

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

Priority Area 08: Functional Limitations and Disability

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www.ahrq.gov

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Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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Preface

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

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

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

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

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

David Meyers, M.D.
Acting Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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

Contents

Executive Summary	ES-1
Background	ES-1
Methods	ES-1
Results	ES-2
Discussion	ES-3
Central Nervous System Disorder Intervention	1
Daclizumab (Zinbryta) for Treatment-Refractory Relapsing- Remitting Multiple Sclerosis	2
Genetic Disorder Interventions	5
Conestat Alfa (Ruconest) for Treatment of Acute Hereditary Angioedema.....	6
Eliglustat Tartrate (Cerdelga) for Treatment of Gaucher’s Disease Type 1	9
Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome.....	12
Exon-Skipping Therapies (Drisapersen and Eteplirsen) for Treatment of Duchenne Muscular Dystrophy	15
Idebenone (Catena) for Treatment of Duchenne Muscular Dystrophy	18
L-Glutamine for Prevention of Vaso-Occlusive Crises in Sickle Cell Disease	21
Migalastat Hydrochloride (Galafold) for Treatment of Fabry Disease	24
Sensory Disorder Interventions	27
Pediatric Vision Scanner Screening for Strabismus and Amblyopia	28
Tasimelteon (Hetlioz) for Treatment of Non–24-Hour Sleep-Wake Disorder	32
Spinal Cord Injury Intervention	35
Intraoral Tongue-Drive Computerized System to Maneuver Electric Wheelchairs	36
Wearable, Battery-Powered Exoskeleton (ReWalk Personal) To Enable Mobility in Community or Home Settings in Patients With Paraplegia	40
Upper Limb Amputation Intervention.....	44
Prosthetic Arm with Body-Machine Interface (DEKA Arm System) to Restore Natural Arm Function After Amputation.....	45
References	49
Figures	
Figure 1. Overall high-impact potential: daclizumab (Zinbryta) for treatment-refractory relapsing-remitting multiple sclerosis.....	4
Figure 2. Overall high-impact potential: conestat alfa (Ruconest) for treatment of acute hereditary angioedema.....	8
Figure 3. Overall high-impact potential: eliglustat tartrate (Cerdelga) for treatment of Gaucher’s disease type 1.....	10

Figure 4.	Overall high-impact potential: elosulfase alfa (Vimizim) for treatment of Morquio A syndrome	13
Figure 5.	Overall high-impact potential: exon-skipping therapies (eteplirsen and drisapersen) for treatment of Duchenne muscular dystrophy	16
Figure 6.	Overall high-impact potential: idebenone (Catena) for treatment of Duchenne muscular dystrophy.....	19
Figure 7.	Overall high-impact potential: L-glutamine for prevention of vaso-occlusive crises in sickle cell anemia.....	22
Figure 8.	Overall high-impact potential: migalastat hydrochloride for treatment of Fabry disease	25
Figure 9.	Overall high-impact potential: Pediatric Vision Scanner screening for strabismus and amblyopia.....	30
Figure 10.	Overall high-impact potential: tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder	33
Figure 11.	Overall high-impact potential: intraoral tongue-drive computerized system to maneuver electric wheelchairs.....	38
Figure 12.	Overall high-impact potential: wearable, battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home settings in patients with paraplegia.....	42
Figure 13.	Overall high-impact potential: prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm function after amputation.....	47

Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice 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 170 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 17 topics for which (1) preliminary phase III data for drugs or pivotal data for devices were available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (This priority area included 138 topics that were being tracked in the system as of May 8, 2015.) We present 13 summaries on 14 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. * Conestat alfa (Ruconest) for treatment of acute hereditary angioedema	Lower end of the high-impact-potential range
2. Corneal collagen cross-linking (VibeX/KXL System) for treatment of progressive keratoconus	Prior high-impact topic (December 2014); no high-impact potential at this time; we continue to track while awaiting further developments
3. * Daclizumab (Zinbryta) for treatment-refractory relapsing-remitting multiple sclerosis	Lower end of the high-impact-potential range
4. Dimethyl fumarate (Tecfidera) for treatment of relapsing forms of multiple sclerosis	Prior high impact topic (December 2014); archived 2 years after FDA approval
5. * Drisapersen for treatment of Duchenne muscular dystrophy	Moderately high
6. * Eliglustat tartrate (Cerdelga) for treatment of Gaucher’s disease type 1	High
7. * Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome	Moderately high
8. * Eteplirsen for treatment of Duchenne muscular dystrophy	Moderately high
9. * Idebenone (Catena) for treatment of Duchenne muscular dystrophy	Moderately high
10. * Intraoral tongue-drive computerized system to maneuver electric wheelchairs	Lower end of the high-impact-potential range
11. * L-glutamine for prevention of vaso-occlusive sickle cell crises	Moderately high
12. * Migalastat hydrochloride (Galafold) for treatment of Fabry disease	Moderately high

Topic	High-Impact Potential
13. * Pediatric Vision Scanner screening for strabismus and amblyopia	Moderately high
14. * Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation	Moderately high
15. Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	Prior high impact topic (December 2014); archived 2 years after FDA approval
16. * Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder	Lower end of the high-impact-potential range
17. * Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home settings for patients with paraplegia	Moderately high

FDA: U.S. Food and Drug Administration

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 2014 Report

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

- **Dimethyl fumarate (Tecfidera) for treatment of relapsing forms of multiple sclerosis:** This drug is a homogenous fumaric acid ester formulation approved by the U.S. Food and Drug Administration (FDA) in March 2013 for treating adults with relapsing forms of multiple sclerosis (MS); this drug is one of several approved oral pharmacotherapies for this indication. Dimethyl fumarate reportedly has neuroprotective and immunomodulatory properties that underlie its efficacy for reducing patient relapse rates and new MS-related brain lesions. In completed and ongoing clinical trials, twice-daily administration is associated with statistically significant improvements in functional and qualitative measures of MS disease severity; these improvements are similar or superior to those observed in other approved MS medications.

Since launching, dimethyl fumarate has been a consistent leader in market share among both second-line MS therapies and all-oral MS medications. As this drug is well-diffused and has been tracked for more than 2 years after approval, we archived the topic in January 2015. For a more detailed discussion of this intervention, including a brief summary of data available through 2014, please refer to the relevant topic entry published in the December 2014 Potential High-Impact Interventions report.

- **Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa:** In the December 2014 report, this topic was deemed by expert comments to have high-impact potential. The implantable Argus® II Retinal Prosthesis System, manufactured by Second Sight Medical Products, Inc. (Sylmar, CA), is the first device available that reportedly 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 Argus II addressed the significant unmet need for restoring visual function to patients with retinitis pigmentosa, experts had commented previously. In February 2013, FDA approved Argus II for marketing. We tracked the intervention for 2 years after approval and archived the topic in April 2014 because it had “timed out,” no longer meeting horizon scanning criteria for tracking.

Eligible Topic Deemed Not High-Impact

- **Corneal collagen cross-linking (VibeX/KXL System) for treatment of progressive keratoconus:** The VibeX/KXL System, manufactured by Avedro, Inc. (Waltham, MA), is an ultraviolet cross-linking device and riboflavin-based solution for stiffening corneal collagen fibrils to prevent further degeneration. In the December 2014 report, this topic was deemed by expert comments to have moderately high potential for high impact and was under FDA consideration for marketing approval. In March 2015, FDA sent a second complete response letter to Avedro regarding its application for approval and requiring additional data. Thus, we will continue to track the topic as we await new developments to determine whether the company can address FDA’s concerns.

Potential High-Impact Interventions

Below are 13 interventions that, according to experts’ comments, have high-impact potential. They are drugs and devices used in treating a number of conditions in this priority area. These conditions are a central nervous system disorder, MS; the genetic disorders hereditary angioedema, Duchenne muscular dystrophy (DMD), Fabry disease, Gaucher’s disease, Morquio A syndrome, and sickle cell disease (SCD); sensory disorders related to vision in children and sleep in blind people; and upper limb amputation and spinal cord injury. The drugs are a monoclonal antibody, two enzyme inhibitors, an enzyme replacement therapy, and a molecular chaperone that ensures an enzyme is folded properly for physiologic action; exon-skipping molecules that modify gene expression; a short-chain benzoquinone, structurally similar to coenzyme Q₁₀; a pharmaceutical-grade amino acid; and a melatonin-receptor agonist. A screening tool checks vision alignment in young children. Devices are an advanced prosthetic arm, a system using a pierced-tongue stud to direct computers and electronic wheelchairs, and an exoskeleton to enable people with paraplegia to stand, turn, and walk.

Central Nervous System Disorder

Daclizumab (Zinbryta) for Treatment-Refractory Relapsing-Remitting Multiple Sclerosis

- **Key Facts:** Despite multiple FDA-approved pharmacotherapies for treating relapsing forms of MS, many patients are unable to achieve adequate symptom remission. Daclizumab is a multifaceted monoclonal antibody with immunomodulatory characteristics that are purportedly effective for treating relapsing forms of MS. Daclizumab is hypothesized to selectively inhibit T-cell activation by competitively inhibiting interleukin-2 (IL-2) receptor subunit CD25 activation; this process potentially prevents the neuroinflammation that underlies severe MS symptoms. Daclizumab is subcutaneously injected as a high-yield process formulation (HYP; DAC HYP); standard dosing protocols are monthly injections of 150 or 300 mg. In several completed phase III clinical trials, daclizumab was superior to placebo and a standard MS treatment for reducing annualized relapse rates and active brain

lesions thought to contribute to disease progression. Ongoing clinical trials are examining daclizumab's long-term safety and efficacy for treating relapsing forms of MS.

In April 2015, daclizumab's co-manufacturers announced that FDA had accepted their biologics license application for daclizumab, branded as Zinbryta™. The application included results from two pivotal trials, DECIDE and SELECT, which investigated outcomes of subcutaneously injected monthly 150 mg daclizumab administration. Neither manufacturer has announced potential daclizumab pricing, but experts anticipate that the drug will be competitively priced with other approved MS therapies.

- **Key Expert Comments:** Although experts acknowledged a substantial need for effective alternative medications for patients with relapsing forms of MS, the experts concluded that daclizumab will address an unmet need for only a relatively small patient subset. Experts thought that daclizumab's moderate comparative efficacy and lack of quality-of-life and long-term outcomes data would limit its use. Additionally, because several alternative oral and injectable medications are available for this indication, experts anticipated that a competitive market could limit daclizumab's overall impact on patient health outcomes.
- **High-Impact Potential:** Lower end of the high-impact potential range

Genetic Disorders

Conestat Alfa (Ruconest) for Treatment of Acute Hereditary Angioedema

- **Key Facts:** Hereditary angioedema (HAE) is a life-threatening disorder. Although several treatments are available for HAE, many patients experience significant side effects, such as thrombosis, with them. The most effective treatment, a human C1 esterase inhibitor (C1INH, also called C1 inhibitor) concentrated from donated blood, is not always available. An unmet need exists for a treatment for acute attacks with few side effects. Conestat alfa (Ruconest®) is a plasma-free, recombinant, human C1INH, approved by FDA in July 2014 that can be self-administered when patients experience an acute attack. Conestat alfa is produced in the milk of transgenic rabbits. Because it is not isolated from human blood, it does not carry a risk of transmission of human infectious agents. However, since it is produced by rabbits, patients who have an allergy to rabbits cannot use the drug. Conestat alfa is given by intravenous (IV) infusion over 5 minutes. A clinician experienced in treating HAE supervises the first dose; then, patients may be trained to self-administer the drug. For patients who weigh less than 84 kg, the dose is 50 IU per kg. For patients who weigh 84 kg or more, the dose is 4,200 IU (2 vials). In a clinical trial, most patients experienced mild to moderate treatment-emergent adverse events. The most common adverse events were headache, nausea, and diarrhea. A serious but uncommon adverse event is anaphylaxis. No reports of thromboembolic events or increased risk of deep vein thrombosis have been associated with conestat alfa, unlike with alternative treatments. In a phase III, randomized, placebo-controlled trial, Riedl et al. (2014) reported reduced median time to the onset of symptom relief (90 vs. 152 minutes) and reduced median time to minimal symptoms (303 vs. 483 minutes), compared with placebo. Moldovan et al. (2012) reported that 87% of patients with acute HAE achieved symptom relief within 4 hours. One observational study is ongoing.

In July 2014, FDA approved the drug for treating HAE attacks in adult and adolescent patients. The wholesale acquisition cost of conestat alfa is \$9,500 for 2 vials, the maximum single dose. The U.S. Centers for Medicare & Medicaid Services has no national coverage determination for conestat alfa. Thus, coverage is left to the discretion of local Medicare prescription drug plans whether to include the drug on their formularies. Our representative

search of third-party payers found seven payers (i.e., Aetna, Anthem, HealthPartners, Humana, Regence, United Healthcare, Wellmark) with policies that outline coverage criteria for conestat alfa. Additionally, Blue Cross Blue Shield of Massachusetts does not provide coverage, but it is reviewing its policy.

- **Key Expert Comments:** Experts commenting on this intervention agreed that conestat alfa may improve patient health, although they differed over how important the unmet need is. Clinical experts stressed that supply issues with alternative treatments make this intervention more crucial in emergency scenarios. Conestat alfa may be readily accepted by clinicians and patients because of its good safety profile, easy administration, and effectiveness, experts commented. Health care infrastructure, patient management, and health disparities are not likely to be greatly affected by use of conestat alfa, experts said.
- **High-Impact Potential:** Lower end of the high-impact-potential range

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

- **Key Facts:** Gaucher's disease, an orphan disease affecting an estimated 6,000 patients in the United States, has long been treated using IV enzyme replacement therapy (ERT); no oral therapy had been available until eliglustat tartrate was developed. ERT costs between \$300,000 and \$350,000 per patient per year (depending on the brand used) and is inconvenient for patients because it requires IV infusions every 2–3 weeks lifelong. Eliglustat tartrate purportedly partially inhibits the enzyme glucosylceramide synthase, resulting in reduced glucosylceramide. Three fully enrolled phase III trials of eliglustat tartrate are ongoing. Mistry et al. (2015) and Cox et al. (2015) reported positive data from two of these trials, showing significant reduction in spleen volume and noninferiority to an IV ERT comparator, respectively.

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

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

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

- **Key Facts:** Morquio A syndrome (mucopolysaccharidosis type IV) is a rare autosomal recessive inherited metabolic disorder caused mutations to the *N*-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) gene, which lead to deficiencies of *N*-acetylgalactosamine-6-sulfatase. *N*-acetylgalactosamine-6-sulfatase normally degrades keratan sulfate and other glycosaminoglycans. In its absence, patients with Morquio A syndrome accumulate excess keratan sulfate in bone, tendons, connective tissue, cornea, urine, and synovial fluid; frequent resulting symptoms include skeletal dysplasia (dwarfism), hydrocephalus, spinal

cord compression, genu valgum (“knock knees”), heart valve abnormalities, and conductive or sensorineural hearing loss. Patients’ life expectancy depends on symptom severity; severely affected pediatric patients may survive only to late childhood or adolescence.

Elosulfase alfa (Vimizim®) is a GALNS ERT, approved by FDA in February 2014, intended to prevent or improve Morquio A syndrome symptoms. The drug is infused at a weekly dosage of 2 mg/kg, delivered over a minimum of 3.5–4.5 hours. In clinical trials, pediatric patients administered weekly IV elosulfase alfa infusions demonstrated limited improvement on two measures of locomotive function. The most commonly observed treatment-related adverse events were fever, headache, nausea and vomiting, and abdominal pain. Additional ongoing clinical trials are investigating elosulfase alfa’s long-term treatment efficacy and safety among various patient subgroups.

Before elosulfase alfa became available, standard of care for Morquio A syndrome was palliative care, including corrective orthopedic surgeries, hearing and visual aids, and assisted mobility devices. Since elosulfase alfa’s approval, its manufacturer has announced that the drug has diffused widely among clinicians and patients with Morquio A syndrome in American and international markets, with sales exceeding \$127 million in its first four retail quarters. In the United States, elosulfase alfa costs approximately \$380,000 per year per patient. Many third-party payers cover the drug as a specialty pharmaceutical with prior authorization required, although patients typically will have co-pays determined by their health plan contract.

- **Key Expert Comments:** Experts evaluating elosulfase alfa thought that the drug addressed an unmet need among patients with Morquio A syndrome as the sole FDA-approved medication for this indication. However, several experts concluded that as a non-curative treatment, this intervention’s potential to improve overall patient health outcomes was inherently limited; these experts also noted that clinical trial data demonstrated narrow treatment efficacy, with multiple patients failing to respond to treatment protocols. Most experts deemed that, as a nonsurgical option for patients, elosulfase alfa’s acceptance would continue to be strong despite its high cost.
- **High-Impact Potential:** Moderately high

Exon-Skipping Therapies (Drisapersen and Eteplirsen) for Treatment of Duchenne Muscular Dystrophy

- **Key Facts:** DMD is a severe, muscle-wasting disorder caused by various dystrophin gene mutations. Dystrophin normally encodes the dystrophin protein, which is vital for muscle cell structural integrity; malfunctioning dystrophin leads to mitochondrial defects that broadly affect muscle cell tissue throughout the body. As a result, as DMD progresses, patients experience symptoms including heart defects, general muscle weakness and fatigue, and respiratory and motor difficulties. No cure exists, and patients rarely survive beyond their fourth decade.

