

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

Priority Area 08: Functional Limitations and Disability

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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Preface

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

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

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

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

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 4 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

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

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy). The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high-impact 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 were available for drugs being developed for labeled indications, or at least early phase data on the intended patient population were available for devices, off-label drugs, or biologics; (2) information was compiled by May 16, 2013, in this priority area; *and* (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Eighty-five topics in this priority area were being tracked in the system as of May 18, 2013.) We present summaries on six topics (indicated below by an asterisk) that emerged as having high-impact potential on the basis of experts’ comments. The material on interventions in this Executive Summary and the report are organized alphabetically by disease state, and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 08: Functional Limitations and Disability

Topic	High-Impact Potential
1. Alemtuzumab (Lemtrada) for treatment of relapsing-remitting multiple sclerosis	No high-impact potential at this time
2. *Computerized walking systems (ReWalk and Ekso) for patients with paraplegia from spinal cord injury	Moderately high
3. *Dimethyl fumarate (Tecfidera) for treatment of relapsing forms of multiple sclerosis	High
4. Dopamine stabilizer pridopidine (Huntexil, ACR16) for treatment of Huntington’s disease	No high-impact potential at this time
5. Droxidopa (Northera) for treatment of symptomatic neurogenic orthostatic hypotension	No high-impact potential at this time
6. Glutamate receptor antagonist (Fycompa) for treatment of partial-onset epilepsy	No high-impact potential at this time
7. Glybera gene therapy for lipoprotein lipase deficiency	No high-impact potential at this time
8. *Icatibant (Firazyr) for treatment of acute hereditary angioedema	High
9. *Intraoral tongue-drive computerized system to maneuver electrically-powered wheelchairs	Moderately high
10. Levadex (MAP-0004) orally inhaled for treatment of migraine headaches	No high-impact potential at this time
11. Mifepristone (Korlym) for treatment of endogenous Cushing’s syndrome	No high-impact potential at this time

Topic	High-Impact Potential
12. N-acetylgalactosamine 6-sulfatase (GALNS) for treatment of Morquio syndrome	No high-impact potential at this time
13. Off-label bevacizumab for treatment of retinopathy of prematurity	No high-impact potential at this time
14. *Recombinant human ocriplasmin (Jetrea) injection for treatment of focal vitreomacular adhesion	High
15. Recombinant porcine factor VIII (OBI-1) for treatment of acquired hemophilia	No high-impact potential at this time
16. *Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	High
17. Terlipressin for reversal of hepatorenal syndrome type 1	No high-impact potential at this time

Discussion

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

Central Nervous System Disorder Intervention

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

- Key Facts:** Multiple sclerosis (MS) is a progressive autoimmune disorder directed against the central nervous system (CNS). Even with available treatments, inflammation and subsequent damage to the spinal cord and brain interfere with a variety of functions, which can eventually lead to the need for long-term institutional care. Relapsing-remitting multiple sclerosis (RRMS) is the most common form of the four MS disease courses and progressive-relapsing multiple sclerosis (PRMS) is the least common. First-line RRMS therapies consist of injectable immunomodulators that dampen autoimmune responses against the CNS. These include interferon beta-1b, interferon beta-1a, glatiramer acetate, and the recently approved oral therapy fingolimod (Gilenya[™]). Natalizumab (Tysabri[™]) and mitoxantrone (Novantrone[®]) are injectable agents that can be used for RRMS or PRMS.

Dimethyl fumarate (Tecfidera[™], Biogen Idec International GmbH, Zug, Switzerland) is an oral fumaric acid ester purported to induce both anti-inflammatory and neuroprotective effects through upregulating the transcription factor Nrf2. In phase III clinical trials, dimethyl fumarate reduced the frequency of relapse, the number and progression of brain lesions, and rate of disability progression in patients with RRMS. The most common adverse events reported in clinical studies included abdominal pain, decreased lymphocyte counts, diarrhea, flushing, and nausea. The U.S. Food and Drug Administration (FDA) approved dimethyl fumarate in February 2013 for treating adults with relapsing forms of MS. Reported costs of dimethyl fumarate are about \$4,850 to \$5,065 per patient per month. Reported costs for the first oral drug approved for RRMS, fingolimod, are about \$4,900 to

\$5,050 per patient per month. The manufacturer offers a \$10 co-pay program for patients with private insurance. Third-party payers (e.g., Aetna) are starting to cover the drug as a specialty pharmaceutical requiring prior authorization, which may include requiring prior use of at least one preferred injectable agent. Anecdotal evidence suggests dimethyl fumarate could diffuse rapidly and comprise up to 25% of the MS market within 2 years.

- **Key Expert Comments:** The experts commenting on this topic stated that a well-tolerated oral agent with high efficacy in patients with RRMS continues to present a significant unmet medical need, despite other recent drug approvals for treating RRMS. Experts were encouraged by the lower relapse rates and delayed disease progression reported in patients treated with dimethyl fumarate compared with those outcomes in patients receiving placebo or glatiramer acetate; they were also encouraged by the drug's tolerability profile.

In other comments on the competing drug, fingolimod, experts stated that fingolimod, the first oral agent approved to treat RRMS, was expected to be widely accepted among clinicians and patients, although costs and the adverse event profile could pose some barriers to diffusion. Two other orally administered MS drugs, teriflunomide (approved for treating RRMS) and laquinimod, (in phase III development), have differing mechanisms of action and are being tracked in the horizon scanning system. However, experts commenting on teriflunomide and laquinimod did not view them as having high-impact potential because, the experts stated, the unmet need these two agents address is already being addressed by fingolimod.

Experts commenting on dimethyl fumarate, however, cited its high efficacy, safety, and purported neuroprotective effects as potentially addressing unmet needs in MS therapy if approved for marketing. If the drug reduces disease progression and the need for assistance with activities of daily living and has a cost comparable to current first-line agents, experts opined, it might become first-line therapy for patients, clinicians, and third-party payers.

- **Potential for High Impact:** High

Genetic Disorder Intervention

Icatibant (Firazyr) for Acute Hereditary Angioedema

- **Key Facts:** Acute hereditary angioedema (HAE) results from a genetic disorder caused by dysfunction or deficiency of C1 esterase inhibitor (C1INH), an inhibitor of the C1 protease that is responsible for activating the complement pathway of the innate immune system. If C1INH is deficient, an acute inflammatory response occurs that leads to swelling, which is the hallmark of HAE. Attacks involving the larynx can be fatal; 15% to 33% of those experiencing a serious attack die as a result. Abdominal attacks can also cause severe pain and disfigurement. Each bout of edema can last 3–5 days; the trigger for attacks is unknown. Icatibant (Firazyr®, Shire, plc, Dublin, Ireland) is a bradykinin receptor-2 antagonist approved by FDA in August 2011 as the only injectable drug to treat acute HAE that can be self-administered by the patient. Thus, icatibant allows patients to self-manage this lifelong condition. In phase III trials, icatibant provided significant symptom relief within about 2 hours and initial symptom relief in less than 1 hour. The average wholesale cost of this drug in the United States is about \$8,400 per 30-mg dose (one dose). The company created its Quick Start and extended OnePath Access programs to offer product-related services and support to patients. After a health care provider prescribes the drug, patients can enroll to be

eligible to receive two syringes of the drug at no cost. In general, third-party payers cover icatibant for patients with type I and II HAE, require preauthorization and prescription by a specialist, and enforce quantity limits.

