume in patients at high CIN risk.[99]

Clinical trials: Two phase III trials and one phase IV trial are ongoing, and a fourth trial is registered but not yet recruiting.[100-103] Two phase III trials have been completed (REMEDIAL II and MYTHOS), and study investigators reported positive data from both trials.[98,104-106]

In the REMEDIAL II trial (n=292), patients received care with either the RenalGuard system or IV sodium bicarbonate. Study authors reported, "Contrast-induced acute kidney injury occurred in 16 of 146 patients in the RenalGuard group (11%) and in 30 of 146 patients in the control group (20.5%; odds ratio, 0.47; 95% confidence interval, 0.24 to 0.92)."[98] In the MYTHOS trial (n=170), patients received either furosemide with matched hydration (FMH) (via the RenalGuard) or IV sodium bicarbonate. Study authors reported, "In the FMH group, no device- or therapy-related complications were observed. Four (4.6%) patients in the FMH group developed CIN versus 15 (18%) controls (p=0.005). A lower incidence of cumulative in-hospital clinical complications was also observed in FMH-treated patients than in controls (8% vs. 18%; p=0.052)."[106]

Manufacturer and regulatory status: The RenalGuard System is under development by PLC Systems, Inc. (Milford, MA).[107] RenalGuard has not yet been approved by FDA, and a phase III pivotal trial (n=326) is under way to support a premarket approval filing.[107] The manufacturer received the Conformité Européene (CE) mark for the system in December 2007 allowing marketing in Europe.[108] The company's first-quarter financial results in 2014 were considered to be very disappointing, and the company announced in mid-May 2014 "a series of proposals for our shareholders that would result in PLC merging with a private company, Viveve Medical, Inc. [Sunnyvale, CA], a private commercial stage, medical device company in the field of women's healthcare.... The objective is to avoid bankruptcy or other alternatives that would destroy any value for our shareholders, and instead provide them with the opportunity to participate in the potential growth of a public company in the medical device arena that is better capitalized."[109,110] The impact of this action on ongoing RenalGuard trials was not mentioned in the press releases. Before this

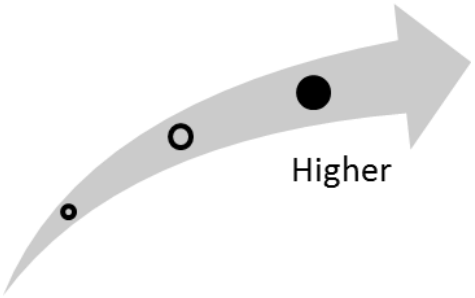
development, some investment analysts had projected that the marketing application for the system would be submitted and considered for approval by FDA in late 2014.

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

Clinical Pathway at Point of This Intervention

No defined standard of care treatment for CIN exists; the primary goal is to prevent the occurrence in patients undergoing imaging procedures requiring contrast who are at high risk of CIN. Periprocedural hydration is often recommended as a simple and effective prevention technique; however, trial data are lacking on whether this approach is effective. Fluids can be administered orally or intravenously; available evidence supports periprocedural hydration, preferably with IV isotonic saline or isotonic sodium bicarbonate solution, without furosemide, mannitol, or dopamine. N-acetylcysteine has had positive results in randomized studies as a preventive therapy in patients at higher risk of developing CIN. However, trial results conflict, using varying procedures, different types and volumes of contrast media, different dosages and timing of N-acetylcysteine administration, and different methods of administration. Overall, limited evidence exists supporting the use of any pharmaceutical agent (e.g., N-acetylcysteine, ascorbic acid, theophylline, fenoldopam, calcium antagonist).[94] Evidence does not support using postprocedural hemodialysis to prevent CIN. If approved in the United States, the RenalGuard System would compete with existing methods of prophylactic hydration to prevent CIN.