Palliative treatments are standard of care for DMD and primarily attempt to address patients’ most severe motor and respiratory symptoms. Common palliative interventions include wheelchairs for patients with limited mobility and various medications and assistance devices to alleviate respiratory declines. An unmet need exists for DMD treatments that can increase patients’ functional independence and delay the need for wheelchairs and other ambulatory assistance. Drisapersen and eteplirsen are investigational injectable therapies that induce skipping of errant sections of the dystrophin gene during RNA transcription; hypothetically, this action allows patients to create functional dystrophin protein, and subsequently results in increased muscle strength. Drisapersen and eteplirsen

are intended to treat patients with dystrophin gene mutations associated with exon 51; an estimated 13% of adolescent male patients with DMD may be eligible for these treatments.

In clinical trials, drisapersen and eteplirsen administrations were well-tolerated and associated with increased systemic and functional dystrophin levels in patients with DMD. These drugs also showed some efficacy for improving patients' ambulatory and respiratory functions and delaying associated declines, although long-term results were inconsistent.

- **Key Expert Comments:** Experts assessing these interventions agreed that a significant unmet need exists for new, effective DMD treatments. These experts also unanimously anticipated that if approved, these drugs would be widely accepted by patients and clinicians, because patients' present medication options are steroids, which have serious side effects. However, experts acknowledged that these drugs' effectiveness is limited in that it is intended for only a subgroup of DMD patients, limiting potential impact. Overall, experts concluded that both drisapersen and eteplirsen have modest potential to positively affect patient health outcomes.
- **High-Impact Potential:** Moderately high

Idebenone (Catena) for Treatment of Duchenne Muscular Dystrophy

- **Key Facts:** Respiratory declines are one of several severe symptoms commonly exhibited by patients with DMD. Normal disease progression is accompanied by significantly compromised respiratory function, forcing many older adolescent and young adult patients to use assisted breathing devices or high-dose corticosteroids. Effective, well-tolerated alternative treatments are needed to address respiratory symptoms and increase functional independence in patients with DMD.

Idebenone (Catena[®]) is an oral short-chain benzoquinone with potent antioxidant and cytoprotective properties. Researchers have associated these properties with facilitated, sustained intracellular energy transfer, through adenosine triphosphate (ATP) production. This mechanism of action is hypothesized to sidestep pathways affected by mitochondrial defects and may offset DMD's characteristic muscle-wasting symptoms. In phase II and phase III clinical trials, investigators reported that patients administered 450–900 mg idebenone daily demonstrated improvements on multiple respiratory function assessments; the drug was well-tolerated at both doses.

Idebenone is the first investigational DMD medication to successfully complete a phase III clinical trial, with peer-reviewed results published in 2015. After this publication, idebenone's developer announced that it had initiated pre-NDA (new drug application) meetings with FDA and is preparing its NDA for submission.

- **Key Expert Comments:** Experts agreed that a significant need exists for effective DMD medications and thought that idebenone could address this need. Commenting experts noted that no approved medications exist for this indication, and idebenone stood to make an impact if it was approved before other investigational drugs. Although idebenone's clinical data indicate that it improved some patient health outcomes, experts noted that this drug does not modify the underlying disease and would likely be prescribed adjunct to palliative therapies, limiting its to overall high-impact potential.
- **High-Impact Potential:** Moderately high

L-Glutamine for Prevention of Vaso-Occlusive Sickle Cell Crises

- **Key Facts:** Standard prophylactic and acute treatment for vaso-occlusive crises (VOCs) in SCD is a myelosuppressive chemotherapeutic agent called hydroxyurea; however, the drug is effective for only two-thirds of affected adults and increases the infection risk.

Researchers are investigating whether pharmaceutical-grade L-glutamine taken prophylactically might prevent VOCs, reduce pain, reduce hospitalizations, shorten hospital stays, and fulfill the unmet need for a therapy without side effects. Researchers speculate that oxidative stress, adhesive leukocytes, and chronic inflammation play roles in VOCs. L-glutamine is a nonessential amino acid that acts as a precursor to nicotinamide adenine dinucleotide (NAD), an electron acceptor that reduces oxidative stress in cells. Supplementing L-glutamine levels may increase the NAD concentration, potentially altering the redox state of red blood cells and preventing VOCs. In clinical trials, pharmaceutical-grade L-glutamine is administered twice daily at a dose of 0.3–0.6 g/kg. Doses are rounded to 5- or 10-g increments with an upper limit of 30 g per day. L-glutamine is a powder that can be mixed with water or unheated beverages and foods (e.g., yogurt, applesauce, cereal).

In a phase III, randomized, placebo-controlled trial, Niihara et al. (2014) reported statistically significant decreases in VOC incidence, hospitalization incidence, cumulative hospital days, acute chest syndrome incidence, and median time to first VOC for patients who took L-glutamine. No clinical trials are ongoing, but the manufacturer expects to initiate a phase III trial and submit an NDA in 2015. FDA has granted the intervention orphan drug and fast-track statuses for treating SCD. No cost, coverage, or payment information is available because FDA has not yet approved L-glutamine for preventing VOCs in patients with SCD. If the drug gains approval, we anticipate third-party payers would provide reimbursement for the drug.

- **Key Expert Comments:** Experts commenting on this intervention agreed that a substantial unmet need to reduce pain, VOCs, and hospitalizations exists. Clinicians and patients may readily adopt L-glutamine because it appears safe, is an oral drug, and will likely be low cost, experts said. Experts noted that it is unlikely to affect health care delivery infrastructure or patient management except by potentially reducing hospital use.
- **High-Impact Potential:** Moderately high

Migalastat Hydrochloride (Galafold) for Treatment of Fabry Disease

- **Key Facts:** Treatment for Fabry disease is ERT using recombinant alpha-galactosidase A (alpha-GAL) enzyme; however, ERT has variable tissue distribution, a requirement for weekly or biweekly IV infusions, and a high cost. Migalastat (Galafold™) is a small-molecule modulator of alpha-GAL activity intended to activate endogenous residual alpha-GAL as a monotherapy or potentiate the activity of exogenously provided alpha-GAL activity as a combination therapy with ERT. Migalastat is intended to function as a pharmacologic chaperone for alpha-GAL to promote the proper folding of endogenous alpha-GAL for appropriate trafficking and function. Restored enzymatic activity of alpha-GAL reduces the levels of globotriaosylceramide (GL-3) and prevents its damaging accumulation. Migalastat may also work as a combination therapy with ERT by binding to and stabilizing the exogenous alpha-GAL and increasing uptake in affected organs. Based on an enzymatic assay, the manufacturer estimates 30% to 50% of patients with Fabry disease have mutations that are suited to migalastat monotherapy. Migalastat is administered orally; the optimal dose is still under study. In clinical trials, it is administered at a dose of 150 mg every other day or 250 mg in cycles of 3 days on and 4 days off. The most commonly reported adverse events include headache, arthralgia, diarrhea, back pain, pain in an extremity, and fatigue.

Migalastat is administered as either a monotherapy or combination therapy with ERT for treating Fabry disease. In February 2004, FDA granted migalastat orphan drug status. Four phase III clinical trials are ongoing. The drug's manufacturer intends to seek accelerated

drug approval after completing these trials. In a clinical trial (n=67) of migalastat's effect on levels of GL-3 inclusions in interstitial capillaries of the kidneys, the primary endpoint was not met. However, in a post-hoc analysis including only patients with amenable mutations (n=42), Barlow et al. (2014) showed a statistically significant reduction of GL-3. In a followup study, glomerular filtration rate remained steady over an average of 32 months for patients with amenable mutations, according to Bichet et al. (2014). Two other studies (Giugliani et al. 2013; Germain et al. 2012) also supported the analysis that only patients with amenable mutations responded to migalastat.

Pricing, coverage, and payment information for migalastat is not available because it is not yet approved by FDA. Treatments for a rare condition such as Fabry disease are likely to be costly, and it is unclear whether the manufacturer will price migalastat lower than ERT. If migalastat is approved, its use is likely to be reimbursed by third-party payers because of the limited treatment options for patients with Fabry disease.

- **Key Expert Comments:** Experts commenting on this intervention agreed that a large unmet need exists for effective and convenient treatment. Migalastat may be readily accepted by clinicians and patients because of its oral administration and good tolerability, experts suggested. As an oral drug, it is unlikely to have a significant impact on health care delivery infrastructure or patient management, experts thought, but it could add to overall costs.
- **High-Impact Potential:** Moderately high

Sensory Disorders

Pediatric Vision Scanner Screening for Strabismus and Amblyopia

- **Key Facts:** The leading cause of preventable monocular vision loss in children is amblyopia, which is most often caused by strabismus. Early amblyopia detection by pediatricians and other primary care clinicians can be difficult because standard screening methods lack sufficient sensitivity and specificity and require infants, toddlers, and young children to sit still for several minutes, making the screening impractical for many infants and toddlers. Thus, common screening technologies miss detection in very young children who should be referred to an ophthalmologist for further evaluation and possible treatment. Treatment success declines as age at identification increases.

The Pediatric Vision Scanner (PVS) is intended for use as a screening tool to enable earlier and more accurate amblyopia or strabismus detection so that patients can be more appropriately referred to specialist care. The system uses proprietary technology called retinal birefringence scanning to screen for amblyopia and strabismus. The PVS simultaneously assesses both eyes during a 2- to 5-second scan to detect both binocular alignment and the eyes' ability to focus on a target. The system's software indicates (with a "pass" or passing grade) whether the patient's eyes accurately fixated on the target. If the eyes did not fixate, a pediatrician refers the patient for further evaluation. Five clinical trials evaluated the sensitivity and specificity of the PVS compared with other screening devices. Investigators from the largest and most recently reported PVS trial (Jost et al. 2014), in children aged 2–6 years, reported that, "The sensitivity of the PVS to detect strabismus and amblyopia (0.97; 95% CI [confidence interval], 0.94-1.00) was significantly higher than that of the SureSight Autorefractor (0.74; 95% CI, 0.66-0.83). Specificity... (0.87; 95% CI, 0.80-0.95) was significantly higher than that of the SureSight Autorefractor (0.62; 95% CI, 0.50-0.73)." FDA has determined the PVS to be a nonsignificant risk device. This means the PVS has abbreviated requirements for labeling; institutional review board approval is all that is

needed to conduct trials (i.e., no prior FDA approval needed to conduct a trial); and reporting rules are streamlined for the regulatory approval pathway.

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

- **Key Expert Comments:** The PVS's use in very young populations is a significant factor in its potential to fulfill the unmet need for early diagnostic tools for amblyopia and strabismus, experts agreed. Experts thought that the capabilities of the PVS to screen younger children and identify possible problems earlier could contribute to improved patient health outcomes. Experts especially liked the ease of use, quick scan time, low risks, and minimal training needed to successfully operate the device in a primary care setting. Experts believe that these factors will contribute to wide acceptance and adoption, which may improve the accuracy of referrals to specialists.
- **High-Impact Potential:** Moderately high

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

- **Key Facts:** About half of all blind people are believed to be affected by non-24-hour sleep-wake disorder (non-24) because of a lack of light receptors to reset the circadian rhythm. Patients with non-24 may experience reduced quality of life and debilitation due to poor sleep quality and excessive daytime sleepiness. Stimulants and sedatives may provide temporary or partial relief of symptoms, but patients need treatment that addresses the underlying cause of the disease. Tasimelteon is a dual melatonin receptor agonist that, according to the manufacturer, resets the circadian rhythm by acting in the hypothalamus. It is taken orally at a dosage of 20 mg, 1 hour before bedtime, at the same time every night. 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. One phase III trial is ongoing.

FDA granted orphan drug status and priority review for the manufacturer's NDA; the drug was approved the drug in January 2014 as HetliozTM. According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, tasimelteon costs about \$86,000 per patient per year. Several third-party payers cover the drug as a specialty pharmaceutical requiring prior authorization and imposing quantity limits.

- **Key Expert Comments:** Overall, tasimelteon's biggest impact on the health care system will likely be its cost, experts agreed. Clinicians and patients are likely to adopt tasimelteon because of its good safety profile and low abuse potential, experts agreed. In terms of improving patient health or altering patient management, experts noted the small amount of data and very modest improvements in sleep and waking times.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Spinal Cord Injury

Intraoral Tongue-Drive Computerized System to Maneuver Electric Wheelchairs

- **Key Facts:** Clinicians recommend conventional manual or 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 affixed to the tongue, most commonly by piercing. This magnetic tracer communicates synergistically with a headset equipped with 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 reportedly 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 small clinical trials in two locations (Atlanta, GA, and Chicago, IL). The trials continue to recruit patients, with about 20 patients participating thus far. According to Kim et al. (2014), 11 patients with spinal cord injuries performed mobility and computer-based communication tasks up to three times faster with TDS than with the sip-and-puff system, which is a long-standing oral mode of directing a powered wheel chair, despite having used the sip-and-puff system for a substantially longer time. The National Science Foundation (Arlington, VA), the Christopher & Dana Reeve Foundation (Short Hills, NJ), and the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health (Bethesda, MD) are providing funding for system development.

The device is not yet FDA cleared. We found no indication that the developers have initiated regulatory proceedings despite their prior prediction of market readiness in 2015. The developers anticipate the per-patient cost of the TDS system to be between \$6,000 and \$7,000.

- **Key Expert Comments:** Most experts commenting thought TDS could be a viable alternative to existing, less effective technologies, although they had diverse perspectives on its potential impact. Some thought the unmet need was not significant, but others who have worked directly with patients with spinal cord injuries in need of assistive devices to control powered wheelchairs saw this intervention as a significant improvement for patient health outcomes, independence, and quality of life, allowing patients to perform daily activities in a less strenuous manner than with sip-and-puff straws. Several experts thought concerns over training and cost could be a barrier to clinician and patient acceptance. 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.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Wearable, Battery-Powered Exoskeleton (ReWalk Personal) to Enable Mobility in Community or Home Settings for Patients with Paraplegia

- **Key Facts:** Wheelchair users with paraplegia can experience pressure ulcers, osteoporosis, depression, and cardiovascular, respiratory, urinary, and gastrointestinal adverse events associated with confinement to power-assisted devices. The ReWalk system is a wearable, battery-powered exoskeleton with motorized leg braces and crutches for support, which is meant to provide mobility and independence in community and home settings. The 35-lb

device uses a tilt sensor, onboard computer, and rechargeable battery to propel the motorized leg braces when patients shift their body weight. It is designed to mimic a natural walking gait and functional speed while allowing users to sit, stand, walk, and turn for about 4 hours at a time. It is customized to fit the patient, although height and weight restrictions apply. Patients with sufficient bone density, flexibility, and cardiovascular health, as determined by a physician's exam, complete device training at a rehabilitation center. Although patients control the exoskeleton, trained caregivers must be present to assist patients while they use the device, even during home use.

Two studies are ongoing to evaluate the ReWalk Personal in community and home settings. Esquenazi et al. (2012) reported that all patients (n=12) were able to transfer to the exoskeleton and walk with it independently for 5–10 minutes. All patients made positive comments about emotional and psychosocial benefits, and some patients reported improvements in pain, bowel and bladder function, and spasticity. In contrast, Benson et al. (2015) reported (after we had already received experts' comments on this intervention) that about two-thirds of candidates for their study of the ReWalk did not meet criteria or were not interested in committing to a 10-week training program. Further, enrolled patients (n=10) reported that the exoskeleton did not reach their high expectations for benefits.

FDA cleared the ReWalk Personal in June 2014 under the de novo pathway. Physician approval and training certification are required to use the assistive device. The manufacturer stated that diffusion has been limited because of the time it takes to evaluate and train patients and process reimbursement claims. The ReWalk Personal costs about \$70,000. Medicare Part B may cover exoskeletons as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. Our searches found six policies from third-party payers that deny coverage of the ReWalk Personal on the basis that it is experimental.

- **Key Expert Comments:** Experts commenting on this intervention agreed that an unmet need exists for a mobility and upright standing device. An exoskeleton for community or home use may prevent complications associated with prolonged wheelchair use, experts agreed. Experts suggested the high cost will have the most effect on patient acceptance and access, possibly contributing to health disparities.
- **High-Impact Potential:** Moderately high

Upper Limb Amputation

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

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

The developer received FDA marketing clearance for the prosthetic arm in June 2014, but has not found a manufacturing partner for commercial distribution. Thus, the prosthesis is not yet commercially available. Cost is unclear but reportedly will be tens of thousands of dollars. Prosthetic arms are covered under Medicare Part B as durable medical equipment;

coverage from private third-party payers is uncertain but may be similar to policies for other prostheses.