- **Key Expert Comments:** Overall, experts commenting on icatibant viewed it as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients with HAE, a potentially life-threatening condition. Experts noted that although other new treatments have just become available for HAE, icatibant has a different mechanism of action and may be self-administered, which could significantly reduce the need for hospitalization and the role emergency personnel play in managing HAE.
- **Potential for High Impact:** High

Sensory Disorder Interventions

Recombinant Human Ocriplasmin (Jetrea) Injection for Treatment of Focal Vitreomacular Adhesion

- **Key Facts:** Current treatment options for symptomatic vitreomacular adhesion are limited to invasive vitreoretinal surgery that is associated with serious side effects of risk of incomplete vitreoretinal separation and/or removal, complications (e.g., development of cataracts), and high costs. Recombinant ocriplasmin (Jetrea[®], ThromboGenics NV, Heverlee, Belgium) is a minimally invasive treatment option. The biologic retains the catalytic characteristics of human plasmin and purportedly has several advantages, including sterility because of recombinant techniques used to generate it, a size that is smaller than plasmin to potentially allow greater penetration into epiretinal tissues, and greater stability than plasmin. Two phase III trials with 652 patients at 90 centers in Europe and the United States were reported to have met their primary endpoints. FDA approved ThromboGenics' biologics license application for ocriplasmin in October 2012 for treating symptomatic vitreomacular adhesion. The labeled recommended dose is 0.125 mg (0.1 mL) of the diluted solution administered by intravitreal injection to the affected eye once as a single injection. ThromboGenics announced the U.S. launch of Jetrea and listed the price for a single-use glass vial at \$3,950. Some major third-party payers provide coverage with prior authorization, although other major payers have decided to not provide coverage at this time. The company reported in May that 40% of the ophthalmologists it targeted with advertising ordered the biologic, and about half of those have re-ordered it.
- **Key Expert Comments:** Experts thought recombinant ocriplasmin injection therapy would offer an alternative to surgery for patients most affected by focal vitreomacular adhesion. They generally agreed that acceptance would likely be high for clinicians and patients alike. Most experts who commented thought that ocriplasmin injection therapy could provide an effective, cost-saving alternative to current standard treatment.
- **Potential for High Impact:** High

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

- **Key Facts:** Medications or devices have not been available to restore lost vision or halt progression of vision loss that occurs because of retinitis pigmentosa (RP). The implantable Argus[®] II Retinal Prosthesis System purportedly restores a level of vision that is sufficient to allow patients greater independent functioning, although it does not restore detailed vision

such as facial recognition. The device is intended to stimulate the retina with electrical impulses, producing images. In clinical studies, patients receiving the device implant were able to perform basic activities such as detecting motion, recognizing letters, detecting street curbs, and distinguishing certain colors. The most common adverse events reported in the studies included conjunctival dehiscence, conjunctival erosion, retinal detachment, inflammation, and hypotony (low intraocular pressure). Appropriate use of the device requires surgeon and technician training in patient selection, device fitting, and implantation and patient training after the procedure. Argus II is the first implanted device FDA approved for marketing for treating adult patients with advanced RP. Reported costs for the device are about \$115,000, which includes the device and the surgical procedure.

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

Spinal Cord Injury Interventions

Computerized Walking Systems (ReWalk and Ekso) for Patients with Paraplegia from Spinal Cord Injury

- **Key Facts:** Conventional manual and powered wheelchairs are the primary assistive devices used to restore some degree of mobility in people with paraplegia. However, these devices do not assist users in walking or climbing stairs. Two reciprocating gait orthosis systems in development, the ReWalk-I™ system (Argo Medical Technologies, Ltd., Yokneam Ilit, Israel) and the Ekso™ system (formerly eLegs, Ekso Bionics, Richmond, CA), are providing greater mobility and freedom to people with paraplegia from spinal cord injury. The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders and who have good bone density and cardiovascular health. The Ekso system incorporates technology similar to that of the ReWalk system. FDA classifies the ReWalk system as powered exercise equipment used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification and premarket application procedures. The ReWalk-I (institutional use) system is FDA-listed for institutional use only, and reported costs are about \$105,000 per system. The company expected to register the ReWalk-P system for personal use with FDA by the end of 2013; the system is available in Europe and Israel. Argo Medical has been quoted in lay press articles as stating that the personal system will cost one-third to one-half that of an institutional system. The company stated that patients seeking the device will be referred to ReWalk Rehabilitation Centers for training. The Ekso institutional system first became available in February 2012 and costs an estimated \$130,000, with anticipated costs for a personalized Ekso exoskeleton version estimated to be \$50,000–\$75,000.

- **Key Expert Comments:** Experts thought that this equipment could offer independence currently unavailable to these patients. However, they thought the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services for patients with paraplegia from spinal cord injury. Staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment. Also, the equipment would likely be appropriate only for patients whose health is robust enough to use it. Experts indicated that the intended population has very limited treatment options, and they agreed upon the vast potential benefit of computerized walking systems.
- **Potential for High Impact:** Moderately high

Intraoral Tongue-Drive Computerized System to Maneuver Electrically-Powered Wheelchairs

- **Key Facts:** Clinicians recommend conventional manual and powered-assisted devices to attempt to improve quality of life for individuals with quadriplegia, but efficacy and safety issues remain a primary concern. The Tongue Drive System (TDS, Georgia Institute of Technology, Atlanta) is a tongue-operated, assistive neurotechnology that consists of a lentil-sized magnetic tracer/stud that is embedded in a dental retainer worn in the mouth with the tracer affixed to the tongue, most commonly by piercing. This magnetic tracer communicates synergistically with a headset, magnetic sensors, and a smartphone device to increase patient mobility and allow patients to participate in daily activities. Using the system would represent a way to purportedly enhance patient mobility and allow patients to perform more daily tasks in a safer, less invasive, and more effective manner than afforded by existing devices. Patients must undergo computer training with the TDS for the computer program to appropriately interpret and calibrate tongue movement, allowing for proper control of the patient wheelchair and computer device. The TDS is in early-phase clinical trials in two locations (Atlanta, GA, and Chicago, IL), and the trial continues to recruit patients. About 20 patients have been reported to have trialed the system thus far. The National Science Foundation (Arlington, VA), the Christopher & Dana Reeve Foundation (Short Hills, NJ), and the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health (Bethesda, MD) are providing funding to support development of the system.
- **Key Expert Comments:** Experts commenting on this intervention had diverse perspectives about some aspects, although most thought that the system could be a viable alternative to existing technologies. Some thought the unmet need was not significant, but others who have worked directly with spinal cord-injured patients in need of assistive devices to control powered wheelchairs saw this intervention as a significant improvement for patient health outcomes and quality of life, allowing patients to perform daily activities in a quicker and less exhaustive manner than existing technologies such as puff straws, joysticks, and head paddles. Several experts thought safety concerns could be a barrier to clinician acceptance, because device malfunction might pose risks to this patient population. Overall, this device's perceived complex nature, the existence of alternatives, and limited safety and efficacy data thus far have made some experts question the device's true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and quality of life when compared with those outcomes with standard mobility devices.
- **Potential for High Impact:** Moderately high

Central Nervous System Disorder Intervention

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

Unmet need: Multiple sclerosis (MS) is a common cause of physical disability in the United States.¹ Inflammation damages the myelin surrounding nerves, impeding the electrical impulses that travel along the nerves. As the disease progresses, it eventually causes interference with vision, speech, walking, writing, memory, sexual function, and bowel and bladder control.^{2,3} Relapsing-remitting multiple sclerosis (RRMS) is the most common form of MS and is usually the earliest form to be diagnosed.⁴ Progressive-relapsing multiple sclerosis (PRMS) is the least common of the four MS disease courses, occurring in about 5% of patients. People with PRMS experience disease progression from the onset and experience periodic relapses.⁵ First-line therapies consist of injectable immunomodulators that dampen autoimmune responses against the central nervous system (CNS). Oral fingolimod became available in 2010.⁶ However many patients' RRMS symptoms do not respond adequately to current therapies or patients are unable to tolerate the treatments, and no effective treatments are available to stop the long-term progression of the disease.^{4,7-9}

Intervention: Dimethyl fumarate (TecfideraTM) is an orally administered, homogenous fumaric acid ester formulation that is purported to have immunomodulatory and neuroprotective effects. Dimethyl fumarate is purported to increase expression of Nrf2, a transcription factor known to upregulate cellular antioxidant pathways. The increased expression and upregulation results in changes in the cellular redox system, leading to an increase in reduced glutathione and intracellular glutathione, which could protect neurons and astrocytes from oxidative stress during inflammatory processes.^{10,11} These changes are also purported to inhibit nuclear factor kappaB translocation and downstream proinflammatory signaling.¹² These anti-inflammatory and neuroprotective effects are purported to reduce the number of active brain lesions that could contribute to disease progression.¹³