Figure 4. Overall high-impact potential: RenalGuard for prevention of contrast-induced nephropathy



Preventing CIN during imaging procedures in patients at high risk (i.e., those with CKD, history of CIN, or AKI) is important, experts unanimously agreed, noting that neither effective prophylaxis nor standard effective treatment is available after CIN occurs. Overall, experts thought RenalGuard seemed like a viable option to reduce the risk of CIN and increase access to imaging that requires contrast media in patients at high risk of developing CIN. Experts thought RenalGuard would face very few barriers to adoption and could be easily implemented into the existing infrastructure. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[111-116] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Overwhelmingly, experts stressed the importance of preventive efforts in the absence of effective treatments for CIN. RenalGuard presents an option for clinicians and patients to minimize risks associated with use of contrast media, noted experts. One expert with a clinical perspective stated, "Preventing acute renal failure is not only important in and of itself, but also may allow some patients the option of having these contrast involved tests that are not able to have them at this time because of the fear of inducing CIN."[113] One expert with a health systems perspective highlighted the novelty of the mechanism of action of RenalGuard in preventing CIN, and another health systems expert noted the possible reduction in morbidity and mortality from CIN if the RenalGuard system were to be implemented.[114,115] Overall, experts called for more data to further support RenalGuard's purported efficacy in reducing CIN incidence, and noted that such data should be forthcoming from ongoing trials.

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

Health care delivery infrastructure and patient management: Experts did not anticipate a major disruption to delivery or infrastructure, largely because of the minimal training and direct patient-care time required for implementation. Overall, experts thought this innovation could be easily implemented. In regards to patient management, experts indicated the system could change patient management by reducing CIN incidence and resulting hospitalizations and followup care. One clinical expert countered that the potential reduction in hospital stays might be offset by an increase in imaging tests using contrast media in patients who were previously ineligible.[113]

Health disparities: Two experts, both with health systems perspectives, suggested RenalGuard has the potential to protect marginalized populations and bridge existing barriers to health and wellness. Both experts noted that preexisting conditions that increase CIN risk are more prevalent in health disparate populations. They thought that using RenalGuard in patients with CKD might therefore increase access to and use of imaging procedures with contrast media to aid diagnosis and treatment protocols.[114,115] The remaining experts did not perceive any issues, one way or another, regarding health disparities.

Sensory Disorder Interventions

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

Unmet need: 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 at this time.

Intervention: CXL is intended to strengthen corneal structure by subjecting it to ultraviolet A (UVA) light after a riboflavin (vitamin B_2) photosensitizing solution has been applied to the cornea. CXL is intended to inhibit the corneal ectasia progression, including keratoconus.[117] 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.[117,118] The procedure is performed in the outpatient setting with the patient awake. Topical anesthesia is used for pain management.[118] 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.[119] However, CXL surgery has also been performed in clinical trials without removing the corneal epithelium.[119,120]

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.[121,122]

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.[123-128] 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.[129] 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 and a weak association with maximum K [keratometry value] and some symptoms were found.[124] 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."[125]

Study investigators further reported on uncorrected distance visual acuity (UDVA), CDVA, and K values at 1 year of 76 patients who underwent CXL treatment (patients were divided into 3 groups based on maximum K location: central cone group, paracentral cone group, and peripheral cone group). Study investigators reported as follows:[126]

> In the combined cohort, maximum K and uncorrected and corrected distance visual acuity significantly improved by -1.60±3.40 diopters (D) (p <0.001), -0.08±0.25 logMAR [logarithm of the minimum angle of resolution] (p=0.001), and -0.10 ±0.18 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.[126]

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)."[127] 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.[130]

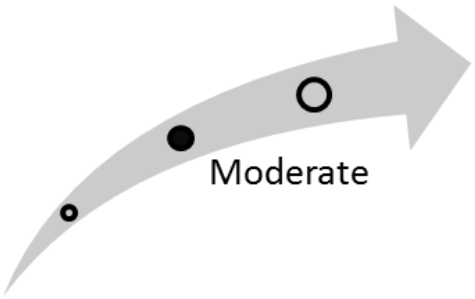
Manufacturer and regulatory status: Avedro, Inc. (Waltham, MA), is developing the system for the U.S. market.[121] The system received a CE mark in 2010 in Europe.[121] In December 2011, the manufacturer announced that FDA had granted orphan drug designation for the system for treating keratoconus and corneal ectasia after refractive surgery.[122] In March 2012, the manufacturer announced that it had submitted an NDA to FDA.[122] In November 2013, the company announced that FDA had granted priority review status for the system. 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.[131] In March 2014, FDA sent a complete response letter to the manufacturer requesting more information. The manufacturer stated it would work with FDA to submit the requested information and continue to pursue approval.[132]

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 at about $3,500 per eye.[133] Although not available in the United States, the Avedro KXL machine reportedly costs approximately $35,000 in markets outside the United States.[133]

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.[117] 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 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.[134-139] 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.[135] 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 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.[135] 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 intensive 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 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.

