Priority Area 08: Functional Limitations and Disability

Prepared for:
Agency for Healthcare Research and Quality
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Contract No. HHSA29020100006C

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June 2012
Statement of Funding and Purpose
This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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

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Preface

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

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

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

We welcome comments on this Potential High Impact 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 e-mail 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 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 11,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas and one cross-cutting area.

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 (COI). 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 potential 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 41 topics for which (1) preliminary phase III data were available for drugs being developed for labeled indications or phase II or III data were available for devices, off-label drugs, or and biologics; (2) information was compiled by April 15, 2012, in this priority area; and (3) we received six to eight sets of comments from experts between February 2011 and April 26, 2012. (A total of 168 topics in this priority area were being tracked in the system as of May 2012.) We present 16 summaries on 16 topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts’ comments and their assessment of potential impact.

**Priority Area 08: Functional Limitations and Disability**

<table>
<thead>
<tr>
<th>Topic</th>
<th>High Impact Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aflibercept for treatment of wet, age-related macular degeneration</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>2. *Biocompatible tissue-bulking agent (Solesta) for treatment of fecal incontinence</td>
<td>High</td>
</tr>
<tr>
<td>3. Bupivacaine extended-release liposome injection (Exparel) for treatment of postsurgical pain</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>4. *Computerized walking systems (ReWalk and Ekso) for patients with paraplegia</td>
<td>High</td>
</tr>
<tr>
<td>5. *Dimethyl fumarate (BG-12, Panaclar) for treatment of relapsing-remitting multiple sclerosis</td>
<td>High</td>
</tr>
<tr>
<td>6. DNA chip to detect lipoprotein lipase (LPL) gene mutations</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>7. Ear implant for treatment of Ménière’s disease</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>8. *Ezogabine (Potiga) for treatment of epilepsy</td>
<td>Moderately high</td>
</tr>
<tr>
<td>9. *Fingolimod (Gilenya) for treatment of relapsing-remitting multiple sclerosis</td>
<td>High</td>
</tr>
<tr>
<td>10. *Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema</td>
<td>Moderately high</td>
</tr>
<tr>
<td>11. Gene-transduced autologous hematopoietic stem cell therapy for severe combined immunodeficiency</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>12. Glutamate receptor antagonist (perampanel) for treatment of partial-onset epilepsy</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>13. High-intensity focused ultrasound for treatment of primary hyperparathyroidism</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>14. *Icatibant (Firazyr) for treatment of acute hereditary angioedema</td>
<td>High</td>
</tr>
<tr>
<td>Topic</td>
<td>High Impact Potential</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>15. Image-guided interventional endovascular management of multiple sclerosis</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>16. *Implantable miniature telescope for treatment of end-stage, age-related macular degeneration</td>
<td>Moderately high</td>
</tr>
<tr>
<td>17. Laquinimod for treatment of relapsing-remitting multiple sclerosis</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>18. *Magnetic pierced-tongue drive for directing mobile wheelchair</td>
<td>Moderately high</td>
</tr>
<tr>
<td>19. Methacetin breath test for (BreathID) to monitor liver function in patients awaiting liver transplantation</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>20. Micro-bypass implant (iStent) for treatment of glaucoma</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>21. Neurostimulation (aura6000) for treatment of obstructive sleep apnea</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>22. Neurostimulation (Inspire) for treatment of obstructive sleep apnea</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>23. *Neurostimulation (remedē System) for treatment of central sleep apnea associated with heart failure</td>
<td>High</td>
</tr>
<tr>
<td>24. Nitroglycerin for prevention of osteoporosis</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>25. NX-001 for prevention of delayed graft function after renal transplantation</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>26. *OBI-1 (recombinant B-domain deleted porcine coagulation factor VIII) for treatment of acquired hemophilia</td>
<td>High</td>
</tr>
<tr>
<td>27. *Off-label propranolol for treatment of life-threatening infantile hemangioma</td>
<td>High</td>
</tr>
<tr>
<td>28. Off-label teriparatide (Forteo) for treatment of hard-to-heal bone fractures</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>29. *Orally inhaled dihydroergotamine (Levadex) for treatment of migraine headache</td>
<td>Lower range of high impact</td>
</tr>
<tr>
<td>30. *PTH (1-84) for treatment of hypoparathyroidism</td>
<td>Moderately high</td>
</tr>
<tr>
<td>31. *Ranibizumab (Lucentis) for treatment of diabetic macular edema</td>
<td>Moderately high</td>
</tr>
<tr>
<td>32. Real-time functional magnetic resonance imaging (fMRI) with cognitive training to treat chronic pain</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>33. *Recombinant human microplasmin injection (Ocriplasmin) for treatment of focal vitreomacular adhesion</td>
<td>Moderately high</td>
</tr>
<tr>
<td>34. Sumatriptan iontophoretic patch (Zelrix) for treatment of acute migraine headache</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>35. Synthetic bone grafts for use in foot and ankle fusion surgery</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>36. Taliglucerase alfa for treatment of Gaucher’s disease</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>37. Telcagepant for treatment of migraine headache</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>38. Teriflunomide for treatment of relapsing-remitting multiple sclerosis</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>39. Terlipressin for reversal of hepatorenal syndrome type 1</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>40. UroLift system for treatment of lower urinary tract symptoms caused by benign prostatic hyperplasia</td>
<td>No high-impact potential at this time</td>
</tr>
<tr>
<td>41. Video game therapy for rehabilitation of stroke survivors</td>
<td>No high-impact potential at this time</td>
</tr>
</tbody>
</table>
Discussion

The AHRQ priority area of functional limitations encompasses a wide range of disease states and conditions that affect the ability to function normally including autoimmune diseases, hematologic diseases, conditions causing chronic pain, degenerative diseases, central and peripheral nervous system disorders, physical limitations incurred because of spinal cord injury, sensory conditions (sight, hearing, touch, taste, smell), sleep disorders, organ failure (other than heart), and certain genetic disorders that are outside of the other priority areas. The material on interventions in this Executive Summary and the whole report is organized alphabetically by disease state, and then by interventions. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Central Nervous System Disorder Interventions

Dimethyl Fumarate (BG-12, Panaclar) for Treatment of Relapsing-Remitting Multiple Sclerosis

- **Key Facts:** Multiple sclerosis (MS) is a progressive autoimmune disorder directed against the central nervous system (CNS). Even with current 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 institutional long-term care. Relapsing-remitting multiple sclerosis (RRMS) is the most common form that is diagnosed. First-line 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™). A drug in development, dimethyl fumarate (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. Dimethyl fumarate is being studied as monotherapy and adjunctive therapy. The most common adverse events reported in clinical studies included diarrhea, flushing, gastrointestinal symptoms, headache, and a mild increase in liver enzymes. The manufacturer submitted a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) in February 2012 for treating RRMS. In May 2012, FDA accepted the NDA, and a decision is expected in late 2012.