Dimethyl fumarate is administered at a starting dosage of 120 mg twice a day, orally, for 7 days, followed by a maintenance dosage of 240 mg twice a day, orally.¹⁴

Clinical trials: In two multicenter phase III, randomized controlled trials, the effects of dimethyl fumarate were evaluated in patients with RRMS. In one trial, the investigators reported on patients (n=1,237) who received 240 mg of dimethyl fumarate either two or three times daily for 24 months. Results demonstrated a statistically significant reduction in the proportion of patients whose disease relapsed at 2 years compared with relapse rates in patients given placebo (27% and 26% for dimethyl fumarate twice and three times daily, respectively, versus 46% with placebo; p<0.001 for both comparisons). Patients given both doses of dimethyl fumarate also demonstrated statistically significant reductions in secondary endpoints compared with those endpoints achieved by administering placebo, including:

- Lower annualized relapse rate (53% and 48% for dimethyl fumarate twice and three times daily, respectively; p<0.001 for both)
- Fewer new or newly enlarging T2 hyperintense lesions seen on magnetic resonance imaging scans (85% and 74% for twice and three times daily, respectively; p<0.001 for both)
- Lower number of new gadolinium-enhancing lesions, (90% and 73% for twice and three times daily, respectively, p<0.001 for both)

Patients given either dose of dimethyl fumarate also exhibited a significant reduction in the rate of disability progression as measured by the Expanded Disability Status Scale.¹³

In the second study, investigators reported that patients with RRMS (n=1,430) who received 240 mg of dimethyl fumarate either twice or three times daily for 24 months had significant reductions in annualized relapse rate (44%, and 51% for dimethyl fumarate twice and three times

daily, respectively; $p < 0.0001$ for both) compared with the annualized relapse rate in patients given placebo. Investigators reported that patients treated with the active comparator glatiramer acetate (20 mg subcutaneous injection, once daily) had a reduction in annualized relapse rate by 29% ($p = 0.01$) compared with patients given placebo.

Additionally, investigators reported that dimethyl fumarate reduced the number of new or newly enlarging T2-hyperintense lesions by 71% and 73% for twice- and three-times-daily regimens, respectively ($p < 0.0001$ for both dosage regimens) compared with placebo, while glatiramer acetate reduced lesions by 54% ($p < 0.0001$ for all three treatments). Dimethyl fumarate reduced new T1-hypointense lesions by 57% and 65% for twice and three times daily, respectively ($p < 0.0001$ for both dosage regimens), and glatiramer acetate reduced lesions by 41% ($p = 0.002$).

In the trial, the proportion of patients who experienced a relapse while taking dimethyl fumarate was reduced by 34% for twice-daily dosing ($p = 0.002$) and by 45% for three times daily ($p < 0.0001$), compared with a 29% drop for patients given glatiramer acetate ($p = 0.01$). Reductions in disability progression with dimethyl fumarate twice-daily, thrice-daily, or glatiramer acetate versus placebo (21%, 24%, and 7%, respectively) were not significant.¹⁵

The prescribing information states that the most common adverse events associated with dimethyl fumarate include abdominal pain, diarrhea, flushing, and nausea. The manufacturer warns that dimethyl fumarate could decrease lymphocyte counts.¹⁴

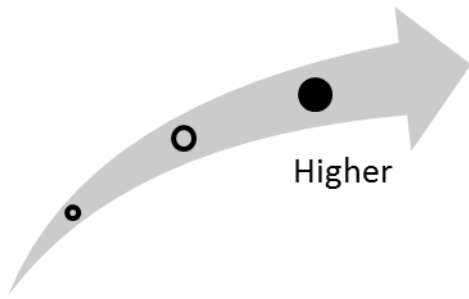
Manufacturer and regulatory status: Biogen Idec International GmbH, of Zug, Switzerland, makes dimethyl fumarate. Following priority review, the U.S. Food and Drug Administration (FDA) approved dimethyl fumarate in February 2013. The indication is for treating adult patients with relapsing forms of MS.¹⁶

Diffusion: A query of GoodRx, a U.S.-based aggregator of pharmacies' pricing, identified a retail cost of \$4,848–\$5,066 per patient per month for dimethyl fumarate.¹⁷ For benchmarking purposes, the oral MS drug fingolimod was listed as having similar cost, from \$4,901 to \$5,047 per patient per month, in a similar query.¹⁸ The manufacturer offers a \$10 copayment program for patients with private insurance.¹⁹ Third-party payers (e.g., Aetna) are starting to cover the drug as a specialty pharmaceutical requiring prior authorization, which may include prior use of at least one preferred injectable agent (i.e., Avonex[®], Copaxone[®], Rebif[®]).²⁰ About half of 55 neurologists surveyed have prescribed dimethyl fumarate, and the drug is projected to occupy about 25% of the MS-drug market within 2 years, according to a survey conducted by a financial analysis firm.²¹

Clinical Pathway at Point of This Intervention

First-line treatments to reduce the frequency and severity of RRMS relapse include the injectable medications interferon beta-1b (Betaseron[®]), interferon beta-1a (Avonex, Rebif), and glatiramer acetate (Copaxone).^{4,7} Oral fingolimod is used as first- or second-line therapy. Natalizumab (Tysabri[™]) and mitoxantrone (Novantrone[®]) are injectable agents that can be used for RRMS or PRMS.⁷ Dimethyl fumarate is intended to be used as first- or second-line monotherapy for relapsing forms of MS.

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



Experts commented that data from phase III trials are encouraging and suggest that the drug could fulfill the unmet need for a well-tolerated, oral therapy that can significantly reduce the frequency of relapse and disease progression (including brain lesions) in a majority of RRMS patients. If the drug can reduce disease progression and delay the need for assistance with activities of daily living while keeping therapy costs comparable to current first-line agents, it could become the first-line therapy of choice for patients, clinicians, and third-party payers, experts thought. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.²²⁻²⁸ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Overall, the experts commented that because MS is a debilitating disease that results in significant morbidity and disability, a large unmet need remains for new treatments with improved efficacy, tolerability, and ease of administration.

Evidence to date of dimethyl fumarate's modestly-improved efficacy against relapse and brain lesions compared with the efficacy of placebo and glatiramer acetate is encouraging, as is the favorable tolerability profile reported, the experts stated. Additionally, the novel mechanism of action, with potential anti-inflammatory and neuroprotective effects, was viewed as potentially improving patient health outcomes.

Acceptance and adoption: Both clinicians and patients would have a high level of acceptance of dimethyl fumarate because of the efficacy and safety profile reported in patients with RRMS, the experts thought. However, two experts representing a research perspective stated cost could be a major barrier to patient acceptance in cases in which patients lack adequate health insurance. The experts expected dimethyl fumarate to have a comparable cost to fingolimod or injectable therapy. If used as an adjunctive therapy, dimethyl fumarate could add significantly to costs. However, if used as monotherapy and if the drug can delay the need for long-term institutional care, the drug may be cost saving. It should be noted that expert comments were received before dimethyl fumarate was approved for treating relapsing forms of MS.

Health care delivery infrastructure and patient management: The experts stated that if effective in delaying disease progression and as an oral therapy that can be administered easily at home, dimethyl fumarate could reduce infrastructure and staffing needs at treatment facilities where injectables are administered as well as at long-term care facilities where patients with advanced disease receive care.

Health disparities: The experts stated that the high cost of dimethyl fumarate might increase health disparities for patients without prescription coverage from a third-party payer. But two of the experts commented that patients with poor access to care, such as those in rural areas, could improve treatment adherence by being able to take a pill at home instead of traveling to a health care provider for routine injections.