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

Unmet need: The efficacy of traditional vitreoretinal surgery for symptomatic vitreomacular adhesion (VMA) is limited by the potential for incomplete vitreoretinal separation and/or removal, complications (e.g., cataract development), and high costs.[140] Therefore, nonsurgical methods are needed that could replace or complement VMA surgery.[141] Ocriplasmin (Jetrea®) is intended as a medical option for VMA.

Intervention: Ocriplasmin is a truncated form of plasmin produced using recombinant methods in a yeast (*Pichia pastoris*) expression system.[142] Recombinant ocriplasmin retains the catalytic characteristics of human plasmin and is purported to have several advantages as a therapeutic agent, including sterility, increased stability over plasmin, and smaller molecular size, allowing for greater epiretinal tissue penetration.[140,143] Ocriplasmin is provided in a single-use, glass vial at a concentration of 2.5 mg/mL. The recommended dose is a single, 0.1 mL injection at a concentration of 1.25 mg/mL.[144] Clinicians must dilute the solution with sterile sodium chloride before use.[145] Intravitreal injections require a local anesthetic (eye drops) to minimize patient discomfort and an antiseptic solution to prevent contamination when injecting the solution into the eye.[146]

Clinical trials: Completed trials of ocriplasmin have reported positive findings. One phase III trial investigated symptomatic VMA resolution 28 days after injection of 1.25 mg/mL or placebo in 652 different eyes (ocriplasmin=464, placebo=188). Study investigators found the following:[147]

> [VMA] resolved in 26.5% of ocriplasmin-injected eyes and in 10.1% of placebo-injected eyes (P<0.001). Total posterior vitreous detachment was more prevalent among the eyes treated with ocriplasmin than among those injected with placebo (13.4% vs. 3.7%, p<0.001). Nonsurgical closure of macular holes was achieved in 40.6% of ocriplasmin-injected eyes, as compared with 10.6% of placebo-injected eyes (p<0.001). The best-corrected visual acuity was more likely to improve by a gain of at least three lines on the eye chart with ocriplasmin than with placebo.

In both completed phase III trials of ocriplasmin, treatment was generally safe and well tolerated. In particular, no increased risk of retinal tear or detachment was associated with ocriplasmin treatment.[148] The manufacturer's prescribing information states that the most commonly reported adverse reactions, with incidence of 5% or more, include vitreous floaters, conjunctival hemorrhage, eye pain, photopsia, blurred vision, macular hole, reduced visual acuity, visual impairment, and retinal edema.[145]

Manufacturer and regulatory status: Ocriplasmin was developed by ThromboGenics NV (Heverlee, Belgium).[149] In October 2012, FDA approved ocriplasmin for treating symptomatic VMA.[150] Ocriplasmin became available in the United States in January 2013.[149]

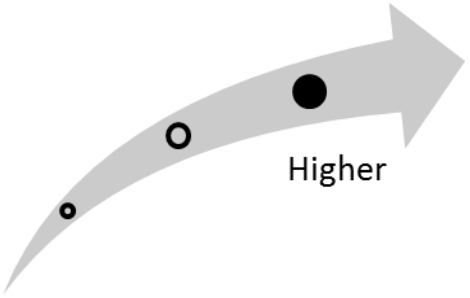
Diffusion and costs: According to the manufacturer at the time of ocriplasmin's launch, the price of the single-use vial of ocriplasmin was $3,950.[149] Based on a June 2014 query of a U.S.-based, online aggregator of prescription-drug prices, a 0.2 mL vial of ocriplasmin at 2.5 mg/mL (1 single-use vial) costs on average about $4,250.[151] Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified only 4 payers with policies that provide coverage for ocriplasmin use in treating VMA.[152-155] The remaining seven payers had no policies mentioning Jetrea. In February 2014, Thrombogenics announced "commercial challenges" regarding sales (about 7,000 U.S. patients had been treated with Jetrea since the drug reached the market) and stated it would seek strategic options.[156] Bloomberg News reported that the company was seeking a

buyer[157] and named as contenders Novartis International AG (Basel, Switzerland), which markets the drug outside the United States, and Shire plc (Dublin, Ireland), among others.