- **Key Expert Comments:** A significant unmet need exists for restoring natural arm function to patients with upper limb amputations, and this device provides functionality beyond any available prostheses, experts agreed. They thought that clinician and patient enthusiasm, likely to be high, might be tempered by high costs and complex training, potentially increasing health disparities because of unequal access. Experts suggested that its overall impact would be mitigated by the small population likely to use the DEKA Arm.
- **High-Impact Potential:** Moderately high

Central Nervous System Disorder Intervention

Daclizumab (Zinbryta) for Treatment-Refractory Relapsing-Remitting Multiple Sclerosis

Unmet need: Multiple sclerosis (MS) is an autoimmune demyelinating disorder ranked as the most frequent debilitating neurologic disease among young adult Americans.¹ Up to 85% of patients initially receive a diagnosis of a relapsing form of MS, although diagnoses can change over time, based on clinical criteria.²

As MS progresses, damage to myelin and nerves causes declining cognitive, motor, sensory, and sexual functioning; patients can experience disease-free periods of varying length, followed by relapses in which symptoms return or intensify.^{3,4} Several first- and second-line MS medications are approved for oral or injectable administration, attempting to treat MS by reducing patients' autoimmune responses and subsequent damage; none of these treatments are curative.^{5,6} Unfortunately, patients may not respond to available pharmacotherapies or may find these drugs' side effects intolerable.^{1,6-8} An unmet need exists for alternative, tolerable therapies for treating symptoms and limiting relapses in patients with relapsing forms of MS.

Intervention: Daclizumab is a humanized, IgG1 subtype, monoclonal antibody that binds to CD25, the alpha subunit of T-cell interleukin-2 (IL-2) receptors.⁹⁻¹¹ By competitively inhibiting IL-2 receptor activation by IL-2, daclizumab prevents T-cell activation.^{10,11} T cells are known to mediate inflammatory processes that potentially underlie autoimmune diseases such as MS, and daclizumab was identified as a potentially effective MS therapy.¹²

Researchers have not established daclizumab's MS-treating mechanisms, but at least three putatively contributory immunomodulatory properties are known. First, daclizumab prevents IL-2 from interacting with activated T cells, inhibiting antigen-specific T cells.^{13,14} Second, daclizumab expands and activates CD56^{bright} NK (natural killer) cells, which can travel into the space under the myelin sheath to kill activated T cells.^{12,15,16} Finally, daclizumab mediates innate lymphoid cell development; when dysregulated, these cells can trigger autoimmune disease states such as those observed in MS.^{13,15,17}

Although intravenous (IV) delivery was also studied in clinical trials, daclizumab—as daclizumab high-yield process (DAC HYP) formulation—is expected to retail as a subcutaneous injectable with a proposed once-monthly 150 or 300 mg dosage.^{18,19}

Clinical trials: Two large completed phase III trials, the DECIDE and SELECT studies, investigated daclizumab's safety and efficacy for treating relapsing forms of MS. In the SELECT study, adult patients with relapsing MS (n=621) were randomly assigned to in a 1:1:1 ratio to receive monthly placebo, 150 mg daclizumab, or 300 mg daclizumab, with more than 92% of patients in each group completing the trial.¹⁸ After 52 treatment weeks, investigators observed that annualized relapse rates (ARR) were reduced for patients administered daclizumab (150 mg daclizumab ARR, 0.21 [54% reduction]; 95% CI [confidence interval], 0.16 to 0.29; p<0.0001; 300 mg daclizumab ARR, 0.23 [50% reduction]; 95% CI, 0.17 to 0.31; p<0.0001) compared to patients receiving placebo (ARR, 0.46; 95% CI, 0.37 to 0.57). Compared with placebo, statistically higher numbers of patients administered daclizumab were relapse-free after the same time elapsed (daclizumab 150 mg, 81% relapse-free; daclizumab 300 mg, 80% relapse-free; placebo, 64%; p<0.0003). Similar treatment-related adverse event rates were observed across groups.¹⁸

The DECIDE study (n=1,841) compared the efficacy of 150 mg monthly daclizumab injections to weekly intramuscularly injected interferon beta-1a.²⁰ Measured after 96 treatment weeks, the daclizumab group exhibited a 45% reduction in ARR compared with the group given interferon beta-1a (p<0.0001). Daclizumab was associated with fewer new or newly enlarging T2-hyperintense lesions after 96 weeks (54% comparative reduction; p<0.0001). Additionally, after 96

weeks, 73% of patients administered daclizumab were relapse-free, compared with 59% of patients administered interferon beta-1a (nominal $p < 0.0001$).²⁰

Across these two studies, daclizumab treatment was associated with increased susceptibility to infections and skin reactions and a heightened risk for elevated liver function tests and systemic immune-mediated adverse events.^{21,22} Seven patients in these trials experienced serious adverse events affecting vital organs; several other patients withdrew from a trial or discontinued daclizumab because they could not tolerate it or they had emerging clinical symptoms.²¹⁻²³ In earlier research, IV daclizumab was also often associated with headache, hypertension, impaired wound healing, tremor, and vomiting;²⁴ ongoing extension studies are examining subcutaneously injected daclizumab's long-term safety and efficacy.

Manufacturer and regulatory status: Biogen (Cambridge, MA) and AbbVie (North Chicago, IL) are partners and cosponsors for American clinical trials investigating DAC HYP for treating relapsing forms of MS. In April 2015, these partners announced that the U.S. Food and Drug Administration (FDA) had accepted their biologics license application for DAC HYP, branded as Zinbryta[™].²⁵ This application is anchored by data from the DECIDE and SELECT trials.²⁵

FDA first approved daclizumab in 1997, marketed as Zenapax, for use in immunosuppressive regimens to prevent organ transplant rejection.²⁶ However, daclizumab's former manufacturer, F. Hoffman-La Roche, Ltd. (Basel, Switzerland) withdrew the drug from major commercial markets in 2009.²⁷

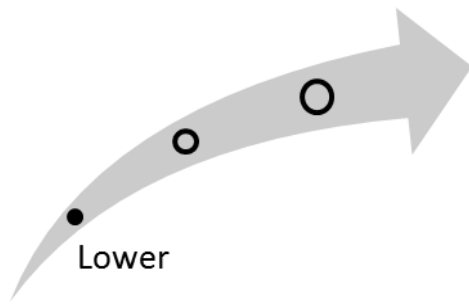
Diffusion and costs: As an investigational medication, daclizumab has no diffusion data. Biogen and AbbVie have not announced potential per-unit or per-patient pricing for this drug, although industry observers anticipate that daclizumab will be priced competitively to other second-line MS pharmacotherapies.

Clinical Pathway at Point of This Intervention

In MS, inflammation and scarring cause demyelination of neurons, broadly affecting systemic nerve signaling and functioning. Resulting symptoms vary and can include dizziness, general fatigue, pain, peripheral numbness or weakness, slurred speech, tremor or unsteady gait, and visual deficits.^{28,29} The severity and location of neural damage at symptom onset determine which symptoms manifest; about half of patients diagnosed with MS exhibit some cognitive impairment symptoms.³⁰

Besides primary-progressive MS, three relapsing forms—progressive-relapsing, relapsing-remitting, and secondary-progressive—are recognized.³¹⁻³³ Standard pharmacotherapies for these disorders attempt to treat inflammation frequency and reduce lesions, potentially minimizing functional limitations and delaying disease progression.²⁸ A cure for MS does not exist, and approved medications have inconsistent efficacy across patients.³⁰ As a likely second-line MS medication, daclizumab could compete with other approved oral and injectable pharmacotherapies including dimethyl fumarate (Tecfidera[®]), natalizumab (Tysabri[®]), and fingolimod (Gilenya[®]).^{7,34-36}

Figure 1. Overall high-impact potential: daclizumab (Zinbryta) for treatment-refractory relapsing-remitting multiple sclerosis



Experts commenting on this intervention agreed that a significant need exists for effective alternative treatments for relapsing forms of MS, and they thought that daclizumab could address this need. Experts concluded that because daclizumab is an injectable medication with demonstrated efficacy, patients with poor responses to other approved drugs would widely accept daclizumab. However, experts anticipated that factors including daclizumab’s unresolved safety profile and broad competition from other drugs could limit its impact. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.³⁷⁻⁴² We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: All experts acknowledged that MS is a disorder that significantly affects patients and health care resources and agreed that an unmet need exists for effective treatment options for patients whose symptoms do not adequately improve using available medications. However, given daclizumab’s market competition and limited efficacy, most experts thought that this drug had limited potential to broadly improve patient health outcomes.

Acceptance and adoption: Experts anticipated that daclizumab would be widely accepted among patients unresponsive to approved MS drugs. Similarly, clinicians would adopt this drug as an alternative treatment option, with two clinical experts anticipating that daclizumab would be adopted as a second- or third-line therapy.^{37,42}

Health care delivery infrastructure and patient management: Experts acknowledged that if approved, daclizumab would be one of several injectable MS treatments. Experts subsequently noted that daclizumab would minimally impact health care delivery infrastructure and patient management.

Health disparities: In general, experts thought that daclizumab would have little impact on health disparities. Several experts noted that with third-party payer coverage and drug manufacturer’s copayment assistance programs, most MS drugs do not present a significant financial burdens to patients; these experts expected that daclizumab would be similarly subsidized.^{37,39,42} However, one research expert concluded that the anticipated cost of daclizumab could exacerbate disparities for some eligible, but economically disadvantaged patients.⁴⁰

Genetic Disorder Interventions

Conestat Alfa (Ruconest) for Treatment of Acute Hereditary Angioedema

Unmet need: Hereditary angioedema (HAE) is a life-threatening condition characterized by sudden and painful angioedema attacks, in which a patient's skin and other organs swell. It affects an estimated 6,000 to 10,000 individuals in the United States. Although several treatments are available, many patients experience significant side effects with them. The most effective treatment, a human C1 esterase inhibitor (C1INH, also called C1 inhibitor) concentrate from donated blood, replaces the protein that is deficient in HAE, but it is not always available.⁴³ The World Allergy Organization recommends that patients with HAE carry on-demand treatment for two attacks and know how to self-administer the drug.⁴⁴ An unmet need exists for a treatment for acute attacks with few side effects. Conestat alfa (Ruconest®) is a plasma-free, recombinant, human C1INH, approved by FDA in July 2014 that patients can self-administer when patients experience an acute attack.^{45,46}

Intervention: Conestat alfa is a recombinant human C1 esterase inhibitor (rhC1INH) for treating acute angioedema attacks in patients with HAE. It is produced in the milk of transgenic rabbits. Because it is not isolated from human blood, it does not carry a risk of transmitting human infectious agents. However, since it is produced by rabbits, patients who have an allergy to rabbits cannot use the drug. The drug's manufacturer states that patients must have a negative immunoglobulin E test for rabbit allergy every year or every 10 treatments, whichever comes first.⁴⁵

Conestat alfa is taken by IV infusion over 5 minutes. For the first dose, a clinician experienced in treating HAE supervises. Patients may be trained to recognize the onset of an acute attack and self-administer the drug. For patients who weigh less than 84 kg, the dose is 50 IU per kg. For patients who weigh 84 kg or more, the dose is 4,200 IU (2 vials). If symptoms persist, a second dose can be given, but no more than 2 doses should be given in 24 hours, according to the manufacturer.⁴⁷ In a clinical trial, most patients were reported to experience mild to moderate treatment-emergent adverse events.⁴⁸ The most common adverse events reported were headache, nausea, and diarrhea. A serious but uncommon adverse event reported was anaphylaxis.⁴⁷⁻⁴⁹ Although thromboembolic events have been reported with plasma-derived C1INH, none were reported with rhC1INH. Additionally, researchers did not identify any risk of deep vein thrombosis.⁵⁰

Clinical trials: One observational study is ongoing.⁵¹ In a phase III, randomized, placebo-controlled trial, authors reported the following:⁴⁹

Median (95% confidence interval) time to beginning of symptom relief at the primary attack location was 90 minutes (61-150) in rhC1INH-treated patients vs 152 minutes (93, not estimable) in placebo-treated patients ($P = .031$) based on the [Treatment Effect Questionnaire] and 75 minutes (60-105) vs 303 minutes (81-720, $P = .003$) based on a [visual analog scale] decrease of at least 20 mm. Median time to minimal symptoms was 303 minutes (240-720) in rhC1INH-treated patients vs 483 minutes (300-1,440) in placebo-treated patients based on the [Treatment Effect Questionnaire] ($P = .078$) and 240 minutes (177-270) vs 362 minutes (240, not estimable; $P = .005$), based on an overall [visual analog scale] less than 20 mm.

Reports from other studies state similar median times to onset of symptom relief and to minimal symptoms.^{48,52,53} Moldovan et al. (2012) reported that 87% of patients with acute HAE achieved symptom relief within 4 hours.⁵⁴

Manufacturer and regulatory status: Pharming Group NV (Leiden, the Netherlands) and Santarus, Inc., a wholly owned subsidiary of Salix Pharmaceuticals, Inc. (Raleigh, NC), jointly

developed conestat alfa under the trade name Ruconest.⁴⁵ In July 2014, FDA approved the drug for treating acute angioedema attacks in adult and adolescent patients with HAE.⁴⁶ Before the approval, FDA had granted conestat alfa orphan drug status. Conestat alfa is contraindicated in patients who have an allergy to rabbits or who have a history of immediate, life-threatening hypersensitivity reactions to C1INH preparations.⁴⁷

The manufacturers are also studying conestat alfa in phase II trials for preventing acute attacks. Patients administer the drug once or twice weekly for prophylaxis.⁵⁵ Conestat alfa has not been proved effective for the potentially fatal manifestation, laryngeal angioedema.⁵⁵

Diffusion and cost: The wholesale acquisition cost of conestat alfa is \$9,500 for 2 vials, the maximum single dose.⁵⁶ Dosing is weight dependent.⁴⁷ For comparison, the cost of one kit of a human C1INH concentrate, Berinert[®], is about \$2,500 per kit.⁵⁷ Pharming reported U.S. sales of about \$670,000 in the first quarter of 2015;⁵⁸ this is about 70 doses at the maximum dose. Between 6,000 and 10,000 people in the United States have HAE.⁴⁶

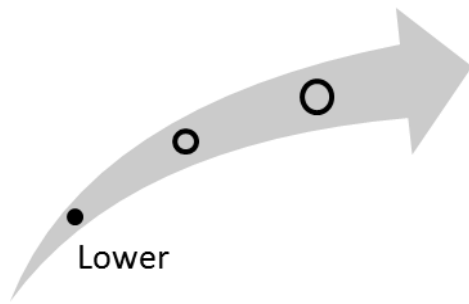
The U.S. Centers for Medicare & Medicaid Services has no national coverage determination for conestat alfa. Thus, coverage decisions are left to the discretion of local Medicare Part D prescription drug plans whether to include the drug on their formularies. To identify coverage policies, ECRI Institute 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 search found seven payers with policies that outline coverage criteria for conestat alfa.⁵⁹⁻⁶⁵ Blue Cross Blue Shield of Massachusetts does not provide coverage but is reviewing its policy.⁶⁶

Clinical Pathway at Point of This Intervention

Epinephrine is used to treat HAE in life-threatening reactions. The most efficacious treatment is a C1INH concentrate such as Berinert.⁶⁷ It is isolated from human blood products, and thus, supply may fluctuate.⁴³ Berinert may be self-administered during acute angioedema and is expected to compete with conestat alfa.⁶⁸ Berinert may cause significant adverse events including subsequent angioedema attacks, pain, muscle spasms, diarrhea, and vomiting.⁶⁸ Frozen plasma that contains C1INH will help during an episode as well. It is available to patients who seek hospital care for acute attacks; in rare cases, it may worsen swelling.^{43,67} During an attack, treatment involves pain relief and IV fluid administration.⁶⁷

Ecallantide (Kalbitor[®]) and icatibant (Firazyr[®]) are available for treating acute attacks by subcutaneous injection but may be less effective than C1INH concentrates. Although the drugs have different targets, both inhibit the effects of bradykinin, which is thought to be involved in HAE, and decrease the rate of C1INH catabolism. Ecallantide may cause anaphylaxis and cannot be self-administered.⁴⁴ Icatibant can be self-administered but may cause injection-site reactions, fever, increased liver enzymes, and rash.⁶⁸ Both drugs may compete with conestat alfa.

Figure 2. Overall high-impact potential: conestat alfa (Ruconest) for treatment of acute hereditary angioedema



Experts commenting on this intervention agreed that conestat alfa may improve patient health, although they differed over how important the unmet need is. Clinical experts stressed that supply issues with alternative treatments make this intervention more crucial in emergency scenarios. Conestat alfa may be readily accepted by clinicians and patients because of its good safety profile, easy administration, and effectiveness, experts commented. Health care infrastructure, patient management, and health disparities are not likely to be greatly affected by use of conestat alfa, experts said. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.⁶⁹⁻⁷⁴ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Although experts were split over the importance of the unmet need, two clinical experts noted a need for emergency treatment for HAE because of supply issues (e.g., Berinert) and lack of response in some patients for other options.^{73,74} Compared with alternative treatments, conestat alfa may improve patient health, experts agreed, because it may decrease time to onset of symptom relief, have fewer side effects, and be administered more easily at home.

Acceptance and adoption: Clinicians and patients are likely to accept conestat alfa because of its low side-effect profile, ease of administration, and effectiveness, experts said. Two experts suggested that supply issues with alternatives may increase adoption of conestat alfa.^{71,73} If comparative studies were performed that demonstrated effectiveness compared with Berinert, adoption may increase, two other experts noted.^{71,74}

Health care delivery infrastructure and patient management: Because conestat alfa is self-administered, experts expect little or no impact on health care delivery infrastructure. Patient management may be mildly disrupted because patients must be trained on administering the drug and be observed for allergic reactions for the first dose, experts said.^{69,74} Care may also be shifted to the home setting if conestat alfa effectively prevents patients from needing to seek emergency care, experts said; however, any reduction in hospital resource use will be limited due to the small patient population.