Genetic Disorder Intervention

Icatibant (Firazyr) for Treatment of Acute Hereditary Angioedema

Unmet need: Hereditary angioedema (HAE) is a genetic disorder caused by dysfunction or deficiency of C1 esterase inhibitor (C1INH), an inhibitor of the C1 protease that is responsible for activating the complement pathway of the innate immune system. If C1INH is deficient, C1 proteases set off the complement pathway, causing an acute inflammatory response that leads to swelling. Part of the inflammatory response is the release of uncontrolled levels of bradykinin (BK), a potent vasodilator that acts much like a histamine.²⁹ During a serious attack, the patient's throat may swell and cause the airway to close, resulting in asphyxiation; in these cases 15% to 33% of patients die.³⁰ Abdominal attacks can also cause severe pain and disfigurement. Bouts of edema can last 3–5 days; the trigger for attacks is unknown.²⁹

Intervention: Icatibant (Firazyr®) is a selective and specific synthetic polypeptide BK receptor-2 (BR2) antagonist.^{29,31} Preclinical study data were reported to have shown that icatibant potently and selectively inhibits BK's effects on vascular permeability, hypotension, and bronchospasm, and early clinical studies have demonstrated reversed vasodilation in humans.²⁹ FDA-approved in 2011 (see details below), icatibant is available as a subcutaneous injection administered 30 mg in 3 mL as needed.³¹ The injection can be administered in a health care setting, most likely on the initial attack, or by the patient during subsequent attacks.

Clinical trials: In two multicenter, double-blind, randomized controlled trials, the effects of icatibant were evaluated in patients with HAE presenting with cutaneous or abdominal attacks.³² In results of one trial (n=56), researchers reported that the primary endpoint of median time to clinically significant symptom relief was 2.5 hours; it was 4.6 hours with placebo (p=0.14). In the second trial (n=74), researchers reported that the primary endpoint of median time to clinically significant symptom relief was 2 hours with icatibant versus 12 hours with tranexamic acid (p<0.001). No icatibant-related serious adverse events were reported.³²

In 2011, data were reported from a phase IIIb trial evaluating patients who self-administered icatibant (n=88) in response to acute HAE attacks.³³ Icatibant significantly reduced the patient-assessed median time to onset of symptom relief versus placebo (2.0 hours vs. 19.8 hours) and the median time to onset of primary symptom relief versus placebo (1.5 hours vs. 18.5 hours; p<0.001 for both comparisons).³⁴ Icatibant also reduced the median time to almost complete symptom relief compared with placebo (8.0 hours vs. 36.0 hours; p=0.012). Researchers stated that patients treated with icatibant reported significantly faster initial symptom improvement than with placebo (0.8 hours vs. 3.5 hours; p<0.001). Researchers also reported that the icatibant group (41%) developed fewer adverse events than the placebo group (51%). Five patients treated with icatibant reported treatment-related adverse events that included diarrhea, nausea, dyspepsia, headache, and injection-site erythema; no patient treated with icatibant experienced a serious adverse event.³⁴ The most common adverse events associated with icatibant's use include (in decreasing order of frequency) injection site reactions, pyrexia, increased transaminase levels, and dizziness.³¹ Patients with HAE attacks affecting the larynx are advised to seek medical attention after self-administration of icatibant.³¹

Manufacturer and regulatory status: In August 2011, FDA approved icatibant for treating type I or type II acute HAE.³⁵ Shire, plc, Dublin, Ireland, makes icatibant, and BioRx, of Cincinnati, OH, has entered into a limited agreement with Shire to distribute icatibant in the United States.³⁶

Diffusion: According to one online pharmacy, the retail cost of one 30-mg dose of icatibant is about \$8,400.³⁷ The retail cost of one 30-mg dose of ecallantide (Kalbitor®), a recently approved competitor to icatibant, was listed at about \$9,500.³⁷ Shire created two programs, Quick Start and extended OnePath Access, to offer product-related services and support to patients. After a health

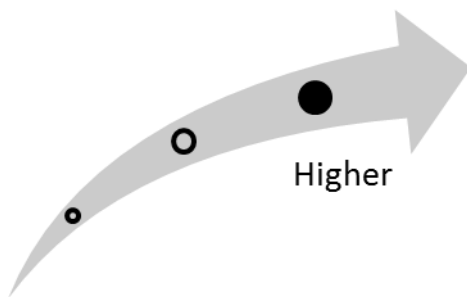
care provider prescribes the drug, patients can enroll to be eligible to receive two syringes of the drug at no cost.³⁵

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that 10 payers list coverage determinations for icatibant for treating HAE.³⁸⁻⁴⁷ Generally, payers cover icatibant for patients with type I and II HAE. The drug may have tier 3 or 4 formulary status and third-party payers frequently require preauthorization and prescription by a specialist and enforce quantity limits.³⁸⁻⁴⁷

Clinical Pathway at Point of This Intervention

Three new drugs have been approved in the United States for treating HAE, in addition to icatibant. Two of the three are given intravenously by a medical professional: Cinryze® and Berinert®, plasma-derived C1INH concentrates purified from human plasma for short-term prophylaxis and acute HAE attacks. The third is given by a medical professional by subcutaneous injection for acute HAE attacks: ecallantide, a plasma kallikrein inhibitor.²⁹ Icatibant can be self-administered and has a novel mechanism for HAE treatment to reduce inflammation during acute HAE.

Figure 2. Overall high-impact potential: icatibant (Firazyr) for treatment of acute hereditary angioedema



Overall, experts commenting on this intervention saw icatibant as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients who experience HAE, a condition that quickly can become life threatening when it occurs. They noted that although other new treatments have just become available for HAE, icatibant has a different mechanism of action and could be self-administered on an outpatient basis, potentially minimizing hospitalizations and the role emergency personnel in managing HAE in a subset of patients. Thus, experts saw the overall impact as high. 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

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.⁴⁸⁻⁵⁴ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A strong unmet need exists for effective, self-administered treatments for HAE, the experts agreed; although emergency department treatment options exist, attacks are acute, unpredictable, and life-threatening. All experts offering comments agreed that the theory behind the mechanism of icatibant action is sound and that the available data from clinical

trials showed promising results that icatibant appeared efficacious in relieving HAE symptoms within a relatively short time. The combination of rapid relief of symptoms and self-administration is expected to improve health outcomes and reduce HAE-related emergency department visits and hospitalizations.

Icatibant is the first and only approved, self-administered treatment option for HAE, and one expert stated that studies should be conducted to compare icatibant with intravenous options so clinicians can fully understand the risk-benefit profile of the drug.

Acceptance and adoption: Patients and clinicians are expected to readily accept the relatively simple and effective home administration of icatibant, thought experts. But one expert representing a clinical perspective stated that a barrier to acceptance for some clinicians could arise from concerns that some patients may not follow up with a physician after an HAE attack, because the drug could provide close to total symptom relief. Patients failing to follow up could experience negative health outcomes.

Health care delivery infrastructure and patient management: Self-administered icatibant is expected to disrupt health care infrastructure and patient management by changing care to the home setting and reducing demands on emergency departments and personnel. However, the rarity of HAE is expected to attenuate these impacts.

Although the cost of icatibant was perceived to be high by most experts, icatibant was still thought to be cost saving because of the high price of hospitalization. However, the rarity of HAE and the unpredictability of attacks could result in some pharmacies losing money from stocking icatibant that expires unused.

Health disparities: Icatibant's high price could add to health care disparities, the experts stated, indicating they suspect that only patients with third-party payer coverage would have access to the drug. However one expert representing a research perspective stated that self-administration could increase access to treatment and improve outcomes for patients who do not live near a hospital.