Clinical Pathway at Point of This Intervention

Patients with asymptomatic or mildly symptomatic VMA typically undergo watchful waiting, and some cases spontaneously resolve. Patients with significant visual impairment caused by VMA typically undergo vitrectomy (i.e., vitreous removal), an invasive surgery that is the standard of care for symptomatic VMA.[158] Enzymatic vitreolysis with ocriplasmin has the potential to obviate the need for surgery in some patients if it induces a therapeutic posterior vitreous detachment. Additionally, intravitreal ocriplasmin injection has the potential to be used in combination with surgical intervention; ocriplasmin given in the days leading up to surgery could make difficult vitreoretinal surgical procedures easier to perform by essentially priming regions of vitreoretinal adherence for detachment.[159]

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



Experts commenting on this intervention suggested ocriplasmin has potential to fulfill the significant unmet need for minimally invasive treatment for VMA. Furthermore, experts anticipated ocriplasmin could reduce the need for invasive surgery, reducing associated risks of surgery. The minimally invasive nature of ocriplasmin, experts agreed, would facilitate clinician and patient acceptance and adoption. If adopted, experts thought, ocriplasmin could shift the care setting for VMA from the surgical center to outpatient care. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.[160-165] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need exists for a less-invasive treatment for VMA, the experts agreed, concluding that ocriplasmin has the potential to address this need. Furthermore, one expert with a health systems perspective indicated that this need will continue to grow as the aging U.S. population continues to expand.[163] Experts also wanted to see long-term efficacy data for this intervention and comparator studies between ocriplasmin and the standard of care, surgery. Available data from randomized controlled trials suggest that the underlying mechanism of action is sound, and these data serve as quantitative proof of the intervention's potential impact, experts noted.

With regard to ocriplasmin's impact on patient health outcomes, experts anticipated that the intervention potentially reduces the need for surgery and avoids its associated adverse events in the

affected population. A clinical expert noted that although ocriplasmin injection has some side effects, they are not as serious as those associated with surgery.[162] Another expert, with a research perspective, stated, "if this technology helps patients retain their visual acuity, it could make a large difference in their health. Loss of visual acuity can lead to other health problems."[164]

Acceptance and adoption: Experts unanimously agreed that both clinicians and patients would readily accept ocriplasmin injections for VMA as a less invasive and safer treatment option than surgery. An expert with a clinical perspective thought that clinicians would eagerly change from a surgical to medical intervention and further noted that the techniques used in ocriplasmin injections are in the realm of the ophthalmologist skill set.[162] This low training barrier would promote clinician acceptance, some experts indicated.

Health care delivery infrastructure and patient management: The treatment paradigm for VMA could shift from an outpatient surgical center to a physician's office for ocriplasmin injection, experts agreed. Most notably, an expert with a health systems perspective indicated that, "it is anticipated that care would shift from a surgical setting to a non-surgical outpatient setting making care more readily available, more cost effective, and possibly making care more available to patients in outlying areas."[164] This paradigm shift may result in patients accessing treatment earlier. Furthermore, experts suggested this change in care delivery could present a cost savings opportunity for clinicians, patients, and payers.