- **Key Expert Comments:** The experts stated that a well-tolerated oral agent with high efficacy in patients with RRMS continues to present a significant unmet medical need. Experts were encouraged by the lower rates of relapse and delayed disease progression reported in patients treated with dimethyl fumarate as well as the drug’s tolerability profile. In other comments received through the Horizon Scanning system, experts stated that fingolimod, the first oral agent approved to treat RRMS, is expected to have wide acceptance among clinicians and patients, although costs (estimated at $48,000 per patient per year) and the adverse event profile could pose some barriers to diffusion and sources of controversy for that drug. Two other orally administered MS drugs in phase III development, teriflunomide and laquinimod, have differing mechanisms of action and are being tracked in the system. However experts commenting on these other drugs in development did not view them as having potential for high impact because, the experts stated, the unmet need these two agents address has been addressed by fingolimod. Experts
commenting on dimethyl fumarate cited the high efficacy, safety, and purported neuroprotective effects as potentially addressing an unmet need in MS therapy. If dimethyl fumarate can reduce disease progression and the need for assistance with activities of daily living while having a cost comparable to current first-line agents, it could become the first-line therapy of choice for patients, clinicians, and third-party payers.

- **Potential for High Impact:** High

**Fingolimod (Gilenya) for Treatment of Relapsing-Remitting Multiple Sclerosis**

- **Key Facts:** First-line therapies for RRMS consist of injectable immunomodulators that dampen autoimmune responses against the CNS and include interferon beta-1b, interferon beta-1a, and glatiramer acetate. Fingolimod (Gilenya™, Novartis International AG, Basel, Switzerland, and Mitsubishi Tanabe Pharma Corp., Osaka, Japan) is a first-in-class drug of sphingosine 1-phosphate receptor modulators. Investigators from fingolimod trials reported that the drug reduced the frequency of relapses compared with interferon beta-1a by dampening the activity of autoreactive lymphocytes and keeping them localized to the lymph nodes, thereby reducing the number of lymphocytes with access to the CNS. The most common adverse events reported in these studies included headache, flu, diarrhea, back pain, abnormal liver tests, and cough. Other less common fingolimod-related side effects included transient, generally asymptomatic heart-rate reduction and atrioventricular block upon treatment initiation, mild blood pressure increase, macular edema, and mild bronchoconstriction. In September 2010, FDA approved fingolimod (0.5 mg) as the first orally administered first-line treatment for RRMS. Fingolimod is generally covered by third-party payers with preauthorization requirements and quantity limits. The drug’s cost is about $48,000 per patient, per year.

- **Key Expert Comments:** Fingolimod is the first oral agent approved to treat RRMS, and experts commenting on this drug expected its oral administration and improved efficacy to result in wide acceptance among clinicians and patients, although costs and the adverse event profile might pose some barriers to diffusion and sources of controversy for the drug. Reported sales figures in early 2011 indicated good acceptance thus far, despite its $48,000 annual per-patient cost. Currently, fingolimod represents about 5% of the estimated MS market for drug therapy.

- **Potential for High Impact:** High

**Endocrine Disorder Intervention**

**PTH (1-84) for Treatment of Hypoparathyroidism**

- **Key Facts:** No approved pharmacotherapy is available for treating hypoparathyroidism (which results in very low calcium levels), signaling a need for effective therapy. Current treatment options for regulating calcium and phosphorus in the body include supplemental calcium carbonate and vitamin D, although these supplements may lead to long-term complications. For life-threatening hypoparathyroidism (extremely low calcium levels), intravenous calcium is administered, typically in a hospital setting. Recombinant human (Rh) parathyroid hormone (PTH) (1-84) (NATPARA™, NPS Pharmaceuticals, Bedminster, NJ), is a synthetic PTH produced in the bacteria Escherichia coli as a single, nonglycosylated, polypeptide chain containing 84 amino acids. It is purified by proprietary
chromatographic techniques. The manufacturer purports that by replicating the actions of natural PTH, rhPTH can help the body maintain near-normal serum calcium levels with little dependence on supplemental calcium or vitamin D. RhPTH (1-84) was granted orphan drug status by FDA in 2007, and based on preliminary results from the REPLACE trial in November 2011, the company anticipated submitting an NDA to FDA the first half of 2012.

- **Key Expert Comments:** Experts providing comments thought this drug’s potential to treat hypoparathyroidism might reduce overall treatment costs by reducing lifetime use of supplemental calcium carbonate and vitamin D and significantly improving patient health outcomes in this patient population.

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

**Epilepsy Intervention**

**Ezogabine (Potiga) for Treatment-Resistant, Partial-Onset Epilepsy**

- **Key Facts:** Partial-onset seizures are the most commonly occurring seizure in patients with epilepsy. According to the Epilepsy Foundation, about 20% of patients with epilepsy do not respond to available pharmacotherapy, and these patients might have to undergo invasive surgical resection or implantation of a vagus nerve stimulator. Therefore, a novel, effective pharmacotherapy would address an important unmet need. Ezogabine (also known as retigabine, Valeant Pharmaceuticals International, Inc., Montreal, Quebec, Canada, and GlaxoSmithKline, Middlesex, UK) is an anticonvulsant purported to act as both a potassium-channel opener and a gamma aminobutyric acid potentiator, representing a new mechanism of action for this indication. It has been investigated as adjunctive therapy for treatment-resistant epilepsy characterized by partial-onset seizures. After more than 18 months of consideration by FDA, including FDA’s issuance of a complete response letter in 2010 to the manufacturers citing nonclinical reasons for not approving the drug, FDA approved the drug in June 2011 as an add-on medication to treat seizures associated with epilepsy in adults. As a condition of approval, FDA recommended the drug be listed under the Controlled Substances Act, which was expected to delay its availability for several months. FDA approval also required a Risk Evaluation and Mitigation Strategy to inform health care professionals who prescribe the drug of the risk of urinary retention and the symptoms of acute urinary retention. Additionally, FDA published information warning patients about risks of neuropsychiatric symptoms, including confusion, hallucinations, psychotic symptoms, and suicidal thoughts. At the time of this report, retail or wholesale costs for the drug in the United States were not yet available.