Sensory Disorder Interventions

Recombinant Human Ocriplasmin (Jetrea) Injection for Treatment of Focal Vitreomacular Adhesion

Unmet need: Before the recent FDA approval of ocriplasmin (formerly called microplasmin), treatment options for symptomatic vitreomacular adhesion were limited to invasive vitreoretinal surgical procedures. However, the efficacy of these invasive procedures is limited by the potential for incomplete vitreoretinal separation and/or removal, surgical complications (e.g., development of cataracts), and high costs.⁵⁵ Therefore, clinicians have significant interest in nonsurgical methods that could replace or complement surgical treatments for vitreoretinal conditions such as vitreomacular adhesion.⁵⁶

Focal vitreomacular adhesions are characterized by a vitreous gel with an abnormally strong bond to the retina; the adhesions play a role in the development and progression of numerous back-of-the-eye conditions and have been associated with a poor prognosis in diabetic retinopathy and age-related macular degeneration.^{57,58}

Retina specialists are greatly interested in finding an intravitreally injected agent that can both induce liquefaction of the vitreous and disrupt adhesion between the vitreous and the retina, leading to completion of posterior vitreous detachment.⁵⁵ Potential targets for anti-adhesive interventions are components of the extracellular matrix, such as laminin, fibronectin, chondroitin, and integrins, that are thought to act as a “molecular glue” between the vitreous and the retina.⁵⁹

Intervention: Recently approved by FDA, ocriplasmin (Jetrea®) is an enzymatic vitreolysis agent that is used as an intravitreal injection for treating symptomatic vitreomacular adhesion.⁶⁰

Ocriplasmin is a truncated form of plasmin produced using recombinant methods in a yeast (*Pichia pastoris*) expression system.⁶¹ Recombinant ocriplasmin retains the catalytic characteristics of human plasmin and purportedly has several advantages as a therapeutic agent, including sterility because of the recombinant techniques used to generate it; smaller size than plasmin, potentially allowing greater penetration of epiretinal tissues; and greater stability than plasmin.^{55,59}

Phase III clinical trials used an intravitreal injection of 125 mcg.⁶² Intravitreal injections require a local anesthetic (eye drops) to minimize discomfort to the patient and an antiseptic solution to prevent contamination when injecting the solution into the eye.⁶³

Clinical trials: In 2010, the most recent available trial results, ThromboGenics reported pooled results from the TG-MV-006 and TG-MV-007 phase III trials conducted on 652 patients at 48 centers in Europe and the United States.⁶² Both trials met the primary endpoints, with 26.4% of the 465 ocriplasmin-treated patients achieving resolution of their vitreomacular adhesions at 28 days, compared with such resolution in 10.2% of 182 patients who received a placebo injection ($p=0.000002$). In patients without epiretinal membrane, 37.4% of 270 patients given ocriplasmin injections achieved nonsurgical resolution of their vitreomacular adhesions at 28 days compared with 14.3% of 119 patients treated with placebo ($p=0.000003$). The pooled results, stated the investigators, confirmed that ocriplasmin was generally safe and well tolerated. The investigators stated that there was no evidence of an increased risk of retinal tear or detachment.⁶²

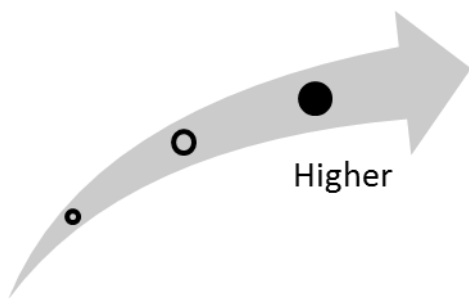
Manufacturer and regulatory status: ThromboGenics NV, of Heverlee, Belgium, makes Jetrea. The company submitted a biologics license application (BLA) to FDA in December 2011.⁶⁴ However, in February 2012, ThromboGenics announced that it had withdrawn the original BLA after FDA stated that it would grant ocriplasmin priority review status, and the company resubmitted the BLA to meet the priority review requirements.⁶⁵ In October 2012, FDA approved ocriplasmin for treating symptomatic vitreomacular adhesion.⁶⁶ The labeled recommended dose is 0.125 mg (0.1 mL) of the diluted solution administered by intravitreal injection to the affected eye once, as a single injection.⁶⁷

Diffusion: In January 2013, ThromboGenics announced the U.S. launch of Jetrea and listed the price for a single-use glass vial at \$3,950.⁶⁸ Bloomberg news reported in May 2013 that 4 months of sales reported by the company indicated about \$10 million in sales; the company stated that about 40% of physicians it targeted ordered the biologic.⁶⁹ Some third-party payers have added the biologic to their formularies for patients who are symptomatic and require prior authorization or offer it on a case-by-case basis with prior authorization;⁷⁰⁻⁷² Other payers, such as Kaiser Permanente⁷³ and Blue Cross Blue Shield of Michigan, have decided not to add it to their formularies.⁷⁴

Clinical Pathway at Point of This Intervention

Patients with vitreomacular adhesion may present with symptoms of decreased or distorted central vision. An optical coherence tomography test may help clinicians arrive at a diagnosis of vitreomacular adhesion. Patients in whom asymptomatic or mildly symptomatic vitreomacular adhesion is diagnosed typically undergo watchful waiting, and some cases of vitreomacular adhesion may spontaneously resolve. Patients with significant visual impairment caused by vitreomacular adhesion typically undergo vitrectomy (i.e., removal of the vitreous).⁷⁵ Intravitreal injection with ocriplasmin may provide a nonsurgical method to resolve vitreomacular adhesion.⁶⁰

Figure 3. Overall high-impact potential: recombinant human ocriplasmin (Jetrea) injection for treatment of focal vitreomacular adhesion



Experts commenting on this intervention thought that, for patients most affected by focal vitreomacular adhesion, recombinant ocriplasmin injection therapy could offer an alternative for a condition in which invasive surgical intervention is the primary standard of treatment. Some experts believe that ocriplasmin injection could serve as first-line therapy for patients and thought that the treatment could eliminate the need for the surgical intervention. A potential shift in care setting and management could occur, transitioning to more outpatient care with care potentially being provided by a retinal specialist. The majority of experts thought that an alternative therapy to surgical intervention would decrease treatment costs. However, one expert noted that the overall costs would increase for patients in whom the condition fails to resolve, so they still need surgery. 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, offered comments on this intervention.⁷⁶⁻⁸¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need: The experts agreed that treatment options for focal vitreomacular adhesion are primarily limited to surgery, and effective and safe noninvasive treatment is necessary for this

population. One expert with a research perspective expressed, “other treatments do exist (vitrectomy); however, they carry significant risks.”⁸¹ However, the same expert noted the limited amount of published research and questioned the efficacy of this intervention. All experts agreed that the underlying mechanism for recombinant ocriplasmin injection appears sound and promising, with several experts citing efficacy in clinical studies as quantitative proof of the intervention’s concept.

Concerning ocriplasmin injection’s impact on patient health outcomes, experts agreed that the intervention has potential to eliminate surgical intervention and reduce associated adverse events in this disease population. An expert with a research perspective indicated that the elimination of surgical intervention would not only improve patient health outcomes, but also quality of life.⁷⁹ However, one expert with a research perspective would like to see more data to determine to what degree this intervention prevents a decline in vision and improves the patients’ quality of life.⁸¹

Health care delivery infrastructure and patient management: Integrating ocriplasmin injection therapy would affect the current intervention model for patients with focal vitreomacular adhesion, the experts unanimously agreed. Regarding setting, one clinical expert opined that the intervention, “can be performed in the office and avoid surgery at the hospital.”⁷⁶ Regarding patient management, most experts believe recombinant human ocriplasmin injection may reduce or eliminate the need for vitreomacular surgery. One expert with a research perspective noted, “This method of treatment should significantly alter current methods for managing the condition.”⁷⁹ But one expert with a health systems perspective believes that there would not be any change to patient management for this disease.