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

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

Unmet need: The leading cause of preventable monocular vision loss in children is amblyopia (lazy eye), which is most often caused by strabismus (misaligned eyes).[166] Early amblyopia detection can be difficult because current standard screening methods, including use of photoscreener instruments, lack sufficient sensitivity and specificity. They either miss cases that should be referred for further evaluation and possible treatment or over-refer cases.[167] 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.[168]

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, PVS simultaneously assesses both eyes to detect both binocular alignment and whether the eyes are focused on a target.[169] PVS performs a 2.5-second scan of the eyes to automatically detect the presence of amblyopia, strabismus, or other serious eye conditions.[168] Testing with 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.[168]

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.[168]

Clinical trials: PVS is under investigation in independent clinical trials.[168] Three registered trials evaluated the sensitivity and specificity of PVS with positive results (sensitivity 98%; specificity 74% to 88%).[170-172] The most recent trial of PVS (compared to SureSight Vision Screener and Randot Preschool Stereoacuity test) enrolled 250 patients 2–6 years of age. Study investigators reported, "The PVS correctly identified 144 of 147 children with strabismus and/or amblyopia; sensitivity=98% (95%CI: 95-100%). The PVS correctly identified 89 of 102 control children; specificity=87% (95% CI, 79%-96%)."[170]

A 2011 study investigated the degree of binocularity of PVS and reported the following:[173]

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

As with any screening tool, the potential for false-positive or false-negative tests results exists with 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, PVS purportedly will reduce the rate of false-positive results associated with other screening methods.[168]

Manufacturer and regulatory status: PVS is under development by REBIScan, Inc. (Cambridge, MA). FDA has determined PVS to be a nonsignificant risk investigational device,[168] 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.[174] Some in the ophthalmology field expect the device to be on the market before the end of 2014.[167]

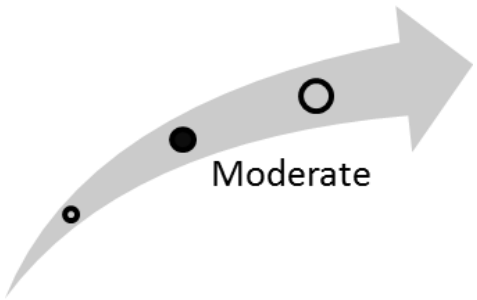
Diffusion and cost: PVS is not yet commercially available in the United States, and its cost, coverage, coding, and payment policies have not yet been established. If it gains FDA approval, PVS testing may be reimbursed by public and private third-party payers in a manner similar to that of other instrumented pediatric vision screening tests that use photoscreening devices, which many insurance companies are now covering under the CPT code for "ocular photoscreening with interpretation and report, bilateral."[167] The reported reimbursement rate is about $25 to $30 per screening. Reported prices for photoscreening devices range from about $4,200 to $7,500.[167]

Clinical Pathway at Point of This Intervention

Amblyopia-associated refractive error is treated with consistent use of corrective lenses.[175] Additionally, any eye condition causing vision problems, such as cataracts, needs to be corrected.[166] Patches and eye-drop treatments are used to force the child to use the nondominant eye, allowing the weak eye to get stronger.[175] Children younger than the age of 5 years 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.[166]

The REBIScan PVS is intended for use as a screening tool for amblyopia and strabismus to allow referral of young children to an ophthalmologist for further evaluation so that treatment can start when the disorder is at a more correctable stage.[168] 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.[166] Both visual acuity testing and photoscreening devices lead to missed diagnoses and false positives leading to unnecessary referrals.[168] The manufacturer has indicated that PVS, if used during annual well-child visits, can reduce expenditures by detecting amblyopia and strabismus in earlier stages and reducing false referrals to specialist care.

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



Overall, experts thought use of PVS in very young children was a significant factor in its potential for fulfilling the unmet need for early diagnostic tools for amblyopia and improving patient outcomes for 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 be fueled by parent awareness and demand for screening. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health devices, health systems, and health administration backgrounds, provided perspectives on this intervention.[176-181] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A need exists for effective early screening tools to identify children needing referral to an ophthalmologist for amblyopia evaluation, the experts agreed. They cited the REBIScan device's applicability to populations younger than 4 years as an important factor in fulfilling this unmet need. Furthermore, experts remarked that the device could meet this need because of its good specificity and sensitivity to guide referral to ophthalmologists that, if followed, allow earlier treatment. Conversely, one expert with a research perspective suggested PVS does not address an unmet need because it does not address the underlying issue of access to care stating, "Adding this to a physician office might improve screening accuracy, but it would not help children who don't get pediatric well visits, for whatever reason."[177]

Experts viewed the purported ability of PVS to aid in early diagnosis of vision problems as important for improving patient health. One expert with a health devices perspective noted that "after the age of 6 or 8, the vision loss [associated with strabismus or amblyopia] is largely permanent, even with surgery, patching therapy, and/or powerful glasses. The sooner the problem can be detected, the proportionally greater chance there is to correct the problem."[181] Overall, the majority of experts agreed the PVS could fulfill a gap in preventive eye screenings and affect the rate at which these issues are fully addressed with earlier diagnosis and treatment.