- **Key Expert Comments:** Overall, experts commenting on this topic (immediately before its FDA approval) were optimistic about the drug’s potential to meet the need for an effective new pharmacotherapy for this patient population because of its novel mechanism of action and clinical trial data thus far. As an oral drug, it could be incorporated easily into the existing care model for epilepsy. If the drug obviates the need for invasive interventions, most experts thought, it could affect several health system parameters by shifting the care setting and patient management and reducing treatment costs.

- **Potential for High Impact:** Moderately high
Gastrointestinal Disorder Intervention

**Nasha/Dx (Solesta) for Fecal Incontinence**

- **Key Facts:** Available therapies for fecal incontinence have had limited efficacy, have been very invasive, or have been associated with adverse events, marking a need for more innovative interventions. Nasha™/Dx (Solesta®; Oceana Therapeutics, Inc., Edison, NJ), is a biocompatible tissue-bulking agent consisting of cross-linked dextran chain microspheres, with dextran biosynthesized by fermentation of the bacteria *Leuconostoc mesenteroides*, and stabilized sodium hyaluronate buffered in a sodium chloride solution. Nasha/Dx can be administered on an outpatient basis in a physician’s office via injection (dextranomer microspheres, 50 mg/mL, and stabilized sodium hyaluronate, 15 mg/mL, in phosphate buffered 0.9 % sodium chloride solution) in the deep submucosal layer of the proximal anal canal. In May 2011, FDA approved Nasha/Dx for treating fecal incontinence in adult patients whose disease is refractory to conservative, traditional therapies. In September 2011, Oceana Therapeutics launched Nasha/Dx in the United States. The average wholesale price of Solesta is reported as $1,107 per 1 mL injection or $4,428 per treatment session. Retreatment is sometimes required and is intended to occur no sooner than 4 weeks after the initial procedure. The procedure is covered by several third-party payers.

- **Key Expert Comments:** Overall, experts commenting on this intervention thought that there was a particular need for more effective therapies for fecal incontinence. Although several experts opined that this intervention will not work for all patients and might not completely resolve fecal incontinence, they thought that Solesta could help patients avoid surgical intervention. Experts see a potential shift from inpatient surgical management to outpatient management. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

- **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 that is the hallmark of HAE. Attacks involving the larynx can be fatal; serious attacks are associated with a mortality rate of 15% to 33%. 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, public limited company [plc], Dublin, Ireland) is a bradykinin receptor-2 antagonist that was 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 manage this lifelong condition on an outpatient basis. In phase III trials, icatibant provided significant relief of symptoms 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 dose. The company’s Quick Start program and extended OnePath Access Program were created 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.
generally requiring preauthorization and prescription by a specialist and enforcing 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 while other, new treatments have just become available for HAE, icatibant has a different mechanism of action and may be self-administered on an outpatient basis, which could significantly minimize hospitalizations and the role emergency personnel play in the management of HAE in a subset of patients.

- **Potential for High Impact**: High

**Hematologic Disorder Intervention**

**OBI-1 for Treatment of Acquired Hemophilia A**

- **Key Facts**: Currently, an estimated 20,000–25,000 individuals have some type of hemophilia in the United States, with acquired hemophilia affecting 1–4 individuals (primarily middle-aged individuals) per million. Current therapies, specifically human factor VIIa (NovoSeven) and FEIBA, work by bypassing the coagulation cascade, producing extremely higher-than-normal levels of factor VIIa to induce coagulation. However, no available therapies address the underlying pathogenesis of acquired hemophilia, in which autoantibodies produced against the body’s coagulation factors result in excessive bleeding episodes. OBI-1 therapy is an intravenous recombinant porcine factor VIII product that serves as factor VIII replacement therapy by activating the natural coagulation cascade. OBI-1 was given orphan drug status by FDA in March 2004; the European Commission also granted orphan drug status for OBI-1 for treating hemophilia. The company anticipates submitting an NDA to FDA in 2014.

- **Key Expert Comments**: Overall, experts commenting on this intervention were generally optimistic about OBI-1 therapy’s potential to meet the need of patients who experience complications from acquired hemophilia, highlighting its apparently sound mechanism of action and limited side effects. Experts commenting on this drug generally believe that if efficacy is confirmed in pivotal trials, OBI-1 therapy has the potential to serve as first-line therapy for patients with acquired hemophilia and may subsequently alter treatment models.

- **Potential for High Impact**: High

**Pain Intervention**

**Inhaled Dihydroergotamine (Levadex) for Treatment of Migraine Headache**

- **Key Facts**: Migraine headache, a condition often associated with chronic pain, affects an estimated 28 million people each year in the United States. Many patients are dissatisfied with their current migraine medication because of an inconsistent response, migraine recurrence after treatment, and/or slow onset of action in relieving pain. Therefore, new treatments for migraine headache are highly desired. One available migraine treatment is the ergot alkaloid dihydroergotamine (DHE). DHE is available as an injectable solution and nasal spray. A new DHE formulation is in development, Levadex® (MAP Pharmaceuticals, Inc., Mountain View, CA) as an orally inhaled formulation that is delivered using the
developer’s proprietary Tempo™ breath-activated metered dose inhaler. Compared with available injectable DHE, Levadex is purported to be more convenient, faster-acting, and associated with fewer side effects. It might also avoid local nasal irritation and inconsistent absorption that has been observed with nasal spray delivery. In August 2011, MAP Pharmaceuticals filed an NDA for Levadex for treating migraine headache, and FDA accepted the filing. In March 2012, FDA issued a complete response letter requesting that the manufacturer address issues relating to chemistry, manufacturing, controls, and a facility inspection at a third-party manufacturer. The manufacturer planned to meet with FDA to address issues raised in the complete response letter.

- **Key Expert Comments:** Overall, experts providing comment on the DHE formulation thought a significant unmet need still exists for improved migraine treatment and that an inhaled DHE formulation that would allow fast, easy, and effective self-administration could address that need. However, this improvement is perceived as largely incremental and experts were unsure whether Levadex would significantly improve pain outcomes more than that achieved by current DHE formulations.