Acceptance and adoption: Experts agreed that patients would likely accept this intervention, because the treatment can provide a seemingly effective alternative to surgical intervention. Regarding acceptance by both patients and clinicians, one clinical expert commented, “The safety profile is excellent. There is no down side to considering the medical approach before offering surgery.”⁸⁰ Most experts agreed that per-patient cost would decrease with reduction of surgical interventions for this patient population. However, one expert with a research perspective noted that the overall costs would increase for patients in whom the condition fails to resolve, so they still need surgery.⁸¹

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

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

Intervention: This retinal prosthesis system is intended to provide “electrical stimulation of the retina to induce visual perception in blind patients with severe to profound retinitis pigmentosa and bare light or no light perception in both eyes.”⁸² It comprises both implanted parts and external equipment. The implanted device is an epiretinal prosthesis that is surgically attached to the one of the patient’s eyes. It contains an antenna, electronics case, and electrode array. The external equipment includes a pair of glasses that are used not for sight but to carry a digital video camera and another antenna, and a video processing unit (VPU). The VPU also houses the battery that runs the entire system. The VPU connects to the glasses via a cable worn by the patient with an over-the-shoulder harness.⁸³

According to the manufacturer, the steps required to use the Argus II System include device implantation, postoperative clinical followup, device fitting and training, and vision rehabilitation. An ophthalmologic surgeon performs the procedure in the outpatient setting while the patient is under general anesthesia.⁸⁴

The Argus II purportedly restores some degree of shape and color recognition by taking advantage of functioning photoreceptors and bypassing damaged photoreceptors, using electrical pulses. When the digital camera registers video, the cable sends the digital information to the VPU, where it is processed and transmitted to the antenna mounted on the glasses. The processed visual information is then transmitted wirelessly from the glasses to the antenna in the implant. When the implant receives the information, an electrode ray emits pulses of electricity to stimulate functioning photoreceptors in the retina. Visual information then travels from the stimulated photoreceptors via the optic nerve to the brain.⁸⁵

The visual information creates patterns of light that the patient can learn to interpret. For example, during use, the patient may be able to interpret the frame of a doorway via the perceived patterns of light the device generates.⁸⁵

Clinical trials: In clinical trials, investigators studied patients performing tasks such as object location, following a crosswalk across a street, and locating bus stops. Patients also performed tasks to detect light and variations of color.^{86,87} In 2012, da Cruz and colleagues published results from a trial of 28 patients with light perception vision to determine letter and word reading and long-term function in patients with profound vision loss. “The mean±SD percentage correct letter identification for 21 subjects tested were: letters L, T, E, J, F, H, I, U, 72.3±24.6% system on and 17.7±12.9% system off; letters A, Z, Q, V, N, W, O, C, D, M, 55.0±27.4% system on and 11.8%±10.7% system off, and letters K, R, G, X, B, Y, S, P, 51.7±28.9% system on and 15.3±7.4% system off. (p<0.001 for all groups). A subgroup of six subjects was able to consistently read letters of reduced size, the smallest measuring 0.9 cm (1.7°) at 30 cm, and four subjects correctly [identified] unrehearsed two-, three- and four-letter words. Average implant duration was 19.9 months.”⁸⁸ Multiple trials are ongoing at locations in the United States and Europe.

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

undergoing short wave or microwave diathermy, electroconvulsive therapy, or magnetic resonance imaging (MRI) procedure with equipment other than a 1.5 or 3.0 Tesla MRI System. If lithotripsy or high output ultrasound must be used, the treatment beam should not be focused near the Argus II Implant. The manufacturer has issued warnings against interference from medical monitoring, diagnostic, or life support equipment: Patients implanted with the device should not use it within 3 feet of this type of equipment. The manufacturer also warns against the use of monopolar electrosurgical equipment in patients implanted with the device. The most common adverse events reported in clinical studies included conjunctival dehiscence, conjunctival erosion, retinal detachment, inflammation, and hypotony (low intraocular pressure).⁸²

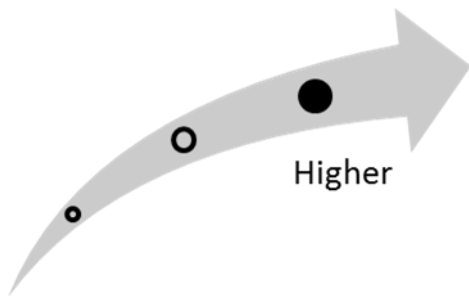
Manufacturer and regulatory status: Second Sight Medical Products, Inc., of Sylmar, CA, makes the Argus II Retinal Prosthesis System. In February 2013, FDA approved marketing of the prosthesis system to “treat adult patients with advanced retinitis pigmentosa (RP).”⁸³ The manufacturer earlier announced that Argus II received Conformité Européene (CE) mark in March 2011, allowing marketing in Europe.⁸⁹

Diffusion: According to manufacturer, the system costs about \$115,000, which includes the device and the surgical procedure.⁹⁰ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark,) found 5 policies, all of which were developed before FDA’s approval of the device. Those payers were Aetna, Anthem, Blue Cross/Blue Shield Massachusetts, CIGNA, and Regence, and all considered the use of artificial retinal devices to be “investigational” and did not cover them because the device was not approved at the time the policy was formulated; we did not identify any updated policies as of this writing, although a few payers indicated they were considering undertaking a medical policy review of the intervention.^{91,92}

Clinical Pathway at Point of This Intervention

RP is a group of genetically based eye diseases that affect the retina, the tissue at the back of the inner eye that converts light to nerve signals.^{93,94} RP results mainly from apoptosis of rod photoreceptors and, less commonly, from apoptosis of cone photoreceptors. Both rods and cones are located in the retina; rods are situated in mid-peripheral retina. RP can be familial, as an inherited autosomal dominant, autosomal recessive, or X-linked defect. The disease has been linked to defects in more than 40 genes.⁹⁵ It can also arise in patients with no family history of the disease. RP signs and symptoms typically manifest in early childhood and progress through early adulthood as more rods and cones break down. Patients experience decreasing night and low-light vision and lose peripheral vision. In advanced cases, patients can lose central vision. To diagnose RP, physicians evaluate the retina using tests for refraction, color vision, visual field, visual acuity, and pupil-reflex response; retina ophthalmoscopy; fluorescein angiography; electroretinography; retina photography; and slit-lamp examination.⁹⁴ No cure exists; however, some treatment options, such as limiting light exposure, are thought to help preserve vision,⁹³ and other treatments under study include high doses of vitamin A palmitate and omega-3 fatty acid DHA.⁹⁴

Figure 4. Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa



Overall, experts commenting on this intervention thought that a significant unmet need exists for treatment options that restore some level of vision and provide greater patient independent functioning. Some experts opined that Argus II has the potential to become the standard of care for vision loss due to RP because no other interventions are available. However, other experts noted the number of adverse events reported in studies and opined that clinical acceptance may be affected by that and by the difficulty of the surgery and the amount of training needed to perform the procedure. Experts generally agreed that potential patient adoption would be high because of patients' desire to be more independent. Most experts agreed that this intervention has the potential to fulfill the unmet need because of the lack of existing therapies and the potential to restore some vision in patients who have this disease. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems, commented on this intervention.⁹⁶⁻¹⁰¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need: The experts agreed that an unmet need exists for treatment options to restore some level of vision for patients with RP. One research expert commented that the technology addressed a large unmet need, because RP leads to blindness and no other treatment is available, even though the affected patient population is small in number.⁹⁶ Although most experts agreed on the importance of visual restoration, one health systems expert commented on the limitations of the intervention, particularly that it does not enable facial recognition, which that expert deemed to be important.⁹⁸

Acceptance and adoption: Experts comments varied regarding the degree to which Argus II will be adopted by clinicians and patients. Several experts noted that the required training and difficulty of surgery could limit clinician adoption. One research expert commented, "Surgeons, clinical staff, technicians, and therapists would all need intensive, product-specific training. The surgery learning curve would be high, and the surgery would be invasive."⁹⁹

The potential for patient acceptance would be high, most experts commenting on this intervention agreed. But they would need to be active partners in their treatment: One research expert noted, "Patients should be willing to fully participate in recommended postoperative clinical followup, visual rehabilitation, and device fitting or training."¹⁰⁰ Some experts commented that some patients might not adhere to the time commitment for followup training and rehabilitation.