Acceptance and adoption: The REBIScan PVS device would be widely accepted and adopted because of its ease of use, especially in young children and its noninvasiveness, experts suggested. One expert with a research perspective noted that because other screening methods are associated with low rates of patient cooperation (because of age), PVS, which requires minimal patient cooperation, would be widely used.[181] A health systems expert indicated that "with the low overhead (pending information on device cost) and great benefit of early detection and treatment, this [PVS] would be a must-have for physician/pediatrician offices."[180]

Experts anticipated parent demand for screening would also fuel PVS acceptance and adoption. One health systems expert thought that as testing and outcomes data become more widely publicized, parents of young children may actively seek providers who offer the screening.[180]

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

Health disparities: Overall, experts did not think PVS use had significant potential to affect health disparities. However, one expert with a health systems perspective thought increased disparity might occur, noting that individuals in health disparate populations who do not have access to regular well-child pediatric visits might not have access to the screening tool.[177]

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

Unmet need: RP is relatively rare, occurring in an estimated 1 in 4,000 people in the United States.[182] Medications or devices to restore lost vision due to retinitis pigmentosa (RP) were not available before the development of implantable Argus® II Retinal Prosthesis System. This system purportedly restores a level of vision that allows patients greater independent functioning, although it does not restore ability to see details such as facial features. Argus II is the first FDA-approved, implanted device for treating adults with advanced RP.

Intervention: 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."[183] 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.[184] 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.[185]

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.[186] Patients using the commercial version of Argus II can perceive only black, gray, and white.[187]

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.[186]

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.[188,189] 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:[190]

> The mean ± SD percentage correct letter identification for 21 subjects tested were: letters L, T, E, J, F, H, I, U, 72.3±24.6% system on and 17.7±12.9% system off; letters A, Z, Q, V, N, W, O, C, D, M, 55.0±27.4% system on and 11.8%±10.7% system off, and letters K, R, G, X, B, Y, S, P, 51.7±28.9% system on and 15.3±7.4% system off. ($p<0.001$ for all groups). A subgroup of six subjects was able to consistently read letters of reduced size, the smallest measuring 0.9 cm (1.7°) at 30 cm, and four subjects 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 implanted with the device should not use it within 3 feet of this type of equipment. The manufacturer also warns against the use of monopolar electrosurgical equipment in patients who have received the implanted device. The most common adverse events reported in clinical studies include conjunctival dehiscence, conjunctival erosion, retinal detachment, inflammation, and hypotony (low intraocular pressure).[183]

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.[184] In January 2014, the first patient with RP received the Argus II implant.[191] Twelve hospitals are offering consultations for patients with RP as they prepare to start Argus II implantation programs.[192]

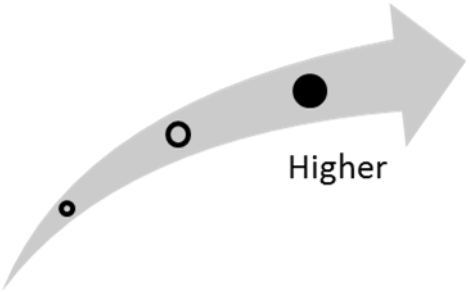
The manufacturer in March 2011 announced that Argus II received the CE mark, allowing marketing in Europe.[193]

Diffusion and cost: According to the manufacturer, the system costs about $115,000–$145,000, which includes the device and the surgical procedure.[187,194] 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.[195-198] CIGNA also denies coverage for artificial retinal devices, but its policy had not been updated since FDA approved the Argus II.[199]

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.[200] 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.[182] No cure exists; however, some treatment options, such as limiting light exposure, are thought to help preserve vision,[201] and other treatments under study include high doses of vitamin A palmitate and omega-3 fatty acid DHA.[182]