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

**Sensory Disorder Interventions**

**Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema**

- **Key Facts:** Currently, the main treatment modality for diabetic macular edema (DME) is macular focal/grid laser photocoagulation, because no pharmacotherapies are FDA-approved for treating the condition. Iluvien (Alimera Sciences, Inc., Alpharetta, GA) is a tiny tube containing 190 mcg of fluocinolone acetonide that is injected into the back of the eye with a 25-gauge needle in a single, in-office procedure. Over 2–3 years, the tube releases a constant, low flow of medication. The exact mechanism by which fluocinolone acetonide functions in DME treatment is unknown, but it is thought to work by means of the combined vasoconstrictive, anti-inflammatory, and antipruritic qualities inherent to corticosteroids such as fluocinolone. In November 2011, FDA issued a complete response letter requesting that the company provide two additional safety and efficacy studies before NDA resubmission.

- **Key Expert Comments:** Overall, experts thought this intervention could offer the first pharmacotherapy alternative to laser photocoagulation for treating DME. While some experts believe the risk of adverse events could affect clinician adoption of this intravitreal implant, experts opined that patients would likely be willing to accept this intervention if restoring vision to any degree was the end result. Experts thought that the intervention would reduce per-patient treatment costs, compared with costs of laser photocoagulation. Experts expected costs to be significantly greater with this intervention than with off-label use of anti-VEGF (vascular endothelial growth factor) agents used for DME but lower than the cost of laser photocoagulation.

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

**Implantable Miniature Telescope for Age-Related Macular Degeneration**

- **Key Facts:** No treatments are available for end-stage, age-related macular degeneration (AMD), and patients experience increasingly diminished vision. The implantable miniature telescope (IMT, VisionCare Ophthalmic Technologies, Inc., Saratoga, CA) approved by
FDA in July 2010 is intended to improve vision in patients 75 years of age or older with stable, severe to profound vision impairment caused by end-stage AMD. FDA, as a condition of approval, requires that patients and their surgeons sign a detailed “acceptance of risk agreement” before surgery to acknowledge the risks, which include testing to determine candidacy and the risk of corneal damage and worsened vision after the implantation. The first implantation of the device after FDA approval was announced by the company in November 2011; the implantation and rehabilitation services are delivered as a package the company calls “CentraSight.” The device reportedly costs about $15,000, which does not include the costs of implantation and rehabilitation. In October 2011, the U.S. Centers for Medicare & Medicaid Services determined that the device met criteria for pass-through payment, making reimbursement possible. Medicare coverage is left to the discretion of local Medicare carriers. The implantation of an IMT does not cure macular degeneration; rather, it is intended as an aid to improve vision. Surgically implanted in one eye, the IMT replaces the natural lens and provides an image that has been magnified more than two times.

- **Key Expert Comments:** Experts who commented on this intervention thought the IMT could offer a new option to restore some degree of vision for a condition with no options. Some experts expected the age ceiling for use would lower after initial diffusion and with longer-term outcomes data. Demand for specialists in retinal surgery is expected to increase as the technology diffuses. Significant costs (device and surgery) are anticipated, and it would change treatment paradigms for AMD. Retina specialists will also require training in the implantation procedure.

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

### Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

- **Key Facts:** According to the World Health Organization people with diabetes who do not receive appropriate eye care have a 25% to 30% chance of developing clinically significant DME with moderate or greater vision loss. Currently, the main treatment modality is macular focal/grid laser photocoagulation, because no pharmacotherapies are approved by FDA for treating DME. Ranibizumab (Lucentis, Genentech subsidiary of F. Hoffmann-La Roche, Ltd. (Basel, Switzerland), and Novartis International AG, Basel, Switzerland) is a humanized recombinant immunoglobulin G1, kappa isotope, monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A), FDA-approved for treating wet AMD and macular edema with retinal vein occlusion (RVO). Ranibizumab’s mechanism of action allows it to bind to multiple subtypes of VEGF-A. This binding action causes an inhibiting effect, which prevents the growth of new blood vessels under the macula. Because growth of new blood vessels is prevented, the likelihood of vascular leakage and neovascularization is reduced; thus, vision loss as a result of fluid and protein buildup under the macula may be slowed. Investigators in two phase III trials (RISE and RIDE trials) tested ranibizumab in patients with DME and reported positive results in June 2011. Genentech filed a supplemental biologics license application with FDA for approval for this indication and the FDA decision date was set for August 2012.

- **Key Expert Comments:** Experts thought that the existence and off-label use of other, less-costly anti-VEGF drugs might pose a barrier to use of an on-label, anti-VEGF agent. However, this intervention has potential as an on-label alternative that might be reimbursed by third-party payers for this indication when off-label use might not be. Availability for on-label DME treatment could significantly increase per-patient costs, however, compared with
off-label use of other anti-VEGF drugs. Also, recent publicity about adverse events occurring as a result of preparation methods of existing anti-VEGFs for ophthalmologic uses may make on-label use more appealing.

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

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

- **Key Facts:** Current treatment options for symptomatic vitreomacular adhesion are limited to invasive vitreoretinal surgical procedures that are associated with serious side effects of risk for incomplete vitreoretinal separation and/or removal; surgical complications (e.g., development of cataracts); and high costs. Recombinant ocriplasmin (ThromboGenics NV, Heverlee, Belgium) is a minimally invasive option in development. It retains the catalytic characteristics of human plasmin and is purported to have several advantages, including being sterile due to recombinant techniques used to generate it, being smaller in size than plasmin to potentially allow greater penetration of epiretinal tissues, and being more stable than plasmin. Investigators reported that two phase III trials with 652 patients at 90 centers in Europe and the United States met their primary endpoints. ThromboGenics submitted a biologics license application (BLA) for ocriplasmin to FDA in December 2011, but it was withdrawn in February 2012 after FDA indicated that the agency would grant ocriplasmin priority review status. The company intended to resubmit a new BLA by mid-2012.

- **Key Expert Comments:** Experts thought recombinant microplasmin injection therapy could offer an alternative to surgical intervention for patients most affected by focal vitreomacular adhesion. They had reservations regarding the actual number of patients who would require this intervention, but most experts who commented thought that ocriplasmin injection therapy might provide an effective, cost-saving alternative to current standard treatment.