Health care delivery infrastructure and patient management: Several experts with research perspectives thought that this intervention would not disrupt the current health care delivery infrastructure. One research expert noted, "This is an operation plus training and followup whereas before no treatment was available. So there will be increased contact with medical professionals for

these patients. But, since it is an uncommon disorder the disruption will not be too large.”⁹⁷ However, some experts thought that this intervention has the potential to greatly disrupt current health care delivery infrastructure for retina specialists. One expert with a clinical expert commented, “For surgeons placing this device, I imagine that it could considerably affect patient flow especially in the OR. Additionally because of the additional patient learning, the surgeon may have to spend time educating the patients. Also, I imagine a whole group of trainers/technical people needed for this.”¹⁰¹

Health disparities: Experts generally agreed the cost of this intervention could significantly affect health disparities. The estimated cost of the device and surgical procedure is approximately \$115,000.⁹⁰ One expert with a clinical perspective commented, “It could potentially increase health disparities in the sense that for those who could not afford (or perhaps don't qualify) for the device would not benefit from the device. Of course this represents an obvious disparity.”¹⁰¹

Spinal Cord Injury Rehabilitation Interventions

Computerized Walking Systems (ReWalk and Ekso) for Patients With Paraplegia From Spinal Cord Injury

Unmet need: Currently, conventional manual and powered wheelchairs are the primary assistive devices used to restore some degree of mobility in people with paraplegia. However, these devices do not help users walk, climb stairs independently, or interact face-to-face with standing adults. Two reciprocating gait orthosis systems in development by separate manufacturers, the ReWalk and Ekso systems, may provide greater mobility and freedom to people with paraplegia from spinal cord injury.

Intervention: The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders for walking with crutches and who have good bone density and cardiovascular health. The wearable support system uses an array of sensors and proprietary computer algorithms to analyze body movements and manipulate the motorized leg braces to help users maintain proper gait using crutches for walking, climbing stairs, and other movements. The onboard computer, sensor array, and rechargeable batteries that power the wearable exoskeleton are contained in a backpack that users wear in addition to the leg braces. The ReWalk system weighs about 35 lb.¹⁰²

The Ekso (formerly eLegs) system is another powered exoskeleton device for patients with paraplegia or lower-extremity paresis due to neurologic conditions, including spinal cord injuries, multiple sclerosis, amyotrophic lateral sclerosis, or Guillain-Barré syndrome. It incorporates technology similar to that of the ReWalk system. The 45 lb Ekso system is based on the Human Universal Load Carrier that the U.S. military uses; it is a motorized exoskeleton designed to allow users to carry up to 200 lb continuously for several hours over any terrain. The manufacturer states that transfer to and from a patient's wheelchair and the powered exoskeleton device takes less than 5 minutes and that the user requires little to no assistance. The company estimates the battery life for this device to be 3 hours.¹⁰³

Clinical trials: ReWalk completed one pilot study on 12 patients and has registered two ongoing trials enrolling a total of 70 patients and expects to complete the trials in 2014. The company is testing the systems for standing, walking, and ascending and descending stairs at 4-, 12-, and 16-week followup.¹⁰⁴

The ReWalk pilot study results were reported at the meeting of the Association of Academic Physiatrists¹⁰⁵ and published in November 2012. The authors reported "After training, all [12] subjects were able to independently transfer and walk, without human assistance while using the ReWalk, for at least 50 to 100 m continuously, for a period of at least 5 to 10 mins continuously and with velocities ranging from 0.03 to 0.45 m/sec (mean, 0.25 m/sec)."¹⁰⁶

Ekso's manufacturer reported that it carried out clinical testing of its system in 12 U.S. rehabilitation hospitals in 2011 and early 2012, but no published study results are available and no ongoing trials are registered at this time.¹⁰⁷

Manufacturer and regulatory status: The ReWalk system is made by Argo Medical Technologies, Ltd., of Yokneam Ilit, Israel. The company makes the ReWalk-I system, and according to a published report, expects to soon register the ReWalk-P for personal use for those who qualify upon medical examination and rehabilitation training.¹⁰⁸ The Ekso system is made by Ekso Bionics, of Richmond, CA. Its system became available to the Craig Hospital in Denver, CO, in February 2012, the company's first commercial health care participant, for institutional use.¹⁰⁷

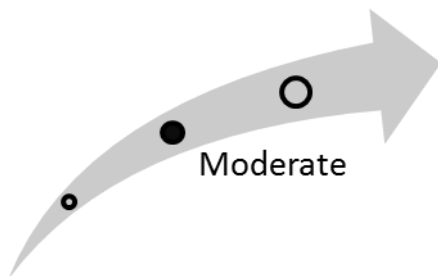
FDA classifies the ReWalk reciprocating gait orthosis as powered exercise equipment (product code BXB) used for medical purposes (e.g., physical therapy), thus making the technology exempt from 510(k) premarket notification or premarketing approval application procedures.¹⁰⁹ Such products require only FDA device registration and listing.

Diffusion: As of November 2011, the ReWalk-I system was listed by FDA for institutional use only, reportedly costing about \$105,000 per system, and the ReWalk-P reportedly will cost about \$20,000, although the manufacturer has not confirmed this pricing.¹⁰⁸ The Ekso institutional system costs about \$130,000, with anticipated costs for personalized Ekso exoskeletons to be \$50,000–\$75,000.¹¹⁰

Clinical Pathway at Point of This Intervention

Occupational and physical therapists work with patients after acute treatment of spinal cord injury to evaluate the patients' functional abilities, determine what type of rehabilitation is appropriate, implement specific exercises and routines, and determine the type of assistive devices that could help them become more independent with daily living skills.¹¹¹ Currently, conventional manual and powered wheelchairs are the primary assistive devices used to restore mobility to people with paraplegia. The ReWalk and Ekso reciprocating gait orthosis systems would be used to assist patients with paraplegia to stand and move, potentially improving their quality of life by increasing their mobility and independence.

Figure 5. Overall high-impact potential: computerized walking systems (ReWalk and Ekso) for patients with paraplegia from spinal cord injury



Experts indicated that patients with paraplegia from spinal cord injury have very limited mobility options, and their comments converged on the vast potential benefit of computerized walking systems. However, they thought the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services treating the intended patient population. Staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment, the experts thought. Further, they thought that the equipment would likely be appropriate only for patients with robust health. Based on this input, our overall assessment is that this intervention is in the moderate end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.¹¹²⁻¹¹⁸ We organized the following discussion of expert comments according to the parameters on which they commented.

Acceptance and adoption: This intervention has significant potential to provide patients with improved overall quality of life, the experts agreed, especially considering the lack of available treatment options. A main benefit of this intervention would be psychological, the experts generally

agreed, saying it would allow patients to have improved self-image, reduced depression, and increased ability to participate in social interactions. However, one expert with a research perspective commented that patients would prefer to use a wheelchair, even after trying a computerized walking system. Experts from both research and clinical perspectives thought that this technology has the potential to spur further technological innovations for treating this patient population.

Health care delivery infrastructure and patient management: Several experts with research perspectives thought that this type of device could greatly disrupt the current health care delivery infrastructure. One expert noted: “Physical therapists, medical professionals, and biomedical engineers would need to be trained on the risks, control, and maintenance of this device.”¹¹⁸ In terms of patient management, several experts thought that besides providing psychological benefits, this intervention might improve pressure ulcer incidence as well. One expert with a clinical perspective noted, “These decubiti can be very detrimental and have significant morbidities. These skin issues can get infected and often require surgical intervention.”¹¹³

Health disparities: Cost was a limiting factor mentioned by experts in terms of access and diffusion, especially to populations affected by health disparities and with limited access to rehabilitative services. The devices’ estimated costs range between \$105,000 and \$130,000 for institutional use and between \$20,000 and \$75,000 for personal use, plus the cost of software programming and adjustments. One expert with a research perspective commented, “[C]ost will be substantial and this will definitely limit diffusion and adoption.”¹¹²

Intraoral Tongue-Drive Computerized System to Maneuver Electrically-Powered Wheelchairs

Unmet need: Although conventional manual and powered-assisted devices are used in an attempt to improve quality of life for individuals with paraplegia, efficacy and safety issues remain a primary concern. In using neuroassistive technology for this patient population, surgical invasiveness and risk of adverse events remain factors that may decrease patient acceptance and overall quality of life. Using a magnetic, pierced-tongue aid system—a tongue-operated assistive neurotechnology—for managing spinal cord paralysis might enhance patient mobility and allow patients to perform more daily tasks in a safer and more effective manner with less-invasive technology.