Costs for patients and third-party payers may increase with use of conestat alfa, due to its high list price, experts said. However, additional treatment costs may be offset if conestat alfa use reduces hospital visits, experts speculated.

Health disparities: Impact on health disparities may be limited, with most impact due to cost of the new drug, experts agreed.

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

Unmet need: Gaucher's disease is caused by a hereditary deficiency of glucocerebrosidase that leads to enlarged and malfunctioning organs, skeletal disorders, and painful neurologic complications because of glucosylceramide accumulation in these tissues. About 6,000 U.S. patients are affected by the disease, although not all of them experience symptoms.⁷⁵ The only oral drug approved for the disorder (miglustat; Zavesca®) is not available as first-line treatment; intravenous (IV) enzyme replacement therapy (ERT) is approved as first-line therapy and is the standard of care.⁷⁶ Eliglustat tartrate (Cerdelga™) is the first orally administered drug approved by FDA for first-line therapy.⁷⁷ It is intended to have fewer side effects than miglustat, which is known to cause diarrhea, abdominal swelling, tremor, and weight loss.

Intervention: Eliglustat tartrate, a self-administered oral compound, is FDA-approved as first-line treatment for Gaucher's disease. The drug purportedly partially inhibits the enzyme glucosylceramide synthase to reduce glucosylceramide production.^{78,79} Dosing depends on a patient's rate of CYP2D6 metabolism, determined by an approved genotype test. Patients who are extensive or intermediate metabolizers take 84 mg, twice daily. Patients who are poor metabolizers take 84 mg, once daily. Patients who are ultra-rapid metabolizers cannot use eliglustat tartrate because they may not achieve adequate concentrations for therapeutic effect. A specific dose cannot be recommended for patients who are indeterminate metabolizers.⁷⁷

Clinical trials: Three phase III trials are ongoing.⁸⁰⁻⁸² The ENCORE trial, which is evaluating the percentage of patients whose disease remains stable during eliglustat tartrate treatment, reported in the per-protocol population, 85% (84/99) patients who completed eliglustat treatment and 94% (44/47) of 47 patients who completed IV ERT with imiglucerase met the composite primary endpoint for non-inferiority. The between-group difference was -8.8% (95% CI -17.6 to 4.2).⁸³

Another phase III trial is the ENGAGE trial (n=40) for evaluating improvement (i.e., reduction) in spleen size. Researchers reported that the least-square mean spleen volume decreased by about 28% (95% CI, -33% to -23%) in the eliglustat group and increased about 2% (95% CI, -3% to 7%) in the placebo group.⁸⁴ (We rounded reported figures to the nearest whole number.)

Manufacturer and regulatory status: Genzyme Corp., a subsidiary of Sanofi (Paris, France), developed eliglustat tartrate for treating type 1 Gaucher's disease.⁷⁹ FDA approved eliglustat tartrate in August 2014 "...for the long-term treatment of adult patients with Gaucher[s] disease type 1 who are CYP2D6 extensive metabolizers (EM), intermediate metabolizer (IM), or poor metabolizers (PM) as detected by an FDA-cleared test."⁷⁷ Eliglustat tartrate is available through specialty pharmacies.⁸⁵

As conditions of FDA approval, Genzyme must complete two postmarketing clinical trials to evaluate the effects of renal and hepatic impairment on eliglustat tartrate pharmacokinetics, to be completed in 2017. Genzyme has further committed to developing 21 mg and 42 mg dose strengths to accommodate dosage adjustments.⁷⁷

Diffusion and cost: The company reported about \$15,778,000 in U.S. Cerdelga net sales the first quarter of 2015.⁸⁶ According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, eliglustat tartrate costs about \$316,000 per patient per year (when taken twice daily, based on costs for 56 capsules of 84 mg each),⁸⁵ compared with \$300,000 to \$350,000 per patient per year for IV ERT.⁸⁷⁻⁸⁹ Genzyme offers a copayment assistance program for U.S. patients who have commercial insurance and prescription drug coverage. The program covers 100% of out-of-pocket expenses including copayments, co-insurance, and deductibles up to the program maximum, regardless of financial status. Patients are ineligible if they have insurance or prescription coverage

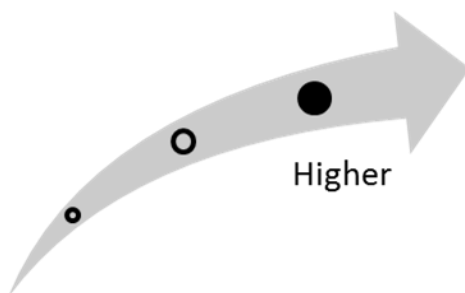
in part or in full from any State or Federal health care program (e.g., Medicare, Medicaid, Medigap, Veterans Affairs).⁹⁰

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 four formularies listing eliglustat tartrate;⁹¹⁻⁹⁴ five payers have policies that may cover eliglustat tartrate with prior approval.⁹⁵⁻⁹⁹

Clinical Pathway at Point of This Intervention

Approaches to Gaucher's disease treatment have taken two routes: administering exogenous glucocerebrosidase enzyme (i.e., ERT) or inhibiting upstream components of the glucosylceramide biosynthetic pathway (i.e., substrate reduction). ERT (e.g., imiglucerase, taliglucerase alfa) is the standard first-line treatment.¹⁰⁰ ERT is expensive and requires lifelong IV infusions every 2–3 weeks.¹⁰¹ A temporary break from ERT because of personal issues or changes in lifestyle can lead to disease progression. 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.¹⁰² Miglustat frequently causes side effects, such as diarrhea, abdominal swelling, tremor, and weight loss that affect patient acceptance. Further, the associated clinical improvements of miglustat are reported to be less effective and slower than that of ERT.¹⁰⁰

Figure 3. Overall high-impact potential: eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1



Overall, experts commenting on this intervention suggested that patients need a more convenient treatment for Gaucher's disease, and the oral compound eliglustat tartrate might increase patient adherence to treatment recommendations. In doing so, they thought, it could lead to improved health outcomes and quality of life. Experts anticipated widespread adoption of eliglustat tartrate, because of its convenience as an oral drug. Furthermore, experts suggested that its adoption could reduce demand on infusion centers and shift the care setting to home care. The experts noted that the drug's impact potential is contingent on eliglustat tartrate being proved as effective as or more effective than the standard of care. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

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

Unmet need and health outcomes: An unmet need exists for a treatment with easier administration than IV ERT, experts agreed. An oral drug might improve outcomes by increasing

patient compliance with treatment and improving quality of life, experts also agreed. Two experts with research perspectives called for more trials comparing eliglustat tartrate to standard treatment and studying its long-term efficacy.^{107,108}

Acceptance and adoption: Acceptance from clinicians is likely to be high, experts agreed. Clinicians are likely to prefer the oral drug if it increases patient compliance with treatment and therefore improves patient health, one expert with a health systems and administration perspective said.¹⁰⁶ Patients are likely to prefer oral administration over IV ERT, experts concurred. For patients for whom cost is not a barrier, acceptance will be high, experts said.^{104,107}

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

Health disparities: The high cost of the drug might prevent some patients from accessing it, especially those who are insured through State or Federal agencies (because they are ineligible for the manufacturer's assistance program) or those without insurance, several experts noted. Conversely, ease of administration might reduce access issues for patients who find it difficult to get IV infusions once every 2–3 weeks, one expert with a research perspective thought.¹⁰³ A clinical expert pointed out that populations that are disproportionately affected by Gaucher's disease (e.g., Ashkenazi Jews) would benefit from this treatment option.¹⁰⁵

Elosulfase Alfa (Vimizim) for Treatment of Morquio A Syndrome

Unmet need: Mucopolysaccharidosis type IV A, commonly known as Morquio A syndrome, is a rare, autosomal recessive inherited metabolic disorder caused deficiencies in *N*-acetylgalactosamine-6-sulfatase, an enzyme that degrades glycosaminoglycans such as keratan sulfate (KS).^{109,110} *N*-acetylgalactosamine-6-sulfatase deficiencies occur when the *N*-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) gene is mutated; deficiencies cause abnormal KS accumulation in bone, the cornea, synovial fluid, connective tissue, tendons, and urine.¹¹⁰⁻¹¹² This excess KS results painful, potentially fatal cardiovascular, locomotor, postural, and sensory signs and symptoms such as conductive or sensorineural hearing loss, hydrocephalus, spinal cord compression, and systemic skeletal dysplasia (dwarfism).^{111,113}

Prior to elosulfase alfa's approval, standard of care for Morquio A syndrome was palliative treatment only, including orthopedic surgeries and assistive devices to address sensory and motor symptoms.^{111,114,115} Disease progression may dictate multiple surgical interventions, especially when patients' respiratory function declines significantly. Additionally, pediatric patients with severe signs and symptoms may survive only to late adolescence. A need exists for treatments that target underlying causes of Morquio A syndrome and provide improvement or relief for the disorder's most incapacitating symptoms.

Intervention: Elosulfase alfa is a purified synthetic human form of *N*-acetylgalactosamine-6-sulfatase, composed to mediate cellular uptake to lysosomes and hydrolyze sulfate from nonreducing ends of glycosaminoglycans.^{116,117} This ERT is intended to address *GALNS* deficiencies and stimulate catabolism of excess KS.^{113,116,118} Theoretically, elosulfase alfa therapy can prevent or treat certain reversible functional symptoms of Morquio A syndrome and may also supplement traditional palliative care.

In its approved formulation, elosulfase alfa is intravenously infused in a weekly dosage of 2 mg/kg, delivered over a minimum of 3.5–4.5 hours.¹¹⁶

Clinical trials: In an ongoing phase III trial (n=176), adolescent patients with Morquio A syndrome are receiving placebo, weekly 2.0 mg/kg elosulfase alfa infusions, or biweekly 2.0 mg/kg elosulfase alfa infusions.¹¹⁹ At 24 treatment weeks, weekly elosulfase alfa administration improved patient ambulation compared to placebo, measured on the 6-minute walk test (estimated mean effect, 22.5 meters; 95% CI, 4.0 to 40.9; p=0.017); however, investigators found no significant treatment-based improvements on another standard ambulation measure, the 3-minute stair climb test. Weekly and biweekly elosulfase alfa treatments were also associated with normalized urine KS levels compared to placebo.¹¹⁹ Infusion-related adverse events were observed in 22.4% of patients, representing 1.3% of all infusions, but no adverse events led to treatment discontinuation.¹¹⁹ Similar findings were reported from smaller clinical trials.^{120,121}

In 2013, an ongoing phase II clinical trial (n=15) reported preliminary data for elosulfase alfa's efficacy in treating pediatric patients younger than 5 years old. After 26 treatment weeks, researchers noted that 8 patients receiving weekly 2.0 mg/kg elosulfase alfa infusions demonstrated statistically significantly decreased normalized urine KS levels; however, they did not report ambulation efficacy data.¹²²

Additional ongoing clinical trials are examining elosulfase alfa's treatment efficacy in American and international patients with Morquio A syndrome.¹²³⁻¹²⁷

Manufacturer and regulatory status: BioMarin Pharmaceutical, Inc. (San Rafael, CA), manufacturers elosulfase alfa, branded in all markets as Vimizim[™].¹¹⁶ In February 2014, FDA approved elosulfase alfa as the first medication for treating Morquio A syndrome.¹²⁸

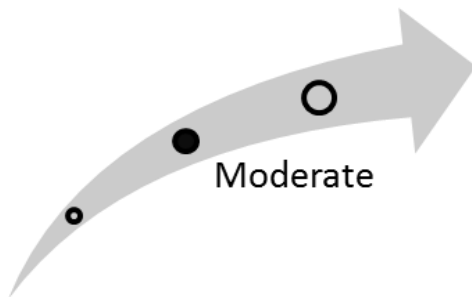
Diffusion and costs: BioMarin’s 2015 first-quarter financial report noted that worldwide elosulfase alfa sales exceeded \$127 million for the four quarters since its initial commercial launch. Projected 2015 elosulfase alfa revenues are between \$200 million and \$220 million, driven by strong patient identification and sales in approved markets.¹²⁹ In an April 2015 earnings call, BioMarin executives noted that, to date, approximately 1,700 patients worldwide are receiving elosulfase alfa. The company anticipates a full global market of 3,000 patients, although country-by-country figures were not disclosed.¹³⁰

BioMarin initially priced elosulfase alfa at \$1,069 per 5 mg, with estimated annual per-patient treatment costs of \$380,000, assuming a pediatric patient weighing approximately 22.5 kg.¹³¹ As a bodyweight-dependent medication, costs vary between patients, mainly based on age.¹¹⁶

Clinical Pathway at Point of This Intervention

Palliative treatments—including surgical procedures to alleviate patients’ associated cardiovascular, respiratory, and sensory symptoms—are the standard of care for Morquio A syndrome.^{115,132} Upper cervical spinal fusion is among the most common palliative surgical procedures for this disorder and is performed during childhood to prevent subluxation of the first cervical vertebra on the second, which can result in spinal cord compression.^{113,132} Elosulfase alfa is the only ERT for treating Morquio A syndrome and is the only FDA-approved medication for this indication.

Figure 4. Overall high-impact potential: elosulfase alfa (Vimizim) for treatment of Morquio A syndrome



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

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.¹³³⁻¹³⁹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts’ consensus opinion was that, as the only approved nonpalliative intervention for treating Morquio A syndrome, elosulfase alfa has significant potential to address an unmet need. These experts, however, thought that elosulfase alfa has only moderate potential to improve patient health outcomes, citing factors such as the drug’s limited demonstrated

efficacy for improving patients' functional independence and potential treatment-related adverse events.^{134,135,139}

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

Health care delivery infrastructure and patient management: Despite requiring patients and clinicians to shift from present standard of care to incorporating regular outpatient infusion therapy, overall, elosulfase alfa use would cause minimal impact on health care delivery infrastructure and patient management, the experts concluded. Two experts stated that any treatment-related patient health outcome improvements would actually lead to reduced patient management burdens, and they anticipated that long-term elosulfase alfa use would better reveal these potential patterns.^{136,138} However, one expert with a research background thought that further elosulfase alfa diffusion could increase clinical staff requirements and subsequent patient management resource use.¹³⁴

Health disparities: Most experts stated that elosulfase alfa would have little effect on health disparities, although two experts noted that the drug's high cost could increase health disparities for eligible economically disadvantaged patients.^{134,139}

Exon-Skipping Therapies (Drisapersen and Eteplirsen) for Treatment of Duchenne Muscular Dystrophy

Unmet need: Duchenne muscular dystrophy (DMD) is a rare, X-linked recessive form of muscular dystrophy, caused by mutations in the dystrophin gene; as an X-linked disorder, DMD primarily affects males.^{140,141} Normally, dystrophin encodes the dystrophin protein, which is important for muscle tissue strength. Dystrophin gene mutations result in a lack of dystrophin protein, compromising muscle cells structural integrity and making those cells increasingly susceptible to damage.¹⁴¹ These muscle deficiencies result in potentially fatal symptoms including heart defects, muscle weakness, and problems with motor skills and respiratory function.^{142,143}

DMD symptoms often manifest by age 6 and may be apparent during infancy.^{140,144,145} Standard treatment for DMD is palliative, concentrated on managing patients' most prominent symptoms.¹⁴⁰ Muscle weakness forces many patients to use wheelchairs in early adolescence, and later respiratory and cardiac symptoms can require other assistive interventions.^{140,141} Advances in cardiac and respiratory care have extended DMD patients' average life expectancy, but most patients succumb to DMD-related symptoms by age 40.^{141,146} No cure exists for DMD, and an unmet need exists for effective treatments that improve patients' severe symptoms and enhance patients' functional independence and overall quality of life.

Intervention: Drisapersen is an investigational 2'-O-methyl phosphorothioate oligonucleotide, synthesized as a single-strand RNA sequence complimentary to the 79-exon dystrophin gene.¹⁴⁷⁻¹⁴⁹ In contrast, eteplirsen is an experimental phosphorodiamidate morpholino oligomer (PMO), a member of a class of synthetic molecules expressly developed to modify expression of various genes.¹⁵⁰ Biochemically, both drugs function as antisense oligomer therapeutics, altering the splicing activity of dystrophin RNA transcript.^{149,150}

Although mutations to multiple dystrophin gene loci can result in nonfunctioning dystrophin gene and subsequent dystrophy disorders, drisapersen and eteplirsen are explicitly designed to treat patients with DMD caused by defects in dystrophin exon 51.^{148,149} By inducing skipping of this defective exon, these drugs purportedly enable production of functioning dystrophin protein, addressing an underlying biochemical cause of severe DMD signs and symptoms and potentially delaying disease progression.^{147,151} Based on genetic studies, as many as 13% of all adolescent male patients with DMD have dystrophin gene mutations associated with exon 51 and may be eligible for drisapersen or eteplirsen therapy.¹⁵²

Investigators have studied multiple delivery routes for drisapersen and at dosages up to 9 mg/kg weekly, but if approved, the drug will likely be marketed as a subcutaneous injectable.^{147,151,153,154} Eteplirsen, on the other hand, is administered via weekly IV infusion; 30 and 50 mg/kg are the most commonly tested doses.^{155,156}

Clinical trials: The DEMAND trial series has enrolled the largest patient population investigating drisapersen's treatment efficacy.^{157,158} Adolescent male patients (n=186), aged 5 years or older, were assigned to receive placebo, 3 mg/kg drisapersen weekly, 6 mg/kg drisapersen weekly, or alternating weekly and biweekly 3 mg/kg drisapersen with a washout period.¹⁵⁷ After 48 treatment weeks, investigators reported "clinically significant" differences in ambulation between patients receiving drisapersen and those receiving placebo;¹⁵⁷ assays also demonstrated that patients administered drisapersen had higher systemic levels of functional dystrophin protein.¹⁵⁹ However, further analyses of these patients' data showed no statistically significant treatment-related improvement in 6-minute walk test performance.¹⁵⁸ Safety analyses noted that drisapersen was relatively well-tolerated across all trials.