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

### Sleep Disorder Intervention

**Neurostimulation (remedē System) for Treatment of Heart-Failure-Associated Central Sleep Apnea**

- **Key Facts:** Many patients with heart failure (HF) have a comorbid condition called Cheyne-Stokes respiration, a type of central sleep apnea (CSA) that affects up to two-thirds of HF patients and is associated with increased mortality. Currently, treatment for CSA in these patients is suboptimal. Pharmacotherapy is sometimes used but is often ineffective or predisposes a patient to other cardiac conditions, prompting some clinicians to suggest the use of continuous positive airway pressure (CPAP), which is associated with low patient adherence. Effective treatment for CSA is needed. The remedē™ System (Respicardia, Inc., Minnetonka, MN) is an implantable stimulator being investigated for treating CSA in these patients. According to the manufacturer, the system is intended to deliver electrical pulses via a transvenous stimulator lead positioned within a vein, near one of the phrenic nerves. The phrenic nerve stimulation is intended to restore natural breathing to enable better oxygenation, less activation of the sympathetic nervous system, and improved sleep. The system consists of three implantable components: a pulse generator comprising electronic circuitry and a battery sealed in a titanium case, a stimulation lead, and a sensing lead that detects respiration. The system also includes an external programmer to change the pulse generator settings or to review diagnostic data via telemetry. The pulse generator, which
appears to be similar to a pacemaker, is implanted under the skin below the collarbone. A phase II trial is ongoing in the United States, and the device is approved in Europe.

- **Key Expert Comments:** Overall, experts who commented on this intervention thought it could have an important impact on many parameters of the health care system, particularly treatment and care models, by offering a very different treatment approach, requiring a different staffing model from usual treatment to implant the device, and requiring infrastructure to accommodate a new surgical procedure for this patient population. Additionally, stimulation parameters of the device would need programming and adjusting. While experts wanted to see more data to determine whether this intervention is safe and effective, they were nonetheless optimistic about the technology’s potential to address the unmet need.

- **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 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-™ system (Argo Medical Technologies, Ltd., Yokneam Ilit, Israel) and the Ekso™ system (formerly eLegs, Ekso Bionics, Berkeley, 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 in 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 currently 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 in the near future. The company has been quoted in lay press articles as stating that the personal system will cost one-third to one-half the cost of an institutional system.

- **Key Expert Comments:** Experts thought that this equipment could offer independence currently not available 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 lessons learned from users of this type of intervention might also pave the way for future similar interventions capable of addressing the needs of many more patients with this condition.

- **Potential for High Impact:** High
Magnetic Pierced-Tongue Aid for Management of Spinal Cord Injury

- **Key Facts:** While conventional manual and powered-assisted devices exist that attempt to improve quality of life for individuals with paraplegia, 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 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. Use of 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 one location, Atlanta, GA, and the trial continues to recruit patients.

- **Key Expert Comments:** Experts commenting on this intervention had diverse perspectives about some aspects, although most thought that the magnetic tongue-directed aid could be a viable alternative to existing technologies. Some experts thought the unmet need was not significant, but others who have worked directly with patients in need of assistive devices to control powered wheelchairs believe this intervention could significantly improve 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 could introduce harm to this patient population. Overall, this device’s perceived complex nature, the existence of alternatives, and limited safety and efficacy data thus far have made some experts question the device’s true impact potential. However, other experts believe this device has the ability to significantly improve patient mobility and quality of life when compared with standard mobility devices.

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

Vascular Abnormality Intervention

**Off-label Propranolol for Treatment of Infantile Hemangioma**

- **Key Facts:** Currently, no FDA-approved pharmacotherapies are available for treating infantile hemangiomas (IHs). Although corticosteroids, interferon alpha, and vincristine are treatment measures used for IHs, limited efficacy, safety concerns, and intolerable adverse events associated with these therapies have prompted investigation for novel therapies with a more efficacious and safer profile. Propranolol (off-patent, multiple manufacturers) is a nonselective beta adrenergic receptor antagonist (beta blocker) that exerts its cardiovascular effects by blocking the action of endogenous catecholamines (e.g., epinephrine and norepinephrine) on beta-adrenergic receptors and is being studied for treatment of IHs. Propranolol is not labeled as treatment for IHs, and its intended use by current institutions for this purpose would be considered off-label. A retrospective study published in August 2011 in *Archives of Dermatology’s* Online First (Price et al., University of Miami) compared propranolol to oral corticosteroids for treating IHs, and investigators reported that propranolol therapy was more effective in treating IHs, with minimal side effects and a cost of about $205 per treatment, about half the cost of corticosteroids.
• **Key Expert Comments:** Experts expressed optimism about propranolol’s ability to meet the need of patients who experience complications from IHs. That optimism was contingent on positive results from ongoing clinical trials, and experts though propranolol has the potential to replace corticosteroids as first-line therapy for treating IHs.

• **Potential for High Impact:** High
Central Nervous System Disorder Interventions
Dimethyl Fumarate (BG-12, Panaclar) for Treatment of Relapsing-Remitting Multiple Sclerosis

Multiple sclerosis (MS) is a common cause of physical disability in the United States.\(^1\) Inflammation damages 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.\(^4\) First-line therapies consist of injectable immunomodulators that dampen autoimmune responses against the central nervous system (CNS). Oral fingolimod became available in 2010.\(^5\) 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.\(^4,6-8\)

Dimethyl fumarate (BG-12, Panaclar®, Biogen Idec International GmbH, Zug, Switzerland) is an oral 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, which 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.\(^9,10\) These changes are also purported to inhibit nuclear factor kappaB translocation and downstream proinflammatory signaling.\(^11\) These anti-inflammatory and neuroprotective effects are purported to reduce the number of active brain lesions that could contribute to disease progression.\(^12\) Dimethyl fumarate has been administered 240 mg twice and three times daily in clinical trials and is being investigated as monotherapy and adjunctive therapy.