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



Overall, experts commenting on this intervention thought that a significant unmet need exists for treatment options that restore some level of vision for patients with RP, although its 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 and by the difficulty of the surgery and the amount of training needed to perform the procedure. Experts generally agreed that patient adoption would be high if the technology was affordable by the patient because of patients' desire to be more independent. Most experts agreed that this intervention might significantly impact patient management due to needed device training, followup care, and vision rehabilitation. Health disparities impacted by costs and device complexity 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.[202-207] 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.[206]

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.[202] 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.[203,207]

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 to 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.[208] 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.[209]

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.[210] 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.[211] Tasimelteon may cause drowsiness or affect mental alertness, so patients are advised to limit activity after taking it.[211] Patients might not notice its effects for weeks to months after initiating treatment, according to a discussion held between FDA and the manufacturer.[212]

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 the following:[213]

> The proportion of patients entrained by tasimelteon was greater compared to placebo as measured by urinary aMT6s and cortisol timing ($p=0.0171$ and $p=0.0313$, respectively). The number of clinical responders…was greater for tasimelteon, and there was also significant improvement in Clinical Global Impression of Change, and measures of total night-time sleep, daytime nap duration, and mid-point of sleep timing (MoST) as compared to placebo ($p<0.05$).

In an extension of the clinical trial (n=20), Lockley et al. reported the following:[214]

> Tasimelteon-treated patients maintained entrainment of their circadian rhythms compared to placebo (aMT6s: 90% tasimelteon vs. 20% placebo $p=0.0026$; cortisol: 80% tasimelteon vs. 20% placebo $p=0.0118$). Total nighttime sleep in the worst quartile of nights was 67.2 minutes longer and total daytime sleep duration was 59.4 minutes shorter in tasimelteon-treated patients ($p< 0.05$). The midpoint of sleep timing from both nighttime and daytime sleep increased 36 minutes in tasimelteon-treated patients ($p=0.0108$).

In both trials, tasimelteon was safe and well tolerated.

Manufacturer and regulatory status: Vanda Pharmaceuticals, Inc. (Washington, DC), manufactures tasimelteon under the brand name Hetlioz.[215] FDA approved tasimelteon in January 2014 as an orphan drug.[209] Tasimelteon is indicated for treating non-24 and has no contraindications.[211] 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. Tasimelteon may harm a fetus, so the drug is contraindicated in women of child-bearing potential. The drug is

also contraindicated in individuals with severe hepatic impairment.[211] 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 is gastroenteritis.[216]

Diffusion and cost: Tasimelteon is a specialty pharmaceutical that was expected to be available through a limited network of pharmacies by mid-2014.[217] As an orally administered pharmaceutical used in an outpatient setting, tasimelteon is not expected to require significant changes to health care staffing or infrastructure.

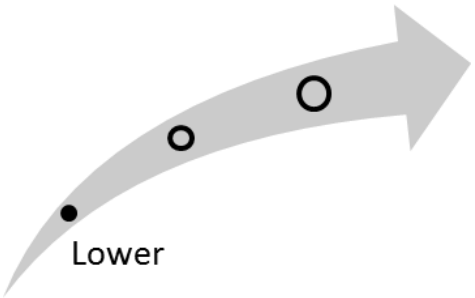
According to a U.S.-based, online aggregator of prescription-drug prices, tasimelteon costs about $60,000 per patient per year.[217] If half (about 35,000 patients) the estimated population with non-24 opted to take the drug, the cost to the health system would be about $2.1 billion.

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 one formulary listing tasimelteon;[218] however, companies may not have yet had time to enter the drug on their formularies. Additional searches to determine inclusion in formularies indicated that several payers besides the 11 we initially searched have the drug under consideration for adding to their formularies. When added to formularies, the drug would likely be listed as a specialty pharmaceutical requiring prior authorization and subject to quantity limits.

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 sleep disorder. 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.[219,220] Nonpharmacologic treatments include chronotherapy and lifestyle changes.[219] Tasimelteon is likely to be used in place of other drugs but potentially in combination with nonpharmacologic treatments.