Eteplirsen has been studied in small cohort of adolescent male patients (n=12), continuously tracked for more than 3 years. In this ongoing clinical trial, patients receive 30 or 50 mg/kg eteplirsen via weekly IV infusion, with ambulation and respiratory measures recorded regularly, most recently after 168 treatment weeks.¹⁶⁰ Although eteplirsen treatment was associated with delayed ambulatory declines and improved stability of respiratory function at 24 and 120 treatment weeks,¹⁶¹ after 168 weeks, ambulatory function in patients receiving eteplirsen had begun to decline at a rate comparable to that observed in untreated patients.¹⁶⁰ Similarly, analysis of long-term respiratory measures demonstrated limited, and inconsistent, benefit for sustained eteplirsen treatment compared to untreated patients with DMD across measured time points.¹⁶⁰⁻¹⁶²

Ongoing clinical trials are examining the long-term safety and efficacy of both drugs, including their impacts on patient quality of life and overall disease progression.

Manufacturer and regulatory status: Drisapersen was originally manufactured and developed by Prosensa Therapeutics (Leiden, the Netherlands); Prosensa was acquired by BioMarin Pharmaceutical in 2015.¹⁶³ FDA has granted this drug breakthrough therapy designation and orphan drug and fast-track statuses.¹⁵² In October 2014, Prosensa began filing a rolling new drug application (NDA) for drisapersen; BioMarin completed this submission in April 2015.¹⁶⁴

Sarepta Therapeutics, Inc. (Cambridge, MA; formerly AVI BioPharma, Bothell, WA), is developing eteplirsen for treating DMD. In 2007, FDA granted fast-track and orphan drug statuses to eteplirsen for treating DMD. Sarepta initially announced intentions to pursue early FDA approval for eteplirsen in fall 2014, but delayed those plans after meetings between company executives and FDA regulators.¹⁶⁵ FDA noted that, to complete its submission, Sarepta needed to include independent assessments of eteplirsen's effect on dystrophin protein, along with additional safety and long-term efficacy data; Sarepta plans to complete a rolling NDA by the end of 2015.¹⁶⁶

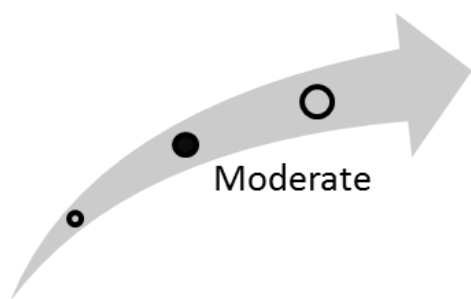
Diffusion and costs: Neither exon-skipping therapy is approved, so diffusion information is unavailable beyond clinical trial enrollment data. Based on reported clinical trial data, approximately 200 to 250 patients have received drisapersen or eteplirsen in clinical trials, with the majority of patients administered drisapersen.

BioMarin and Sarepta have not publicized anticipated pricing for drisapersen or eteplirsen. BioMarin has priced its recently approved, chronically administered therapies for genetic diseases with significantly lower incidence rates than DMD at up to \$1,200 per patient, per day.¹³¹ Drisapersen may be priced similarly or lower due to demand and imminent market competition. BioMarin has established financial assistance programs to offset patients' direct costs for pharmaceuticals to treat rare and orphan diseases; if approved, drisapersen might be integrated into these programs.¹⁶⁷ Comparatively, Sarepta may price eteplirsen to compete with drisapersen, depending on both drugs' approval dates; as a putative "tent pole" product for its company, eteplirsen could also be initially priced at a premium to drisapersen.

Clinical Pathway at Point of This Intervention

DMD standard of care is principally palliative, with interventions addressing patients' most pronounced symptoms. Orthopedic devices—including wheelchairs and braces—can compensate for lost mobility; steroids treat declining cardiac and general muscle function; medications and assisted breathing devices address respiratory issues; and educational interventions mediate any associated learning disabilities.^{140,168,169} Exon-skipping therapies could be prescribed prior to or adjunct to palliative care, in an attempt slow symptom progression and delay or reduce reliance on supportive devices.

Figure 5. Overall high-impact potential: exon-skipping therapies (eteplirsen and drisapersen) for treatment of Duchenne muscular dystrophy



Consulted experts agreed that a significant unmet need exists for effective, nonpalliative therapies for treating DMD. Despite noting limited clinical efficacy, overall, these experts thought that exon-skipping therapies, if approved, offer new options that could improve patient health outcomes. Accordingly, experts also anticipated that these two drugs would be widely accepted by patients and adopted by clinicians. Several experts reserved full support for these interventions because of a lack of clear treatment efficacy but still thought that the drugs would have substantial impact. Based on this input, our overall assessment is that these interventions are in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical and research backgrounds, offered perspectives on drisapersen for treating DMD,¹⁷⁰⁻¹⁷⁵ and six experts, with similar backgrounds, commented on eteplirsen for treating the same indication.¹⁷⁶⁻¹⁸¹ Of the consulted experts, two clinical respondents offered opinions on both interventions.^{170,174,177,181} We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Evaluating the limited treatment options for patients with DMD, experts' consensus opinion was that an important unmet need exists for effective, nonpalliative therapies for this patient population. These experts concluded that drisapersen and eteplirsen have significant potential to address this unmet need and could improve patient health outcomes including quality of life and, potentially, life expectancy. Although this opinion was shared by all experts, multiple experts tempered their support by noting that only a subset of patients with DMD would be eligible for these interventions, somewhat limiting their impact.^{170,171,181}

Acceptance and adoption: All consulted experts concluded that the paucity of nonpalliative therapies for treating DMD would drive widespread acceptance and adoption by clinicians and patients, despite any limitations in treatment efficacy or eligible patient population.

Health care delivery infrastructure and patient management: Given the significant resource and patient management demands required to serve patients with DMD, most commenting experts considered drisapersen and eteplirsen to have minimal potential impact in these domains. However, one research expert evaluating drisapersen stated that if the drug were to be widely used long-term, it could potentially lead to significant disruptions in patient management compared to present standards.¹⁷⁴

Health disparities: Experts were divided in their opinions on exon-skipping therapies' potential effect on health disparities. Although many experts foresaw no or minimal impact, the remaining experts thought that drisapersen and eteplirsen could have moderately or significantly exacerbate disparities, with all dissenting experts citing the potential drug costs as the sole contributing factor.^{171,172,176,178}

Idebenone (Catena) for Treatment of Duchenne Muscular Dystrophy

Unmet need: Patients who have DMD often exhibit respiratory dysfunction, with worsening symptoms as the disease progresses.^{142,143} Respiratory problems are the cause of death in more than 70% of patients with DMD.^{141,146} Palliative care is standard treatment for DMD, but these interventions have limited efficacy, particularly among older adolescent and young adult patients.¹⁴⁰

An unmet need exists for effective therapies that can improve respiratory function and delay respiratory declines, positively affecting patients' quality of life and potentially extending patients' lifespans.

Intervention: Idebenone is a short-chain benzoquinone, structurally similar to coenzyme Q₁₀ but with significantly higher therapeutic potential.^{182,183} Prior studies established that idebenone has potent antioxidant and cytoprotective properties.¹⁸² Because DMD is associated with excessive, mitochondrial defect-driven oxidative cell damage, these properties suggest that idebenone may be an effective therapy for patients with DMD.¹⁸²

Hypothetically, idebenone functions as a transporter molecule, moving electrons directly from the cytoplasm to complex III of the mitochondrial respiratory chain.^{182,184} This direct transit bypasses pathways affected by mitochondrial defects, supporting sustained adenosine triphosphate (ATP) production and offsetting muscle-wasting symptoms commonly observed in patients with DMD.^{182,185}

Idebenone is an oral medication, formulated as a 150 mg tablet. In clinical trials, the drug is administered in dosages between 450 mg and 900 mg (3–6 tablets) daily and is well-tolerated by patients.^{186,187}

Clinical trials: DELOS was a phase III clinical trial (n=64) examining the comparative efficacy of idebenone to placebo on several measures of respiratory function; the primary endpoint was percent change from baseline in predicted peak expiratory flow rate (PEFR). This trial concluded in 2014, with initial peer-reviewed results reported in an April 2015 issue of *The Lancet*.¹⁸⁸ In the trial, American and European corticosteroid-free adolescent patients with DMD were randomly assigned to receive 900 mg idebenone or placebo daily.

After 52 treatment weeks, percent of predicted PEFR declined significantly (-9.01% predicted; 95% CI, -13.2 to -4.8; p<0.001) in the placebo group, while percent of predicted PEFR did not decline significantly in patients administered idebenone (-3.05% predicted; 95% CI, -7.1 to 0.97; p=0.134). Between-group comparison of percent of predicted PEFR was statistically significant (5.96% predicted; 95% CI, 0.16 to 11.8; p=0.044) after 52 weeks. Idebenone was associated with a 66% reduction in loss of percent predicted PEFR over the trial week at 52, with significant treatment effects also observed after 26 (p=0.007) and 39 (p=0.034) treatment weeks. Of note, the investigators based their sample size calculations on a 10.3% between-group difference in percent predicted PEFR, which presumably is a clinically important difference.

Overall, compared to the placebo group, patients administered idebenone showed improvements after 52 treatment weeks on 7 additional measures of respiratory function, including forced vital capacity at 52 weeks.^{187,188} Investigators also observed fewer respiratory tract infection-related adverse events among patients receiving idebenone than in patients receiving placebo.¹⁸⁸

Manufacturer and regulatory status: Takeda Pharmaceutical Co., Ltd. (Osaka, Japan), initially developed idebenone as an investigational Alzheimer's disease drug. Santhera Pharmaceuticals Holding AG (Liestal, Switzerland) presently develops and manufactures idebenone for treating DMD. FDA granted orphan drug status to idebenone for treating DMD in February 2007 and granted fast-track status for the same indication in April 2015.^{189,190} Following FDA's

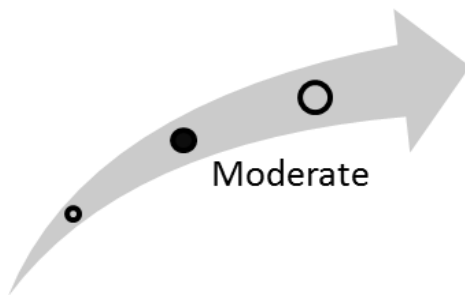
fast-track designation, Santhera announced that it was preparing an NDA for idebenone and has started pre-NDA meetings with FDA.^{190,191}

Diffusion: Idebenone has not been approved for treating DMD. With optimistic NDA submission and approval timelines, idebenone's earliest prospective commercial availability may be in the first-half of 2016. Accordingly, this drug has not diffused beyond clinical trial patients.

Clinical Pathway at Point of This Intervention

No disease-modifying therapies are approved for treating DMD; standard of care is primarily palliative care addressing one or more most-severe symptoms. As a medication that does not modify the disease, idebenone is projected as an adjunct to palliative intervention, primarily intended to delay or prevent respiratory declines associated with DMD. We note that if eteplirsen and drisapersen, the exon-skipping therapies discussed earlier, are approved, they may also compete with or complement idebenone.

Figure 6. Overall high-impact potential: idebenone (Catena) for treatment of Duchenne muscular dystrophy



Experts commenting on this intervention acknowledged that a substantial need exists for additional, effective DMD medications and thought that idebenone could address this need. These experts thought that idebenone's demonstrated treatment efficacy and patient tolerance would support its broad acceptance by clinicians and patients. Experts anticipated that this intervention would minimally disrupt patient management and health care delivery infrastructure, while also having limited impact on health disparities. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Five experts, with clinical and research backgrounds, provided perspectives on this intervention.¹⁹²⁻¹⁹⁶ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts unanimously agreed that a significant unmet need exists for interventions that effectively treat severe DMD symptoms. Experts also stated that idebenone has demonstrated effectiveness in clinical trials for improving patients' respiratory function and has substantial potential to improve patient health outcomes.¹⁹³⁻¹⁹⁵

Acceptance and adoption: Experts anticipated that idebenone would likely be widely accepted by clinicians and patients, favorably noting its oral formulation, solid safety profile, and potential benefits to patients' quality of life. Experts also anticipated that a lack of competing approved DMD medications could drive acceptance and adoption.

Health care delivery infrastructure and patient management: Overall, experts concluded that because idebenone is an oral medication, it would not dramatically affect health care delivery

infrastructure and patient management. Some experts stated that idebenone diffusion could eventually lessen patient management demands, but desired long-term efficacy data to support these opinions.^{193,194,196}

Health disparities: Experts thought that idebenone, with its relatively small intended patient population, would not significantly impact health disparities. However, experts also acknowledged that idebenone's potential cost could increase health disparities, although they anticipated that third-party coverage and financial support programs may minimize patients' financial burdens.

L-Glutamine for Prevention of Vaso-Occlusive Crises in Sickle Cell Disease

Unmet need: Sickle cell disease (SCD) is characterized by painful vaso-occlusive crises (VOCs) caused by an accumulation of sickled red blood cells that block blood vessels and may lead to death. Standard prophylactic and acute treatment is a myelosuppressive chemotherapeutic agent called hydroxyurea; however, the drug is effective for only two-thirds of affected adults and increases the risk of infection.¹⁹⁷ Therefore an unmet need exists for treatment alternatives for patients with SCD. Researchers are investigating whether pharmaceutical-grade L-glutamine taken prophylactically might prevent VOCs, reducing pain and hospitalizations for patients with SCD.

Intervention: Although the exact mechanisms leading to VOCs are unclear, researchers speculate that oxidative stress, adhesive leukocytes, and chronic inflammation play roles. When sickled red blood cells start to accumulate in blood vessels, they activate a feedback loop that exacerbates inflammation and produces reactive oxygen species. Ischemia caused by the blockage contributes to the feedback loop. Together, these dynamic events may lead to a VOC.¹⁹⁸

L-glutamine is a nonessential amino acid naturally produced by the body. Among its many roles, L-glutamine acts as a precursor to nicotinamide adenine dinucleotide (NAD), an electron acceptor that reduces oxidative stress in cells. Therefore, supplementing L-glutamine levels may increase the NAD concentration, potentially altering the redox state of red blood cells. This mechanism potentially interrupts the feedback loop involving reactive oxygen species and could prevent VOCs.¹⁹⁹ Pharmaceutical-grade L-glutamine differs from an over-the-counter dietary supplement because it is manufactured according to FDA standards regarding purity, stability, concentration, batch-to-batch consistency, and reliability.²⁰⁰ In clinical trials, it is administered twice daily at a dose of 0.3–0.6 g/kg. Doses are rounded to 5 or 10 g increments with an upper limit of 30 g per day. L-glutamine comes in the form of a powder that can be mixed with water or unheated beverages and foods (e.g., yogurt, applesauce, cereal). It should not be mixed with alcohol, soda, or highly acidic juices.^{199,201} In one clinical trial, adverse events for patients taking L-glutamine were similar to those observed in patients taking placebo.¹⁹⁹

Clinical trials: No ongoing trials are registered at the National Clinical Trials database (ClinicalTrials.gov). A phase III, randomized, placebo-controlled trial (n=230) was conducted to evaluate the effect of L-glutamine on reducing the incidence of VOCs. Patients in the trial were stratified by hydroxyurea use and assigned to treatment with L-glutamine or placebo in a 2:1 ratio. The drug was administered daily for 48 weeks and tapered off over 3 weeks before the final evaluation was made 2 weeks later. Niihara et al. (2014) reported that the median incidence of VOC was lower in the treatment group than the placebo group (3 events vs. 4 respectively; p=0.008). The median incidence of hospitalization was also lower in the treatment group than placebo group (2 events vs. 3 events respectively; p=0.005), and median cumulative hospital days were reported to be lower by 41% (6.5 days treatment group vs. 11 days placebo group, p=0.022). Acute chest syndrome occurred in 11.9 % of the L-glutamine group and 26.9% of the placebo group (p=0.006). The median time-to-first crisis was 54 days in placebo group and 87 days in treatment group (p=0.010).¹⁹⁹

Manufacturer and regulatory status: Emmaus Life Sciences, Inc. (Torrance, CA), is developing pharmaceutical-grade L-glutamine for preventing VOCs in patients with SCD. FDA has granted the intervention orphan drug and fast-track statuses for treating SCD.¹⁹⁷ Emmaus completed a phase III trial in March 2014. After meetings with FDA in June and October 2014, Emmaus has indicated that it intends to submit an NDA to FDA sometime in 2015 while simultaneously initiating a confirmatory phase III trial.²⁰²

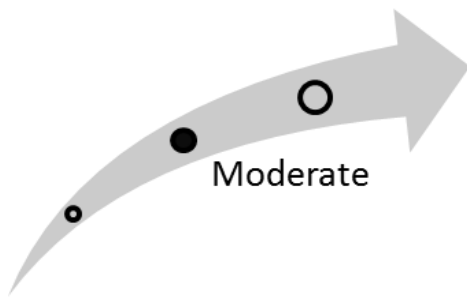
Diffusion and cost: No cost information is available because FDA has not approved L-glutamine for preventing VOCs in patients with SCD. However, Emmaus Life Sciences produces a powdered form of L-glutamine, Nutrestore[®], approved for nutritional support in patients with short bowel syndrome; it costs about \$300 for 84 packets of 5 g each.²⁰³ For patients with SCD taking the maximum daily dose (30 g), this is a 2-week supply.