In two randomized, multcenter, phase III trials, the effects of BG-12 were evaluated in patients with RRMS. In one trial, the investigators reported patients (n=1,237) who received 240 mg of dimethyl fumarate either two or three times daily for 24 months demonstrated a statistically significant reduction in the proportion of patients whose disease relapsed at 2 years compared with patients given placebo (p<0.0001).\(^13\) Patients given both doses of dimethyl fumarate also demonstrated statistically significant reductions in secondary endpoints including annualized relapse rate, the number of 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), and the mean number of new gadolinium-enhancing lesions, (90% and 73%, respectively, p<0.001 for both), compared with placebo.\(^14\) Patients given either dose of dimethyl fumarate also exhibited a significant reduction in the rate of disability progression as measured by the Expanded Disability Severity Scale.\(^13\) Patient-reported outcomes also revealed that treatment with dimethyl fumarate was associated with significant improvements in physical functioning and general well-being.\(^15\)

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 (ARR) (44% and 51%, respectively; p< 0.0001 for both) compared with patients given placebo.\(^16\) Investigators reported that patients treated with the active comparator glatiramer acetate (20 mg subcutaneous injection, once daily) had a reduction in ARR by 29% (p<0.02) compared with placebo. Additionally, dimethyl fumarate was reported to reduce the number of new or newly enlarging T2-hyperintense lesions by 71% and 73% (p<0.0001 for both dosage regimens) compared with placebo, while glatiramer acetate reduced lesions by 54% (p<0.0001).\(^16\) Dimethyl fumarate reduced new T1-hypointense lesions by 57% and 65% (p<0.0001 for both dosage regimens), while glatiramer acetate reduced lesions by 41% (p<0.003). The
proportion of patients who experienced a relapse while taking dimethyl fumarate was reduced by 34% for twice daily dosing (p<0.003) and by 45% for three times daily (p<0.0001), compared with 29% for glatiramer acetate (p<0.01).16

FDA granted dimethyl fumarate fast track designation in 2008.17 In February 2012, Biogen Idec submitted a new drug application (NDA) to FDA for treating RRMS.18 In May 2012, FDA accepted the NDA,19 and a decision is expected in late 2012.20

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® International GmbH, Zug, Switzerland; Rebif®), and glatiramer acetate (Copaxone®).4,6 Oral fingolimod is used as first- or second-line therapy. Dimethyl fumarate is intended to be used as first- or second-line monotherapy for RRMS or as an adjunct to existing therapies.

Figure 1. Overall High Impact Potential: Dimethyl fumarate (Panaclar) for treatment of RRMS

Experts commented that data from phase III trials are encouraging and suggested that the drug could fulfill the unmet need of 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, the drug 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-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.21-27

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

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

Although several experts thought the high expected price of dimethyl fumarate might increase health disparities for patients without prescription coverage from a third-party payer, two experts representing a research perspective stated 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. 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.

The experts stated that both clinicians and patients are expected to have a high level of acceptance of dimethyl fumarate because of the efficacy and safety profile reported in patients with RRMS. However, two experts representing a research perspective stated cost could be the 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 could delay the need for institutional long-term care, the drug may be cost saving.
Fingolimod (Gilenya) for Treatment of Relapsing-Remitting Multiple Sclerosis

Current first line-therapies for RRMS consist of injectable immunomodulators that dampen autoimmune responses against the CNS. However, no effective treatments are available to stop the long-term progression of the disease.\(^6\) Fingolimod (Gilenya\(^\text{TM}\), Novartis International AG, Basel, Switzerland, and Mitsubishi Tanabe Pharma Corp., Osaka, Japan) is the first oral drug approved (September 2010) by FDA as first-line therapy for RRMS.

Fingolimod is a synthetic derivative of myriocin and is the first in a new class of oral drugs for treating MS called sphingosine 1-phosphate receptor (S1PR) modulators.\(^28\) The active metabolite of fingolimod is thought to act initially as an S1PR-1 agonist; however, S1PR-1 binding eventually results in the reduction in cell-surface levels of S1PR-1 through receptor internalization and subsequent degradation.\(^28,29\) By modulating the sphingosine 1-phosphate receptor pathway, fingolimod is purported to dampen the activity of autoreactive lymphocytes by keeping them localized to the lymph nodes. In this way, fingolimod is thought to reduce the number lymphocytes with access to the CNS and limit damage to the myelin sheath.\(^29\) Fingolimod is administered once daily in a 0.5 mg capsule with or without food.\(^7\)

In three large, randomized, multicenter, phase III trials, the effects of fingolimod were evaluated in patients with RRMS. In one trial, the investigators reported that patients (n=1,272) who received either 0.5 or 1.25 mg of fingolimod or placebo once daily for 24 months had annualized relapse rates of 0.18, 0.16, and 0.40, respectively (p<0.001 for either dose vs. placebo).\(^30\) The cumulative probability of disability progression (confirmed after 3 months) was 17.7%, 16.6%, and 24.1%, respectively. Fingolimod at both doses significantly reduced the risk of disability progression during the study (p=0.02 vs. placebo, for both comparisons). At 24 months, both doses of fingolimod were superior to placebo with regard to magnetic resonance imaging–related measures (number of new or enlarged lesions on T(2)-weighted images, gadolinium-enhancing lesions, and brain-volume loss; p<0.001 for all comparisons).\(^30\)

In the second study, investigators reported that patients (n=1,292) who received either 0.5 or 1.25 mg of fingolimod daily or intramuscular injection of 30 mcg interferon beta-1a weekly for 12 months. The annualized relapse rate was significantly lower in both groups receiving fingolimod 0.16 (95% confidence interval [CI], 0.12 to 0.21) and 0.20 (95% CI, 0.16 to 0.26) in the 0.5- and 1.25-mg groups respectively compared with the interferon group (0.33; 95% CI, 0.26 to 0.42; p<0.001 for both comparisons).\(^31\) No significant differences were seen among the study groups with respect to progression of disability.\(^31\) The most common adverse events reported in these studies included headache, flu, diarrhea, back pain, abnormal liver tests, and cough. Other fingolimod-related side effects included transient, generally asymptomatic heart-rate reduction and atrioventricular block upon treatment initiation, mild blood pressure increase, macular edema, and mild bronchoconstriction.