Intervention: The Intraoral Tongue-Drive System (TDS) is a computerized, tongue-operated, assistive neurotechnology. It consists of a lentil-sized magnetic tracer/stud that is embedded in a dental retainer worn in the mouth with the tracer affixed to the tongue, most commonly by piercing.^{119,120} The tracer/stud creates a magnetic field around the pierced glossal area, and magnetic sensors located on a wireless headset and headphones communicate with a wheelchair.

The tongue is an ideal target for this neuroassistive technology because it does not tire easily and is generally spared in spinal cord injuries and neuromuscular diseases.¹²¹ The change in magnetic field (prompted by tongue movement) in the mouth is detected by the magnetic sensors on the headset, transmitting information wirelessly to a smartphone carried by the patient. The smartphone can then transmit information to a wheelchair or computer, commanding these devices to perform tasks such as wheelchair movement or daily computer tasks (e.g., email).¹²¹ This system can be recharged via USB after 2 days of continuous use. A standby mechanism allows patients to perform daily tasks, such as eating, sleeping, and conversing, without unnecessary use of the TDS.¹²¹ Patients must undergo computer training for the computer program to appropriately interpret and calibrate tongue movement, allowing proper control of the wheelchair and computer device.¹¹⁹

Clinical trials: In 2009, Ghovanloo and colleagues published results from a pilot study of five patients with tetraplegia to determine the usability of the TDS for patients with spinal cord injury.¹²² “Each subject completed the course at least twice using each strategy while the researchers recorded the navigation time and number of collisions. Using discrete control, the average speed for the five subjects was 5.2 meters per minute and the average number of collisions was 1.8. Using continuous control, the average speed was 7.7 meters per minute and the average number of collisions was 2.5.”¹²² A trial is ongoing at two rehabilitation centers, one in Atlanta, GA, and the other in Chicago, IL.¹²⁰

Manufacturer and regulatory status: Georgia Institute of Technology, Atlanta, is investigating the TDS. Funding for development is being provided by The National Science Foundation, of Arlington, VA; the Christopher & Dana Reeve Foundation, of Short Hills, NJ; and the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health, of Bethesda, MD.

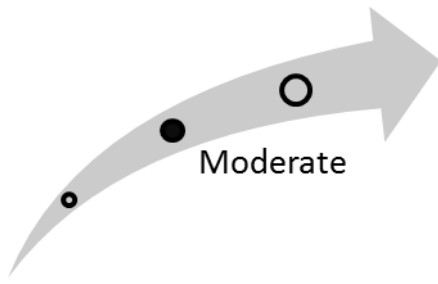
Diffusion: The TDS is in development. Anticipated cost information is unavailable at this time.

Clinical Pathway at Point of This Intervention

After patients receive acute treatment for spinal cord injuries, they work with occupational therapists who evaluate their functional abilities and determine what type of rehabilitation is appropriate and who work with patients to implement specific exercises and routines and determine what type of assistive devices could help patients become more independent with daily living

skills.¹¹¹ Conventional manual and powered wheelchairs currently used have considerable limitations in restoring mobility and improving quality of life for patients who have spinal cord injuries. The magnetic pierced-tongue aid would provide patients with the ability to perform tasks, such as wheelchair movement or daily computer and phone tasks, through synergistic communication between the tongue-mounted magnetic tracer, magnetic sensors, smartphones, computers, and wheelchairs.

Figure 6. Overall high-impact potential: intraoral tongue-drive computerized system to maneuver electrically-powered wheelchairs



Experts commenting on this intervention thought that the intraoral, magnetic, tongue-directed aid could be a viable alternative to existing technologies. Although some experts thought the unmet need was not extremely significant, other experts who have worked with patients using assistive devices to control powered wheelchairs believe this intervention could significantly improve health outcomes and quality of life, allowing patients to perform daily activities in a quicker and less exhausting manner. Safety concerns could be a barrier to clinician acceptance, several experts thought, because device malfunction might harm the user. The device's perceived complex nature, the existence of comparators, and limited safety and efficacy data thus far made some experts question device's true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and quality of life, compared with standard mobility devices. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Nine experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.¹²³⁻¹³¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Generally, experts opined that a significant need exists for new assistive technology to restore mobility in patients with spinal cord injury. But they were split on whether the TDS would fill the gap. Several experts thought this device might not significantly affect this patient population, suggesting that alternatives exist to effectively restore mobility, including sip-and-puff, chin-control, head-control, and speech-control assistive devices. However, several other experts reported the magnetic tongue-directed neuroassistive device could become a viable technology for this patient population. One research expert wrote: "I've worked with people using puff-straws, joysticks, and head-paddles, but this looks appropriate for patients with a much higher degree of impairment than [those who use] head paddles and joysticks. Also, unlike air puff, this system is more sensitive and can speed up communication and control tasks. Air puff systems take forever to get anything done and I've seen users get frustrated."¹²³ Another research expert believes the TDS has the ability to replace currently available assistive devices, stating, "it is

relatively discreet, quick to respond to commands, unobstructive to one's senses, and can be used for long periods of time without excessive strain."¹²⁴

This novel neuroassistive device has potential to address an unmet need of this patient population, the experts believe, as long as further studies evaluate the technology's efficacy and safety and provide evidence of benefit. A research expert summarized the opinions of those experts, believing in this device's ability for high impact, stating the TDS "could be a cost-effective way to help improve the quality of life, mobility, and degree of interaction with electronic devices for patients with high-level spinal cord injuries with limited effects on current healthcare infrastructure."¹²⁴

This intervention does not have clear potential to improve patient health outcomes: experts were divided in their opinions. The TDS might not improve health outcomes, a clinical expert thought, because it does not directly affect a patient's health. And a research expert stated that although this device could improve mobility and increase patient quality of life, concerns over potential device malfunction and collision remain. However, a health systems expert opined that the technology seems usable according to available studies and would allow patients to communicate at "normal or near-normal" speed. It seems likely to provide significant mobility improvement over conventional assistive devices, allowing for more patient participation in daily social activities.¹²³ Another expert stated this intervention could allow patients to perform daily activities with a greater degree of ease than with available comparators. This expert states "the key here is the technologies involved to capture, interpret, and transmit intent - and then further, the devices, systems, and equipment that carry out such intent. I believe use of smart phones, in several of these roles, is a good start. Working towards systems that are easy to replace and control is a must..."¹²⁹

Acceptance and adoption: Potential acceptance of the TDS by both clinicians and patients would be high, the experts generally believe. Most experts agreed that, provided this device proves safe and effective, it would be easily accepted by clinicians and physical therapists. Three of these experts believe the potential of this device to improve patient independence would increase patient acceptance. One research expert stated that the device would pose minimal health risks to this patient population while increasing patients' accessibility and communication with society, significantly improving patient outcomes. However, in terms of patient acceptance, a health systems expert questioned, "How does it affect speech? Does this offend culturally? Religiously? Infection?"¹²⁹ Negative perceptions regarding the required tongue piercing for this device seems to be a predominate issue that would affect adoption by elderly patients, according to several experts. One research expert opined that elderly patients may have more reservations than a younger patient population, stating "the elderly patients had already been trained to use other assistive devices and did not want theirs to be replaced."¹²⁴

Health care delivery infrastructure and patient management: This device would not significantly disrupt the current health care delivery infrastructure or patient management, most experts thought, stating that a system is in place is for this device's implementation and adoption. But its adoption might require increased hiring of rehabilitation specialists, computer specialists, and biomedical hardware specialists to train patients and ensure proper functioning of the device, several experts noted. One expert believes that the anticipated increase in specialists for the device in combination with the device's potential complexities may increase time in patient management.

Health disparities: Experts generally agreed this neuroassistive device would not significantly affect health disparities, although one clinical expert opined that the anticipated cost of this device could increase disparities.

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