Figure 9. Overall high-impact potential: tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder



Overall, tasimelteon's cost of about $60,000 per patient receiving the drug will likely have the biggest impact on the health care system, experts agreed. The manufacturer has aggressively marketed tasimelteon in direct-to-consumer advertising, 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 thought the effects are likely to have much less impact because of the small amount of data and modest

improvements observed thus far in sleep and waking times. 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.[221-226] We 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.[221,222] 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.[222] 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 used 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."[221] 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.[223,226]

Spinal Cord Injury Intervention

Intraoral Tongue-Drive Computerized System to Maneuver Electric Wheelchairs

Unmet need: Although power-assisted devices to maneuver electric wheelchairs are used to help improve quality of life for individuals with quadriplegia for whom powered wheelchairs are the only mobility option, efficacy, safety, and quality-of-life issues remain a primary concern. Other technologies, such as neuroassistive technology, are surgically invasive and pose risk of adverse events. Sip-and-puff technology, another commonly used modality, sends signals to a device using air pressure exerted by the patient "sipping" (inhaling) and "puffing" (exhaling) on a straw, tube, or wand. The amount of air pressure exerted directs the wheelchair to perform the desired task. This method of controlling a motorized wheelchair can be very exhausting. For people with spinal cord paralysis and no arm function, a computer-operated powered wheelchair controlled through use of a magnetic tracer/stud that is pierced through the tongue is a novel 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.[227] The smartphone transmits information to a computer, commanding it to perform daily tasks (e.g., email).[228] A standby mechanism allows patients to perform daily tasks such as eating, sleeping, and talking without unnecessary TDS use.[228]

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.[229] Patients must undergo computer training with the TDS for the software to appropriately interpret and calibrate tongue movement.

Clinical trials: In a published study of 11 subjects with spinal cord injury (SCI) at level C6 or above, "All performance measures improved over the course of the trial…. Despite participants with SCI already having familiarity with the SnP [sip and puff wheelchair control method], their performance measures were up to three times better with the TDS than with the SnP and continued to improve."[230]

In another study of able-bodied subjects and individuals with high-level SCIs (level C3 to C5), researchers combined TDS with speech recognition software and reported the following:[231]

> Preliminary evaluation results based on 14 able-bodied subjects and three individuals with high level spinal cord injuries at level C3-C5 indicated that the [dual] TDS headset, combined with a commercially available speech recognition software, can provide end 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.

The developers have not published information regarding patient safety issues. 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 estimate that the technology is about 2 years away from receiving FDA clearance.[232]

Diffusion and cost: The developers anticipate the per-patient cost of the TDS system to be between $6,000 and $7,000.[232] 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.

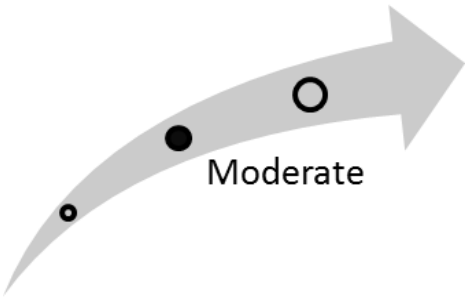
Medicare Part B covers power-operated wheelchairs as durable medical equipment (DME) for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a DME supplier doesn't accept being paid the Medicare rate directly from Medicare, Medicare 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.[233] 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.[234]

Emergency SCI treatment involves immobilizing the spine as gently and quickly as possible. Acute stages of treatment include maintenance breathing, preventing shock, immobilizing the neck, and avoiding possible complications. Medications, prolonged immobilization, or surgery may be required.[235] Ongoing treatment such as physical therapy, occupational therapy, or other rehabilitation therapies, as well as muscle spasticity medications, may be needed.[234] 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 were split on whether this intervention could accomplish that. 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 believed 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.[236-241] We 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 affect this patient population, suggesting that alternatives exist to restore mobility, 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.[240] 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.[239]

Acceptance and adoption: Experts offered varied viewpoints on the 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 limited evidence for improving patient independence and by the ongoing maintenance of the hardware and software, which might require specialized staff. 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.[239] Patient acceptance would likely depend on personal cost and feelings about the tongue piercing, a health systems expert noted.[240]

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.[240] Another expert with a research perspective noted that patients will likely still need extensive daily care even as patients may gain some independence with this device.[236]

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."[240]

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