No coverage, coding, or payment information is available yet; if the drug gains approval, we anticipate third-party payers would reimburse for the drug, although co-pays may be high.

Clinical Pathway at Point of This Intervention

The only possible cure for SCD is bone marrow or stem cell transplant. Because of the high risks associated with these procedures, they are usually done only in severe cases for children with minimal organ damage.²⁰⁴ Treatment primarily focuses on pain management and symptom control.^{205,206} Antibiotics prevent infections, which patients with SCD are vulnerable to, while pain relievers help during a VOC.²⁰⁵ An expert-panel report issued by the National Institutes of Health in 2014 also recommends the use of hydroxyurea,^{206,207} which stimulates the production of fetal blood cells, but this has potential risks of cytopenias (decrease in number of any of the cellular blood components) and increased infection.²⁰⁵ If approved, L-glutamine may be used as first- or second-line therapy in patients who cannot tolerate hydroxyurea.

Figure 7. Overall high-impact potential: L-glutamine for prevention of vaso-occlusive crises in sickle cell anemia



Experts commenting on this intervention agreed that a substantial unmet need exists for reducing pain, VOCs, and hospitalizations. Clinicians and patients may readily adopt L-glutamine because it appears safe, is an oral drug, and cost will not be prohibitive, experts said. Experts noted that it is unlikely to affect health care delivery infrastructure or patient management. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.²⁰⁸⁻²¹³ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A substantial unmet need exists for an SCD therapy that prevents VOCs, hospitalizations, and pain, without intolerable side effects, experts agreed. L-glutamine may improve patient health by reducing the incidence of VOCs and the total days spent in the hospital, experts thought, basing their opinions on the limited data available. One clinical expert suggested L-glutamine is suited for second-line therapy in patients who do not tolerate hydroxyurea, a drug that lowers mortality risk associated with VOC.²¹²

Acceptance and adoption: Acceptance from clinicians and patients is likely to be high, experts agreed. Positive features of the drug that experts cited to support their opinions include its oral, at-home administration, good safety profile, and likely acceptable cost.

Health care delivery infrastructure and patient management: As an oral drug, L-glutamine is unlikely to have an impact on health care delivery infrastructure, experts said. Most experts noted that L-glutamine use may decrease the frequency and duration of hospital visits. Patient management may involve less clinician monitoring for side effects and fewer hospitalizations with use of L-glutamine, experts thought. The cost of the drug is unlikely to significantly increase overall health care costs and may offset some costs by reducing hospital use, experts noted.

Health disparities: Health disparities among minority ethnic groups disproportionately affected by SCD (e.g., African Americans, Asians) may improve with use of an oral drug that may be taken at home, experts thought.

Migalastat Hydrochloride (Galafold) for Treatment of Fabry Disease

Unmet need: Fabry disease is a genetic disorder characterized by cellular buildup of globotriaosylceramide, a type of fat that causes a wide range of symptoms and can lead to heart attack, stroke, and kidney damage. Treatment for Fabry disease is enzyme replacement therapy (ERT) using recombinant alpha-galactosidase A (alpha-GAL) enzyme; however, ERT has multiple shortcomings, including variable tissue distribution, a requirement for weekly or biweekly IV infusions, and the high cost and complexity of recombinant protein manufacturing.²¹⁴ Migalastat (Galafold™) is an orally administered, small-molecule modulator of alpha-GAL activity intended to potentiate the activity of endogenous residual alpha-GAL as a monotherapy or potentiate the activity of exogenously provided alpha-GAL activity as a combination therapy with ERT.²¹⁵

Intervention: Migalastat is intended to function as a pharmacologic chaperone for alpha-GAL, which is deficient in Fabry disease. Chaperones ensure proper folding of target proteins, an essential process for full enzymatic activity and proper trafficking within the cell.²¹⁶ Many of the mutations that cause Fabry disease are missense mutations (in which one amino acid is changed), causing misfolded proteins to be prematurely degraded in the endoplasmic reticulum instead of moved to the lysosome to carry out their function. Migalastat is intended to promote the proper folding of endogenous alpha-GAL for proper trafficking and function.²¹⁵ Restored enzymatic activity of alpha-GAL reduces the levels of globotriaosylceramide (GL-3) and prevents its damaging accumulation. Migalastat may also work as a combination therapy with ERT by binding to and stabilizing the exogenous alpha-GAL and increasing uptake in affected organs.²¹⁷

To test a patient's potential response to migalastat, the manufacturer has developed a cell-based in vitro assay with a third party to test the enzymatic activity of each patient's alpha-GAL when it is exposed to migalastat.^{218,219} Based on this test, the manufacturer estimates 30% to 50% of patients with Fabry disease have mutations that are suited to migalastat monotherapy.²¹⁸ Migalastat is administered orally; the optimal dosage is still under study. In clinical trials, it is administered at a dosage of 150 mg every other day or 250 mg in cycles of 3 days on and 4 days off.²²⁰ The manufacturer reported that migalastat was generally well tolerated in phase II and III clinical trials. No severe adverse events have been reported. The most commonly reported adverse events include headache, arthralgia, diarrhea, back pain, pain in an extremity, and fatigue.²²⁰⁻²²²

Clinical trials: Four phase III clinical trials are ongoing.²²³⁻²²⁶ In a clinical study (n=67) of migalastat's effect on levels of GL-3 inclusions in interstitial capillaries of the kidneys, the primary endpoint was not met. However, a post-hoc analysis including only patients with amenable mutations (n=42) showed a statistically significant reduction of GL-3.²²⁷ In a followup study, glomerular filtration rate remained steady over an average of 32 months for patients with amenable mutations.²²² Two other studies supported the analysis that only patients with amenable mutations responded to migalastat.^{228,229}

Manufacturer and regulatory status: Amicus Therapeutics, Inc. (Cranbury, NJ), is developing migalastat as a monotherapy and a combination therapy with ERT for treating Fabry disease. In February 2004, FDA granted orphan drug status to Amicus for migalastat. Phase III trials are under way with some data already reported and an open-label extension trial ongoing; the company intends to seek accelerated drug approval when these trials are completed.²¹⁵

Cost: Pricing information for migalastat is not available because it is not yet approved by FDA. ERT for Fabry disease costs more than \$200,000 per patient per year.²³⁰ Although a small-molecule drug such as migalastat has the potential to be manufactured at a lower cost than recombinant protein therapy, treatments for a rare condition such as Fabry disease are likely to be of high cost. Whether Amicus will price migalastat lower than ERT is unclear.²³⁰ If migalastat is approved, its

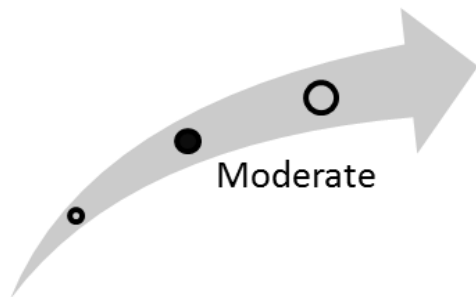
use is likely to be reimbursed by third-party payers because of the limited treatment options for patients with Fabry disease.

Clinical Pathway at Point of This Intervention

No cure exists for Fabry disease. Because of the disease's systemic nature, the patient's primary treatment requires a multidisciplinary team to manage symptoms.^{214,231} Analgesics are required for pain management, but nonsteroidal anti-inflammatory drugs (NSAIDs) are ineffective. Lifestyle changes may be recommended to reduce some symptoms, such as pain, gastrointestinal, and kidney problems.^{214,232} Cardiac symptoms are managed with medication, pacemakers, or surgery.²³² ERT using agalsidase beta, a recombinant form of alpha-GAL, is available to target the buildup of globotriaosylceramide. ERT breaks down the lipid deposits in many cells and improves overall symptoms.^{214,232}

Patients on migalastat may experience fewer symptoms of Fabry disease, and therefore require less symptom management. However, any pain or other manifestations would still need treatment as they arise.

Figure 8. Overall high-impact potential: migalastat hydrochloride for treatment of Fabry disease



Experts commenting on this intervention agreed that a large unmet need exists for effective and convenient treatment. Migalastat may be readily accepted by clinicians and patients to meet that need because of its oral administration and good tolerability, experts suggested. As an oral drug, it is unlikely to have a significant effect on health care delivery infrastructure or patient management, experts thought, but it could add to overall costs. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.²³³⁻²³⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A large unmet need exists for convenient and effective treatment of Fabry disease, experts agreed. Migalastat may improve quality of life for patients by providing an oral option that can be taken at home with few adverse events, the experts thought. It may decrease symptoms of Fabry disease if its convenience and safety profile improve patient adherence to treatment, but more studies focused on patient-oriented outcomes are needed, experts said. One clinical expert suggested that it could become the standard of care if used in combination with ERT.²³⁸

Acceptance and adoption: Clinicians and patients are likely to favor a well-tolerated, oral option over ERT given by IV infusion, most experts agreed. However, an expert with a research perspective thought that clinicians may be less likely to accept migalastat without additional data

from clinical trials.²³⁴ The same expert also thought cost, especially if migalastat is used in combination with ERT, may hinder patient adoption.²³⁴

Health care delivery infrastructure and patient management: A small decrease in demand on health care delivery infrastructure and patient management may result from use of migalastat because it is an oral drug taken at home that may replace IV infusion of ERT for some patients, two experts thought.^{233,238} However, experts agreed that any impact would be minimal because the patient population is small.

Cost impacts may depend on whether migalastat replaces or complements ERT. When migalastat is used as a solo treatment, overall health care costs may decrease slightly by removing costs associated with IV infusion. If used in combination with ERT, costs to patients and third-party payers may be substantial, experts thought.^{234,237}

Health disparities: Health disparities may increase because migalastat is likely to be an expensive drug, some experts thought. An expert with a research perspective stated that adherence issues may be less likely than with ERT, which may reduce health disparities.²³³

Sensory Disorder Interventions

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).²³⁹ Early amblyopia detection can be difficult because standard screening methods identify only risk factors for amblyopia and lack sufficient sensitivity and specificity. They either miss cases that should be referred for further evaluation and possible treatment or over-refer cases.²⁴⁰ Standard screening methods 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 used either as a portable, handheld device or mounted on a table.²⁴¹

According to the manufacturer, the device uses proprietary technology called retinal birefringence scanning, which measures polarized light reflection by the retina. It can distinguish between light reflected by the fovea and light reflected by the paracentral retina. The PVS simultaneously assesses both eyes to detect both binocular alignment and whether the eyes are focused on a target.²⁴² The screening device performs a 2.5-second scan of the eyes to automatically detect the presence of amblyopia, strabismus, or other serious eye conditions.²⁴¹ Testing with the PVS requires minimal cooperation and no verbal response from the individual being screened. During the scan, the patient looks at a fixed target within the device as a focal point. The device is designed to determine when the patient looks away from the target during the scan, which allows for these measurements to be discarded and for measurements to continue until a requisite minimum of five scans has been obtained. The software then provides a result as to whether the patient's eyes were accurately fixating on the target, indicating a "pass" or passing grade, or if one or both eyes were not properly fixating, indicating the need to refer the patient to a specialist for further testing.²⁴¹

The PVS is designed for use in a pediatric office as an early detection screening tool to promote preventive care and reduce false referrals for ophthalmic specialist care.²⁴¹

Clinical trials: Five registered trials evaluated the sensitivity and specificity of the PVS with positive results (sensitivity 94% to 98%; specificity 74% to 88%).²⁴³⁻²⁴⁷ The most recent trial of the PVS (compared with the SureSight Vision Screener test) enrolled 300 patients 2–6 years of age. Study investigators reported the following:²⁴⁶

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

As with any screening tool, the potential for false-positive or false-negative tests results exists with the PVS. False-negative results could lead to a delay in care for amblyopia or strabismus; false-positive results could lead to unnecessary specialty referrals. However, the PVS purportedly will reduce the rate of false-positive results associated with other screening methods.²⁴¹

Manufacturer and regulatory status: The PVS has been developed by REBIScan, Inc. (Cambridge, MA). FDA has determined the PVS to be a nonsignificant risk investigational device,²⁴¹ 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.²⁴⁸ Some in the ophthalmology field expected the device to be on the market before the end of 2014,²⁴⁰ however, as of June 2015, the device had not been approved.

Diffusion and cost: Reimbursement for pediatric vision screening has been long established; the company indicated it expects its screening exam cost to fall within the reimbursed amount. Thus, PVS testing may be reimbursed by public and private third-party payers in a manner similar to that of other instrumented pediatric vision screening tests that use photoscreening devices, which insurance companies cover under the procedural terminology code (CPT; published by the American Medical Association) for "ocular photoscreening with interpretation and report, bilateral."²⁴⁰ The reported reimbursement rate is about \$25 to \$30 per screening. Reported prices for photoscreening devices range from about \$4,200 to \$7,500.²⁴⁰

REBIScan is collaborating with VisionQuest 20/20 (Phoenix, AZ), a nonprofit organization that addresses preventable vision loss in children, to establish a nationwide vision screening program. Pediatric offices and preschools are expected to use the PVS to screen for amblyopia and strabismus. A tracking system will monitor children referred to specialists to ensure they receive proper followup care.²⁴⁹

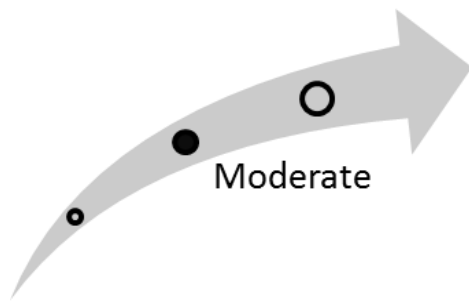
The company has established a crowd-funding site to raise funds to complete its development to meet regulatory requirements.²⁵⁰

Clinical Pathway at Point of This Intervention

Amblyopia-associated refractive error is treated with corrective lenses. Patches and eye drops are used to force the child to use the nondominant eye, allowing the weaker eye to become stronger.²⁵¹ Children younger than 5 years of age who receive treatment typically recover to almost completely normal vision; however, delaying treatment can result in permanent vision problems, and after the age of 10 years, only partial vision recovery can be expected.²³⁹

The REBIScan PVS is intended to enable more appropriate referrals and referrals of children at younger ages to an ophthalmologist for further evaluation so that treatment can start when the disorder is at a more correctable stage.²⁴¹ 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.²³⁹ Visual acuity testing and photoscreening devices lead to both missed diagnoses and false positives that lead to unnecessary referrals.²⁴¹ The REBIScan manufacturer has indicated that the PVS, if used during annual well-child visits, can reduce health care expenditures by detecting amblyopia and strabismus at earlier stages and reducing false-positive referrals to specialist care.

Figure 9. Overall high-impact potential: Pediatric Vision Scanner screening for strabismus and amblyopia



Overall, experts commenting on this intervention thought use of the PVS in very young children was a significant factor in its potential for fulfilling the unmet need for early screening tools for amblyopia and improving patient outcomes for affected patients. The quick, noninvasive screening procedure, low associated risks, and minimal training requirements to use the device could aid in wide acceptance and adoption, experts anticipated. They suggested widespread use would improve the accuracy of referrals to specialists. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.²⁵²⁻²⁵⁷ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for earlier screening, diagnosis, and treatment of amblyopia and strabismus, most experts agreed. Experts speculated that patients would achieve better outcomes with earlier treatment and clinicians would make more accurate referrals to specialists. However, one expert with a health systems and administration perspective expressed skepticism for the unmet need and was "...not compelled to believe that earlier scanning actually saves the patient any time, money, pain, or quality of life."²⁵³

Acceptance and adoption: Acceptance among clinicians, young patients, and their parents is likely to be high, experts agreed. The PVS is easy to use, noninvasive, and allows earlier diagnosis of amblyopia and strabismus, experts said, which will contribute to clinician adoption. If used in schools, "...one could [imagine] the holy grail of childhood vision screening. That is, all children screened cheaply and effectively without having to see an eye doctor," one clinical expert suggested.²⁵² However, several experts thought patients and parents would not distinguish the novel screening from any other testing conducted as part of a well-child visit.

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

Initial costs may increase as providers purchase the PVS and train staff. However, if minimally trained staff could perform the screening instead of pediatricians or specialists, costs would decrease, one clinical expert said.²⁵² Lifetime vision care costs may decrease if children receive earlier and more effective treatment, experts noted. Likewise, overall health care system costs might decrease if fewer false positive referrals are made to specialists, one expert with a research perspective pointed out.²⁵⁶

Health disparities: If the PVS is used in low-cost clinics or preschools, health disparities might decrease for children who do not have insurance, experts said. However, as one research expert noted, disparities will not be affected unless early screening is followed by corrective vision care for those who have the condition.²⁵⁶ If the PVS is primarily used in pediatrician offices, disparities are unlikely to be affected, other experts thought.