In the third study, the investigators reported that patients (n=1,083) with RRMS who received either 0.5 or 1.25 mg (later switched to 0.5 mg) of fingolimod had a statistically significant 48% reduction in annual relapse rates compared with placebo at 24 months.\(^32\) Additionally, patients treated with fingolimod had a significant reduction in brain volume loss compared with patients treated with placebo.\(^32\)

In September 2010, FDA approved fingolimod (0.5 mg) for the first-line treatment of RRMS.\(^33\) Reported sales figures in March 2011 indicated broad acceptance by the MS clinical and patient communities thus far, despite its $48,000 annual per-patient cost.\(^34\) According to one financial analyst, fingolimod currently represents about 5% of the MS market while injectables represent about 85% of the market.\(^35\) Increasing acceptance and use of fingolimod and its oral competitors
dimethyl fumarate and teriflunomide (if they are approved) are expected. New agents could even bring patients back for treatment after they had discontinued previous options. However, injectables were still theorized to remain an important part of MS therapy.35

Clinical Pathway at Point of This Intervention

First-line treatments to reduce the frequency and severity of relapses for RRMS include the injectable medications interferon beta-1b (Betaseron®), interferon beta-1a (Avonex®; International GmbH, Zug, Switzerland Rebif®), and glatiramer acetate (Copaxone®).4,6 Fingolimod represents the first oral agent approved in the United States to treat RRMS.

Figure 2. Overall High Impact Potential: Fingolimod (Gilenya) for treatment of relapsing-remitting multiple sclerosis

Experts commenting on this drug expected the simple oral administration and improved efficacy to result in wide acceptance among clinicians and patients. However, they also thought that costs (estimated at $48,000 per patient, per year), coverage by payers, and the adverse event profile of fingolimod could be barriers to diffusion and sources of controversy for the drug. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.36-42 Overall, the experts stated that MS is a debilitating disease that results in significant morbidity and disability. There remains a large unmet need for new treatments with improved efficacy and ease of administration. The experts stated that fingolimod may address this unmet need and improve patient health outcomes by increasing the time between relapses and delaying the accumulation of physical disability. As an agent with a new mechanism of action, fingolimod might improve outcomes in patients who did not respond to previous first-line therapies, two experts representing a clinical perspective stated. Experts thought the safety profile of fingolimod, including sudden deaths after administration of the drug, is cause for some concern.

Although several experts thought the high price of fingolimod might increase health disparities for patients without prescription coverage from a third-party payer, one expert representing a research perspective stated that patients with poor access to care are now able to take a pill at home instead of requiring routine visits for injections. Overall, the experts stated that upon initiating fingolimod treatment, additional monitoring for cardiovascular and ophthalmologic adverse events could add minimally to demands on infrastructure and staffing at treatment centers, because monitoring for cardiac adverse events occurs only after the first dose is administered. However, one expert representing a clinical perspective stated that neurologists would likely administer the first dose but would not want to be responsible for monitoring cardiovascular responses. Thus, the first
dose may need to be administered by a primary care physician or a cardiologist. The expert also stated that future trials could demonstrate only patients with preexisting cardiac conditions would need to be monitored.

Although physicians might be hesitant to use fingolimod because of its adverse-event profile, some experts stated that the increased efficacy of the drug and ease of administration are likely to increase acceptance of the drug. Many of the experts also thought patients would be highly receptive to an oral therapy that might slow disease progression. Fingolimod and injectables have roughly the same costs. Some experts stated that if patients are already taking injectable therapy and their insurance covers fingolimod, cost would provide a minimal barrier to diffusion because fingolimod is expected to be used as monotherapy; if the drug were used as adjunctive therapy costs could rise markedly. The cost of monitoring patients for serious adverse events after the first dose of fingolimod could also add to costs minimally. One expert representing a research perspective stated that controversy could arise if third-party payers are reluctant to authorize fingolimod therapy for patients on other treatments that are ineffective in stabilizing or relieving their symptoms and neurologic abnormalities.
Endocrine Disorder Intervention
PTH (1-84) for Treatment of Hypoparathyroidism

Hypoparathyroidism is an endocrine disorder characterized by abnormally low levels of parathyroid hormone (PTH), which can lead to low calcium levels in blood and bones and an increased amount of phosphorus. Symptoms include anxiety, depression, fatigue, headaches, memory problems, muscle cramps and/or tingling of the extremities, muscle spasms, painful menstruation, brittle nails, dry skin, and patchy hair loss. Hypoparathyroidism (low levels of PTH) affects approximately 4 of every 100,000 persons in the United States. Current treatment options for regulating calcium and phosphorus in the body include supplemental calcium carbonate and vitamin D, although these supplements can lead to long-term complications. In life-threatening hypoparathyroidism (extremely low calcium levels), intravenous calcium may be administered by a physician. Currently, no pharmacotherapy is approved for treating hypoparathyroidism, signaling a need for more effective therapy.

Recombinant human (rh)PTH (1-84) (NATPARA™, NPS Pharmaceuticals, Bedminster, NJ) is a synthetic PTH produced in the bacteria Escherichia coli as a single, nonglycosylated, polypeptide chain containing 84 amino acids, and it is purified by proprietary chromatographic techniques. In the human body, PTH, or parathormone, is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. PTH increases the concentration of calcium in the blood by acting upon PTH receptors in three parts of the body: bones, kidney, and intestine. The manufacturer purports that by replicating the actions of natural PTH, rhPTH can help the body maintain near-normal serum calcium levels without much dependence on supplemental calcium or Vitamin D. RhPTH (1-84) has been considered as a potential antiosteoporotic agent and as a bone formation stimulant that may stimulate osteoblasts and reduce both vertebral and nonvertebral fractures. In clinical trials, rhPTH (1-84) is being given by subcutaneous injection at doses of 50, 70, or 100 mcg per day for treating hypoparathyroidism.

In 2011, Bilezikan and colleagues reported results from the recent phase III REPLACE trial, a 28-week, double-blind, placebo-controlled study evaluating rhPTH for treating hypoparathyroidism. In this study, “53 percent (48/90) of NPSP558 [rhPTH]-treated patients achieved the primary endpoint versus 2 percent (1/44) of placebo-treated patients (p<0.0001). At week 24, 43 percent (36/84) of patients treated with NPSP558 were able to achieve independence from active vitamin D therapy and a calcium supplementation dose of 500 mg/day or less, as compared to five percent (2/37) for patients treated with placebo (p<0.0001). Thirteen of the 134 randomized subjects discontinued the study early, of which seven were placebo-treated and six were NPSP558-treated.”

RhPTH (1-84) was granted orphan drug status by FDA in 2007, and based on preliminary results from the REPLACE trial in November 2011, the company anticipates submitting a biologics license application to FDA in 2012.