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

Unmet need: The National Sleep Disorders Foundation estimates that, of people who are totally blind in the United States, 65,000–95,000 experience a disorder called non-24-hour sleep-wake disorder (non-24). The disorder arises from a lack of light receptors to reset the circadian rhythm.²⁵⁸ Besides having 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-24.²⁵⁹

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.²⁶⁰ 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 dosage of 20 mg, 1 hour before bedtime, at the same time every night. Tasimelteon may cause drowsiness or affect mental alertness, so patients are advised to limit activity after taking it.²⁶¹ Patients might not notice its effects for weeks to months after initiating treatment, according to a discussion held between FDA and the manufacturer.²⁶²

Clinical trials: A clinical trial (n=84) assessed circadian rhythm by measuring urinary 6-sulphatoxymelatonin (aMT6s) and cortisol. Clinical responders were defined as patients whose circadian rhythm was entrained (adjusted) by tasimelteon who scored 3 or higher on the Non-24 Clinical Response Scale. In results of this study, Lockley et al. reported that the proportion of patients entrained by tasimelteon was greater than placebo, as measured by urinary aMT6s and cortisol timing ($p=0.0171$ and $p=0.0313$, respectively). They also reported that the number of clinical responders was greater for tasimelteon than placebo, and greater improvement was seen in the Clinical Global Impression of Change and measures of total nighttime sleep, daytime nap duration, and mid-point of sleep timing (MoST) than in the placebo group ($p<0.05$).²⁶³ In an extension of the clinical trial (n=20), Lockley et al. reported that patients receiving the drug maintained their circadian rhythms (as measured by aMT6s and cortisol levels) better than those taking placebo (aMT6s: tasimelteon, 90%; placebo, 20%; $p=0.0026$; cortisol: tasimelteon, 80%; placebo, 20%; $p=0.0118$). Total nighttime sleep was 67.2 minutes longer in the worst quartile of nights and total daytime sleep duration was 59.4 minutes shorter in tasimelteon-treated patients ($p<0.05$). The MoST from both nighttime and daytime sleep increased 36 minutes in tasimelteon-treated patients ($p=0.0108$).²⁶⁴ In both trials, tasimelteon was reported to be safe and well tolerated. One phase III trial is ongoing to evaluate tasimelteon's safety.²⁶⁵

Manufacturer and regulatory status: Vanda Pharmaceuticals, Inc. (Washington, DC), manufactures tasimelteon under the brand name Hetlioz.²⁶⁶ FDA approved tasimelteon in January 2014 as an orphan drug²⁵⁹ that is indicated for treating non-24. It is contraindicated in women of child-bearing potential and individuals with severe liver impairment.²⁶¹ 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.

According to a medical review from FDA, common adverse events associated with tasimelteon included headache, increased alanine aminotransferase levels, abnormal dreams/nightmares, cardiac

conduction disorder, sleep disorder, upper respiratory tract infection, somnolence, and urinary tract infection. The most common serious adverse event was gastroenteritis.²⁶⁷

Diffusion and cost: Tasimelteon is a specialty pharmaceutical that is available through a small network of pharmacies.²⁶⁸ As an orally administered pharmaceutical used in an outpatient setting, tasimelteon is not expected to require significant changes to health care staffing or infrastructure.

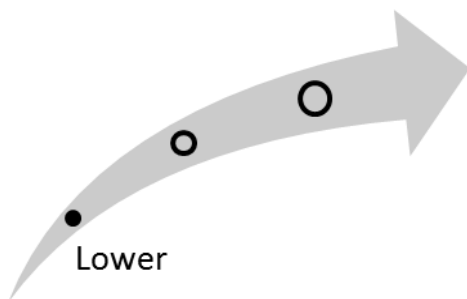
According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, tasimelteon costs about \$86,000 per patient per year.²⁶⁹ According to the manufacturer, the number of patients on tasimelteon rose by 22% in the first quarter of 2015 compared with the last quarter of 2014.²⁷⁰ If half (about 35,000 patients) the estimated population with non-24 opted to take the drug, the cost to the health system would be about \$3 billion annually.

ECRI Institute routinely searches 11 representative, private, third-party payers that publish their policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark). Our searches found 10 policies for tasimelteon that require prior authorization;²⁷¹⁻²⁸⁰ several policies list tasimelteon as a nonpreferred drug,^{272,274-276,280} subject to quantity limits,^{271,272,277,280} and approved only after failure of over-the-counter melatonin therapy.^{271,274,279}

Clinical Pathway at Point of This Intervention

Other drugs that may have an effect on regulating the circadian rhythm are melatonin and ramelteon, although neither is FDA approved for non-24. Benzodiazepines or nonbenzodiazepine hypnotics have also been prescribed to improve night-time sleep quality; to limit daytime sleep, patients have been prescribed caffeine in various forms.^{281,282} Nonpharmacologic treatments include chronotherapy and lifestyle changes.²⁸¹ Tasimelteon is likely to be used in place of other drugs, but potentially in combination with nonpharmacologic treatments.

Figure 10. Overall high-impact potential: tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder



Overall, tasimelteon's cost will likely be the biggest impact on the health care system, experts agreed. Clinicians and patients are likely to adopt tasimelteon because of its good safety profile and low abuse potential, experts agreed. In terms of improving patient health or altering patient management, experts noted the small amount of data and modest improvements in sleep and waking times when suggesting the drug is likely to have a lesser impact. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.²⁸³⁻²⁸⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A modest unmet need exists for improving productivity and quality of life for patients with non-24, experts agreed. Studies report that the majority of patients respond well to tasimelteon, experiencing improved entrainment and willingness to continue using the drug, experts noted. Several experts suggested comparative studies are needed with other therapies (e.g., melatonin, sleep hygiene) to determine whether tasimelteon sufficiently improves patient health, especially relative to its high cost.

Acceptance and adoption: Because tasimelteon is the only drug approved to treat non-24, clinicians are likely to accept it, experts thought. Its positive safety profile and low potential for abuse may contribute to clinicians' acceptance, experts said. One research expert thought clinician acceptance may be small because of the length of time (i.e., weeks to months) it may take for patients to experience an effect.²⁸⁵ For patients who have coverage for tasimelteon, acceptance is likely to be high, experts stated.

Health care delivery infrastructure and patient management: Little to no impact will be evident in health care delivery infrastructure and patient management, experts agreed, because tasimelteon is an oral drug taken at home. A research expert noted that the additional monitoring for weeks or months to see an effect may have a small impact on patient management.²⁸⁵ The high cost of tasimelteon is likely to be the largest impact factor, experts concurred, especially among third-party payers that are providing coverage. One clinical expert suggested that limited total health care resources mean that payers that weigh the overall societal benefit could limit drug coverage to more severe cases.²⁸⁸

Health disparities: Health disparities may increase due to the drug's high cost and uneven coverage from third-party payers, experts agreed, which may limit access for some patients, especially the economically disadvantaged. Patients who use tasimelteon may experience reduced disparities related to quality of life, a health systems expert speculated.²⁸⁷

Spinal Cord Injury Intervention

Intraoral Tongue-Drive Computerized System to Maneuver Electric Wheelchairs

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

Intervention: 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.²⁸⁹ The smartphone transmits information to a computer, commanding it to perform daily tasks (e.g., email). A standby mechanism allows patients to perform activities such as eating, sleeping, and talking without unnecessary TDS use.²⁹⁰

According to a registered clinical trial protocol, 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.²⁹¹ Patients must undergo computer training with the TDS for the software to appropriately interpret and calibrate tongue movement.

Clinical trials: The most recent published TDS study enrolled 21 individuals with quadriplegia from SCI at two centers (Shepherd Center in Atlanta, GA, and Northwestern University, Chicago, IL) for a 6-week evaluation of TDS usability. Ten participants dropped out during the trial because of disqualification during screening, loss of interest, noncompliance with scheduled study visits, loss of the tongue barbell, transportation difficulties, and medical issues unrelated to the study. The remaining 11 participants (9 male; 2 female) aged 38.6 ± 9.8 years (range: 27–56 years), completed the study and the quality-of-life questionnaires. All participants had been driving their powered wheelchairs on a daily basis using either a sip-and-puff (54.5%) or a modified joystick (45.5%) tool. Of the participants, 36.4% did not use computers on a regular basis, 36.4% (with C5 and C6 level SCI) had some limited hand motion, and 36.4% used other technologies, such as a mouth stick, head controller, or speech recognition software. Participants were given a 75-question post-study system-usability questionnaire that included factors related to the piercing experience, TDS accessibility, usability, satisfaction, and comparison with other technologies they had used. The majority of questions were designed on a five-point Likert-type scale; two yes/no questions and four open-ended questions were included. Study authors reported that overall, participants “had no major issues with the tongue piercing, and more than 70% would have been willing to keep a tongue

barbell for ongoing use of the system. More than 60% of participants had no concerns about the appearance of the headgear, and ~50% of participants said that the TDS was easy to access.” Participants rated TDS performance as satisfactory at the end of the study, with half of users assessing the TDS as more effective than sip-and-puff or their current assistive technology despite the brief experience with the TDS.²⁹²

Another study enrolled 14 able-bodied subjects and 3 individuals with high-level SCIs (level C3 to C5); researchers combined TDS with speech recognition software and reported preliminary results. Authors reported that the (dual) TDS headset, combined with commercially available speech recognition software, provided users with significantly higher performance than either unimodal forms based on the tongue motion or speech alone, particularly in completing tasks that required both pointing and text entry.²⁹³

The developers have not published information regarding patient safety or adverse events. 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). The developers had speculated that the device could be on the market in 2015;²⁹⁴ however, we found no evidence that clearance from FDA is imminent.

Diffusion and cost: The developers anticipated the per-patient cost of the TDS system to be between \$6,000 and \$7,000.²⁹⁴ This cost does not include the powered wheelchair. Costs could be lower than for other brain-computer interface devices, because TDS does not require invasive brain surgery.

Medicare Part B covers power-operated wheelchairs as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a durable medical equipment supplier does not accept direct Medicare reimbursement, Medicare cannot limit the amount a supplier can charge. In certain geographic areas, Medicare’s competitive bidding program may be in effect, which means that Medicare pays for the equipment and related supplies only if they are obtained from contracted suppliers. These suppliers cannot charge patients more than 20% coinsurance and any unmet yearly deductible for any equipment or supplies included in the competitive bidding program.²⁹⁵ 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.

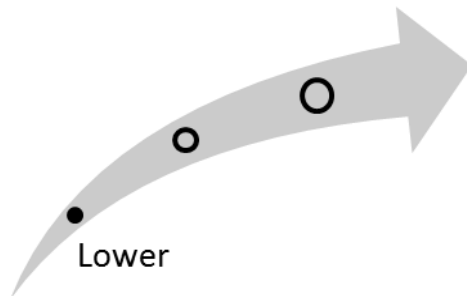
Clinical Pathway at Point of This Intervention

Acute 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.²⁹⁶

Emergency SCI treatment involves immobilizing the spine as gently and quickly as possible. Acute stages of treatment include maintaining breathing, preventing shock, immobilizing the neck, and avoiding possible complications. Medications, prolonged immobilization, or surgery may be required.²⁹⁷ Ongoing treatment such as physical therapy, occupational therapy, or other

rehabilitation therapies, as well as muscle spasticity medications, may be needed.²⁹⁶ 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 11. Overall high-impact potential: intraoral tongue-drive computerized system to maneuver electric wheelchairs



Overall, experts commenting on this intervention thought an unmet need exists for restoring more mobility and independence to patients with SCI who are quadriplegic. Experts' opinions differed on whether this intervention could accomplish that better than existing options already do. One expert thought that TDS is unlikely to come to market because a manufacturer is not attached to the project. Acceptance would likely vary based on clinicians' and patients' willingness and ability to learn to use the new technology, experts thought. Although additional training of patients is needed to use TDS, providers and technical support are already in place to mitigate that impact, experts agreed. Some experts believe TDS might increase disparities if cost and coverage differed among third-party payers. Based on this input, our overall assessment is that this intervention is in the 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.²⁹⁸⁻³⁰³ 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 improved independence and communication for patients with severe SCI and quadriplegia, the experts agreed. Several experts noted that less invasive alternatives (e.g., sip-and-puff) are available that provide comparable mobility. Although TDS may improve quality of life and psychosocial states, it is unlikely to improve patients' overall health because it does not restore physical function or provide an alternative to wheelchair use, experts said.

Acceptance and adoption: Moderate clinician acceptance is likely, experts thought, because of the potential performance gains and low risk of harm for patients. One expert with a research perspective speculated that clinicians are unlikely to favor TDS because of insufficient evidence of benefit.³⁰³ Patient adoption is also likely to be moderate, experts said. Two clinical experts suggested that a high mental capacity and willingness to learn new technology are needed for patient acceptance, which may make younger patients more likely to try TDS.^{298,300}

Health care delivery infrastructure and patient management: Additional training for clinicians, staff, and patients, and ongoing maintenance of TDS would be the major changes to health care delivery if TDS is adopted, experts agreed. Physical therapists, rehabilitation specialists, and biomedical engineers may experience a mild to moderate impact from TDS; however, the care setting and infrastructure are unlikely to change, experts said. Patient management may involve additional staff and time for piercing, training, and maintenance, a likely minimal impact, experts

noted. Several experts noted the similarities in care between TDS and the sip-and-puff, which is already established.

A modest cost impact may emerge for patients, payers, and hospitals, experts agreed. Hospitals and rehabilitation centers that provide training on TDS may have increased staffing costs. Eventual coverage determinations will affect whether payers or patients bear the additional cost of TDS, which is not substantially greater than sip-and-puff. Cost increases will be mitigated for hospitals and payers by the small patient population likely to use TDS, experts explained.

Health disparities: Increased disparities in function and independence may result if costs prevent all patients from accessing TDS. Coverage from third-party payers may reduce the disparities, experts agreed. Two research experts noted that disparities between patients who use TDS and able-bodied people may decrease due to improving quality of life and independence for users.^{299,302}

Wearable, Battery-Powered Exoskeleton (ReWalk Personal) To Enable Mobility in Community or Home Settings in Patients With Paraplegia

Unmet need: Conventional manual and powered wheelchairs improve quality of life for individuals with paraplegia; however, mobility, independence, and safety issues remain a primary concern. Wheelchair users can experience pressure ulcers, osteoporosis, depression, and cardiovascular, respiratory, urinary, and gastrointestinal adverse events associated with confinement to power-assisted devices. To address these issues in a home or community setting, a wearable, battery-powered exoskeleton has been developed to enable select patients with paraplegia to “walk” upright.

Intervention: The ReWalk Personal exoskeleton is a wearable, battery-powered exoskeleton with motorized leg braces and crutches for support. The device uses a tilt sensor near the chest to propel the motorized leg braces when patients shift their body weights. The onboard computer and rechargeable batteries are contained in a backpack.³⁰⁴ A waistband provides additional support and holds the leg braces together. Heel plates fit into the user’s shoes.³⁰⁵ The ReWalk system weighs about 35 lb and is activated by a controller on a wrist band.^{305,306}

The ReWalk system is designed to mimic a natural walking gait and functional speed. Patients using the device can sit, stand, walk, and turn.³⁰⁴ Although the manufacturer claims the exoskeleton can be used on stairs, FDA has not approved it for this use.^{307,308} The system can be used on multiple surfaces and terrains for indoor and outdoor use. It can be used for 4 hours of continuous walking (generally one day of use) and recharged overnight.^{305,307}

The ReWalk Personal exoskeleton is customized to fit the patient. However, patients must be 160–190 cm tall (5 feet, 3 inches to 6 feet, 3 inches) and weigh less than 100 kg (220 lb).³⁰⁷ Patients must have sufficient bone density, flexibility, and cardiovascular health, as determined by a physician’s exam. Although patients control the exoskeleton, trained caregivers must be present to assist during use of the device, even during home use.³⁰⁴ It is intended for daily, personal use by patients with paraplegia who complete device training at a rehabilitation or training center.³⁰⁶

A significant potential safety issue with wearable exoskeletons is a computer problem or other device malfunction that puts the user at risk of harm in certain environments or situations (e.g., device failure while crossing a street, traversing a ramp, or in crowds). However, a trained caregiver must be with a patient using the exoskeleton and could aid in these scenarios.³⁰⁴ Patients are also at risk for pressure sores, bruising or abrasions, falls and associated injuries, and diastolic hypertension during use.³⁰⁸ No safety issues for clinical staff are anticipated with the exoskeleton.

Clinical trials: Two studies are ongoing to evaluate the ReWalk Personal in community and home settings.^{309,310} One study reported in 2012 that all patients (n=12) were able to transfer to the exoskeleton and walk with it independently for 5–10 minutes. All patients made positive comments about emotional and psychosocial benefits, and some patients reported improvements in pain, bowel and bladder function, and spasticity.³¹¹ Another study of 6 patients from 2012 reported that no adverse safety events occurred and that the system was well tolerated.³¹²

A study published in 2015, after experts commented on this intervention, reported that 10 of 60 candidates (17%) were enrolled and 5 (8%) completed the training program. Primary reasons that candidates were not enrolled included ineligibility (24) and lack of interest in a 10-week training program (16). Five of 10 enrolled subjects experienced grade I/II skin aberrations. Walking speeds were faster and walking distances were longer in all exoskeleton users than in individuals not using the device; subjects indicated the exoskeleton did not generally meet their high expectations in terms of hoped for benefits.³¹³

Manufacturer and regulatory status: ReWalk Robotics, Ltd. (Yokneam Ilit, Israel; formerly Argo Medical, Inc.), is developing the ReWalk Personal system. FDA cleared the ReWalk Personal in June 2014 under the de novo pathway, which is for first-of-a-kind devices of low to moderate risk.³⁰⁸ Wearable exoskeletons are expected to be used by patients with paraplegia who retain use of their hands and shoulders, can stand using crutches, have good bone density, and have good cardiovascular health. Patients using the equipment need to be comfortable using a computer-controlled device and undergoing extensive training in a rehabilitation facility. Physician approval and training certification are required to use the assistive device. The technology is contraindicated for people who have a history of neurological injuries other than SCI, severe spasticity, significant contractures, unstable spine, unhealed limb or pelvic fractures, or other severe concurrent medical issues.³⁰⁸

Patients using the systems require extensive training on a ReWalk Rehabilitation unit with rehabilitation specialists before they can purchase a ReWalk Personal. Patients must also be trained how to troubleshoot or compensate for possible malfunctions that occur while using the device. A trained caregiver, such as a family member or home health aide, assists when patients use the device.³⁰⁸

Diffusion and cost: The manufacturer states that it sold 13 ReWalk systems in the first quarter of 2015 and 31 in the previous quarter;³¹⁴ it is unclear how many were ReWalk Personal systems (as opposed to the ReWalk Rehabilitation device used institutionally). The manufacturer stated that diffusion is limited by the time it takes to evaluate and train patients and process reimbursement claims.³¹⁴ The ReWalk Personal costs about \$70,000.³¹⁵ Medicare Part B may cover exoskeletons as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a durable medical equipment supplier does not accept direct Medicare reimbursement, Medicare cannot limit the amount a supplier can charge. In certain geographic areas, Medicare's competitive bidding program may be in effect, which means that Medicare pays for the equipment and related supplies only if they are obtained from contracted suppliers. These suppliers cannot charge patients more than 20% coinsurance and any unmet yearly deductible for any equipment or supplies included in the competitive bidding program.³¹⁶

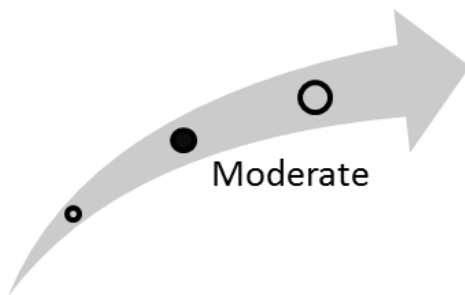
To identify coverage policies, ECRI Institute routinely searches 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield of Alabama, Blue Cross/Blue Shield of Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark). Our searches found six policies pertaining to the ReWalk Personal exoskeleton. Those payers—Aetna, Anthem, Blue Cross/Blue Shield of Alabama, Blue Cross/Blue Shield of Massachusetts, Humana, and Regence—consider use of exoskeletons to be experimental and do not cover them.³¹⁷⁻³²²

Clinical Pathway at Point of This Intervention

Acute SCI requires immediate medical attention. A physician completes a physical exam, including neurological exam, to identify the location of the injury. Magnetic resonance imaging, computerized tomography, or spine radiography may be ordered.²⁹⁷ Emergency treatment of an SCI involves immobilizing the spine as gently and quickly as possible. Acute treatment includes maintaining breathing, preventing shock, immobilizing the neck, and avoiding possible complications. Medications, prolonged immobilization, or surgery may be required.²⁹⁷ Ongoing treatment such as physical therapy, occupational therapy, or other rehabilitation therapies, as well as muscle spasticity medications may be needed.²⁹⁶

Conventional manual and powered wheelchairs are the primary assistive devices for mobility in many patients with paraplegia and compete with exoskeletons to provide mobility. Powered wheelchairs can be controlled by one of several available methods. Examples of controls include joysticks, sip-and-puff straw, chin paddle, head paddle, and speech. Other devices that provide upright support, such as stationary standers, compete with exoskeletons to provide benefits associated with upright weight-bearing postures.

Figure 12. Overall high-impact potential: wearable, battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home settings in patients with paraplegia



Overall, experts commenting on this intervention agreed that an unmet need exists for a mobility and upright-standing device. An exoskeleton for community or home use may prevent complications associated with prolonged wheelchair use, the experts agreed. They suggested the high cost will have the most effect on patient acceptance and access, possibly contributing to health disparities. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.³²³⁻³²⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An alternative to prolonged wheelchair use, associated with functional limitations and health complications, is an important unmet need for patients with paraplegia, the experts agreed. The exoskeleton may potentially improve mobility, independence, pain, bowel and bladder function, spasticity, bone density, and skin integrity, experts speculated, although they also conceded that more studies are needed.

Acceptance and adoption: Experts were split over how readily clinicians may accept the exoskeleton for patients with paraplegia. Clinicians who are slow to adopt may point to other options, fall risks, costs, and the amount of training required by staff and patients as reasons for abstaining, experts said. Alternatively, some clinicians may believe the benefits of improved mobility, independence, and quality of life outweigh the risks and recommend consideration of the device, experts suggested. Patients are likely to be guided by their physicians' views of the exoskeleton and are initially limited to using it in a rehabilitation setting, thus requiring clinician buy-in for training before using the exoskeleton in a home setting, two clinical experts stated.^{327,328} Patients who are highly motivated to walk, who can commit to intensive training, and who can afford the device may readily adopt the exoskeleton, experts noted.

Health care delivery infrastructure and patient management: Health care delivery infrastructure is likely to be minimally impacted by use of the exoskeleton, experts agreed. The biggest impact will be in the additional training needed for physical therapists, biomedical

engineers, and other staff, experts noted. Patient management may also be impacted by the amount of training needed for patients and caregivers in rehabilitation and home settings, experts concurred.

Rehabilitation centers need to purchase an exoskeleton for patient training and may need additional staff to provide it, factors that will impact cost to the centers, experts said. Patients and third-party payers may face substantial costs because of the high price of the exoskeleton and a need to replace it every 5 years, experts stated. A clinical expert suggested any overall effects would be limited because the patient population is small.³²⁷ An expert with a research perspective speculated that any controversies over costs may be minimal because many in the affected population are likely combat veterans.³²⁶

Health disparities: Health disparities may increase based on the high cost of the exoskeleton, all experts agreed. A clinical expert noted that patients must pay for 20% of the cost of durable medical equipment that is covered by Medicare, which may be prohibitive for some.³²⁸ Two experts mentioned that additional training and maintenance of the device may be required, adding to costs that may affect access.^{323,326}

Upper Limb Amputation Intervention

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

Unmet need: Patients in whom an upper limb has been amputated have options for prostheses, but prosthesis function is generally limited to sequential movements that require deliberate effort to control. Patients do not have options that provide natural movement, intuitive controls, or tactile sensations.³²⁹ As a result, many patients with an arm prosthesis are still functionally limited. Advances incorporating miniaturized computer components, lightweight but strong materials, and body-machine interfaces combined into a prosthetic hand and arm have resulted in the DEKA Arm System, a device that has up to 10 powered degrees of freedom and multiple unique features.³³⁰

Intervention: The following information is based on descriptions of the Gen 3 DEKA Arm used in clinical studies. Whether the features of this arm will be available in the commercially produced prosthesis is unclear.^{330,331} DEKA Arm features movable joints, a wrist, and independently movable fingers. The device has a metallic external structure with no exposed mechanics, does not require a fabric sleeve, and is dust and water resistant. The entire arm is resistant to light rain, and the fingers up to the base can be immersed in water.³³¹

An embedded LED wrist display alerts the user to grip, mode, power, battery charge, and system faults. An audible vibration indicates when the mode changes between hand and arm, when it moves in or out of standby, and when grip mode or grip pressure is changed.³³⁰

The Arm is designed for three configurations: shoulder, humeral, and radial.³³⁰ It can be used only by patients who have limb loss at the shoulder joint, mid-upper arm, or mid-lower arm—not at the elbow or wrist.³³² The humeral and shoulder configurations can accommodate an internal battery while all configurations can use an external battery worn on a belt or harness.^{330,331} The internal battery has a run time of about 1 hour and the external battery, about 6 hours.³³¹ The shoulder configuration weighs 9.8 lb, the humeral configuration weighs 6.8 lb, and the radial configuration weighs 2.8 lb.³³¹

The shoulder configuration has 10 powered degrees of freedom and additional passive degrees of freedom that allow for simultaneous, coordinated movement at the shoulder, humeral rotator, elbow, forearm, wrist, thumb, index finger, or fingers three to five.³³⁰ Although several movements can be performed at once by combining foot controls, myoelectrodes, pneumatic bladders, manual switches, and other common input devices, the DEKA Arm must switch between hand and arm modes to accomplish many tasks.^{330,331} A limited number of hand movements can be performed when in arm mode.³³¹ The hand mode has six programmed grips for objects of various sizes and shapes.³³¹ The detent feature allows users to manipulate an object in the hand without losing the grip on it (e.g., holding and using a spray bottle).³³¹ The wrist has four powered movements.³³¹ The shoulder configuration has an endpoint control system that uses software to coordinate joint movements to bring the end of the prosthesis into a desired position from one command instead of a series of commands.³³¹ A dynamic socket controller regulates inflatable bladders inside transhumeral sockets to stabilize the device and provide pressure relief. Patients control this function using buttons.³³⁰

Patients using the DEKA Arm can perform several tasks that are reportedly too complex for other prosthetic devices, including using keys and zippers.³³² Several features have been incorporated into the DEKA Arm to prevent accidents and user errors. For example, the device is able to recognize when it is moving toward the head and reduce its speed to avoid a collision. It can distinguish between intentional foot controls and walking, trips, or stumbles.³³¹

Before using a DEKA Arm, patients may need targeted muscle reinnervation to expand the number of distinct electromyographic signal sites available for surface myoelectrodes. In targeted muscle reinnervation, surgeons transfer nerve connections that once controlled a patient's hand or

arm to remaining muscles. The procedure offers more intuitive control of a prosthesis because the nerves that once controlled the amputated limb control the reinnervated muscles. Signals from the transferred nerves are amplified by the reinnervated muscle and are more easily detected by surface electrodes.³²⁹

Clinical trials: In one study of 37 patients using second- and third-generation DEKA Arms, researchers reported that 79% of Gen 2 and 85% of Gen 3 users indicated they wanted to receive or might want to receive a DEKA Arm; 95% of Gen 2 and 91% of Gen 3 prior prosthesis users reported that they were able to perform new activities that were beyond the capabilities of their own prosthetic devices.³³³ Researchers further reported that patients rated satisfaction and usability higher for the third-generation device than the second-generation device.³³⁴ A prospective, observational cohort study with 75 patients is ongoing to evaluate the change in quality of life while using the device at home for 13 weeks.

Manufacturer and regulatory status: The DEKA Arm System was developed by DEKA Integrated Solutions (Manchester, NH) in conjunction with prosthetic engineers from Next Step Bionics and Prosthetics, Inc. (Manchester, NH), and Biodesigns, Inc. (Westlake Village, CA).^{335,336} The U.S. Defense Advanced Research Projects Agency's "Revolutionizing Prosthetics" program provided funding to DEKA with the goal of developing a prosthetic arm with natural control.³³⁶ In May 2014, FDA cleared the DEKA Arm System through its de novo classification process.^{332,337} The system is not yet commercially available because the developer is seeking a partner to manufacture and commercialize the prosthesis.

Diffusion and cost: DEKA Integrated Solutions does not yet have a manufacturing partner, so no cost information is available.³³² In an interview with the Boston Business Journal, the developer said the cost will depend on the number made, but would ideally be in the range of tens of thousands of dollars.³³⁸

Medicare Part B covers artificial limbs as durable medical equipment for beneficiaries whose physician has prescribed it for home use. Patients must pay 20% of the Medicare-approved amount. If a durable medical equipment supplier does not accept direct Medicare reimbursement, Medicare cannot limit the amount a supplier can charge. In certain geographic areas, Medicare's competitive bidding program may be in effect, which means that Medicare pays for the equipment and related supplies only if they are obtained from contracted suppliers. These suppliers cannot charge patients more than 20% coinsurance and any unmet yearly deductible for any equipment or supplies included in the competitive bidding program.³³⁹

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

Clinical Pathway at Point of This Intervention

After a patient's amputation site has completed primary healing, long-term care is often provided by physical medicine and rehabilitation physicians, who focus on pain management, medications, and occupational and physical therapy.³⁴⁰ They coordinate care for emotional health, prosthetic treatment, occupational and physical therapy, social services, and return-to-work

issues.³⁴⁰ Occupational therapists also address pain control, self-care strategies, work needs, and prosthetic training.³⁴¹

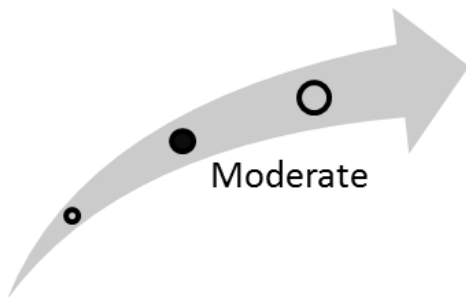
Prosthesis options for patients depend on the degree of amputation and remaining function. Amputations on the limb closer to the trunk need prostheses that have more functions to control more joints. Four types of prostheses are commonly available, as follows:^{341,342}

- Passive: requires use of another limb to reposition it; may be functional or cosmetic
- Body-powered: operated by moving a cable often connected to opposite shoulder or by a switch often controlled by the chin
- Myoelectric: composed of an external battery, electric motor, and microprocessing unit that responds to transcutaneous electric signals sent by remaining muscles
- Hybrid: combines body-powered and myoelectric mechanisms for controlling prostheses

Tasks using a prosthesis are performed in sequential steps. Some myoelectric devices use pattern recognition to improve response speed and decrease operation burdens.³²⁹

Patients choose a prosthesis based on factors including function, weight, aesthetics, cost, and ease of use. Not all prostheses can be configured for all degrees of amputation and many prostheses have no fine motor control and cannot use multiple joints at once. They may look unnatural, can be heavy or uncomfortable, may not be waterproof, and have no tactile sensation.³⁴³ Patients commonly use prostheses for only a portion of the day or specific tasks because of these disadvantages.³⁴²

Figure 13. Overall high-impact potential: prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm function after amputation



Overall, experts commenting on this intervention thought a significant unmet need exists for restoring natural arm function to patients with upper limb amputations, and this device provides functionality well beyond any available prostheses. Experts thought that clinician and patient enthusiasm might be tempered by high costs and complex training, potentially increasing health disparities due to unequal access. Experts suggested that the prosthesis' overall impact would be mitigated by the small population likely to use the DEKA Arm. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.³⁴⁴⁻³⁴⁹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for a prosthetic arm that restores natural arm functions to patients who have had an amputation, experts agreed. The DEKA Arm System has more degrees of freedom, better coordinated gross and fine motor functions, and greater potential to improve quality of life than available prostheses, experts concurred. Some experts

tempered their enthusiasm by noting that this device lacks sensory perception and is not suitable for all patients who have had an arm amputated.

Acceptance and adoption: Acceptance among clinicians may vary greatly, as indicated by contrasting expert comments. The experts thought that clinicians focusing on the improvement in quality of life and function for patients will readily accept the device but that other clinicians may be reluctant because of the cost and complexity of the prosthesis. One expert with a health systems and administration perspective suggested that doctors might not want to invest time and effort in training themselves on the device if only a limited number of their patients would benefit.³⁴⁵

Patient adoption is linked to clinicians' viewpoints, one clinical expert noted.³⁴⁴ Cost and complexity may be barriers to patient adoption, experts agreed. Highly motivated patients who desire the increased function of the device will overcome these barriers, some experts said. One clinical expert suggested the device may be best suited for use in the Veterans Affairs system, which may have more consistent clinician training.³⁴⁴

Health care delivery infrastructure and patient management: No infrastructure changes are necessary because the DEKA Arm will be offered in the same setting as other limb prostheses, the experts noted. Increased staffing and training will be necessary for providing initial and ongoing care to patients who use the device, experts said. Patients will need device-specific surgery to use the device and extensive device maintenance provided by biomedical engineers, the experts thought. However, the overall impact of these changes will be limited because of the small number of individuals expected to use the device, two experts said.^{344,348}

Initial costs for the device, surgery, and complex training will be high, experts agreed. Ongoing maintenance will also be expensive because of the complexity of the prosthesis, experts said. One research expert suggested that improved quality of life and function will reduce depression and other psychological issues, potentially reducing associated costs.³⁴⁷

Health disparities: Health disparities may be increased because of the high cost and complexity of the device, the experts agreed. Patients without any insurance or inadequate insurance may have difficulty paying for the device; even patients who have 80% of the cost covered by Medicare Part B as durable medical equipment might not be able to afford the remainder, two experts noted.^{345,349} The complexity of the device means patients will need access to maintenance and technical-support experts, which may be a barrier for rural patients, two other experts pointed out.^{344,346} Experts commented that patients with low literacy or mental capacity may be unable to learn how to use the device.

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