Clinical Pathway at Point of This Intervention

Once a diagnosis of hypoparathyroidism is made, treatment options to restore the body’s calcium and phosphorus to normal levels include calcium carbonate and vitamin D supplements, which usually must be taken for a lifetime. Blood levels are measured regularly to ensure appropriate dosages are being taken, because overtreatment with vitamin D and calcium can cause hypercalcemia, which can adversely affect kidney function. A high-calcium, low-phosphorous diet is recommended, and in cases of life-threatening attacks of low calcium levels or prolonged muscle contractions, calcium is given intravenously in the emergency department. In these cases, cardiac monitoring for abnormal rhythms is also conducted. A dietitian is part of the multidisciplinary team to manage this condition in stable patients. Currently, there is no approved prescription
therapy for hypoparathyroidism.\textsuperscript{46} RhPTH (1-84) is a synthetic PTH under study as a daily injection for treating hypoparathyroidism to reduce or replace calcium and vitamin D supplementation.

**Figure 3. Overall High Impact Potential: PTH (1-84) for treatment of hypoparathyroidism**

Experts commenting on this intervention thought the drug’s potential to treat parathyroidism could reduce overall treatment costs accumulated by lifetime use of supplemental calcium carbonate and vitamin D, in addition to treatment of toxicity associated with excessive use of these supplements. They also thought this intervention could significantly improve quality of life and patient health outcomes, because rhPTH (1-84) might decrease incidence of vertebra fractures and other complications of the disease besides reducing or eliminating the need for supplemental calcium and vitamin D. Experts opined that while lack of safety and efficacy studies and an increase in per-patient costs might serve as barriers to adoption, this intervention has the potential to significantly affect this patient population. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

**Results and Discussion of Comments**

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.\textsuperscript{54-60} Experts’ opinions were mixed regarding importance on pharmacologic agents needed for treating hypoparathyroidism. Several experts argued there are several treatment options available for this disease, and current treatment modalities are typically effective in managing hypothyroidism. These experts indicated there may not be much of an unmet need for this patient population, considering there is a small subset of patients receiving a diagnosis of hypoparathyroidism whose disease is not currently managed by supplemental calcium carbonate and vitamin D. However, experts who agreed there is an unmet need for this intervention argued that rhPTH (1-84) might significantly improve patient health outcomes and quality of life, potentially reducing or eliminating the need for supplemental calcium and vitamin D, currently needed for duration of life.

Experts generally agreed this intervention’s underlying theory is sound, although more studies need to be conducted to further evaluate rhPTH (1-84)’s efficacy and safety. One research expert indicated that rhPTH (1-84) dose levels and frequency of administration need to be determined for proper evaluation of efficacy and safety. One clinical expert cautioned that while this intervention’s theory appears logical, “[hormone] replacement is never truly physiologic and thus outcomes may not be as desired.”\textsuperscript{59} Opinions regarding this intervention’s potential to improve patient health outcomes were mixed. Four experts believe this synthetic hormone could treat the underlying cause of disease rather than managing complications of disease with current treatment modalities. One clinical expert explained that “potentially reducing or [eliminating] the need for other supplements and dietary restrictions would have a large positive outcome for patients, allowing them to live more normal lives.”\textsuperscript{60} A health systems expert noted that the potential reduction in vertebrae fractures and other bone-related issues would significantly improve patient outcomes and quality of
life. Other experts remained uncertain of this therapy’s ability to improve patient outcomes, citing the need for long-term efficacy studies to make a proper determination.

The majority of experts agreed that the intervention would not significantly affect the current patient care model or health care delivery infrastructure, indicating self-administration with an injectable therapy would require minimal adjustment for this patient population. All experts cautioned that patient and clinician acceptance of this intervention might be difficult, given the treatment transition to daily self-administered injections of rHPTH (1-84). Experts indicated clinicians might not adopt a therapy that poses regimen-adherence issues for their patients. In terms of patient acceptance, however, one clinical expert explained that patients might be willing to comply with this therapy, considering that adhering to dietary restrictions could be more difficult than adhering to this therapy.

Expert opinions regarding per-patient costs for this intervention were mixed. Several experts opined while initial per-patient costs could increase, potential reduction and elimination of supplemental therapies might decrease these costs long term. One expert indicated that there is not yet enough information regarding this therapy’s effect on costs in terms of decreased hospitalizations, reduction in therapy, and other associated financial factors. Two experts strongly indicated that per-patient costs might increase significantly with adoption of this therapy. One research expert stated, “depending on the optimal dose and drug costs, if a patient needs 100 micrograms daily, based on cost estimated in the report this could add about $200.00/day to treatment costs.” Another research expert echoed this sentiment, but added that self-administration of this therapy in the home setting may obviate the need for inpatient hospitalizations for intravenous calcium supplementation, potentially mitigating substantial per-patient costs.

Overall, questions surrounding this therapy’s efficacy and safety when compared with existing treatment options and overall costs left several experts skeptical of rHPTH (1-84)’s potential to have high impact for patients in whom hypoparathyroidism has been diagnosed. However, several experts believe that given initial study results, there is potential for this therapy to significantly improve outcomes in patients for this indication where traditional therapies have failed and where there is currently no FDA-approved pharmacologic therapy.
Epilepsy Intervention
Ezogabine (Potiga) for Treatment-Resistant, Partial-Onset Epilepsy

Partial-onset seizures are the most common form of epileptic seizures. According to the Epilepsy Foundation, about 20% of patients with epilepsy do not respond to currently available pharmacotherapy, and these patients may have to undergo invasive surgical resection or implantation of a vagus nerve stimulator. Therefore, a novel, effective pharmacotherapy would address an important unmet need for these patients.

Ezogabine (Potiga™, Valeant Pharmaceuticals International, Inc., Montreal, Quebec, Canada, and GlaxoSmithKline, Middlesex, UK) is an anticonvulsant purported to act as both a potassium-channel opener and a gamma aminobutyric acid (GABA) potentiator, representing a new mechanism of action for this indication. In its role as a potassium-channel opener, ezogabine is purported to stabilize potassium channels in the open position, which allows the stabilizing membrane current to increase. These effects are purported to prevent the action-potential bursts that occur during the sustained depolarization observed during seizures (i.e., reducing cellular excitability). Researchers have also suggested that ezogabine increases the concentration of GABA, the major inhibitory neurotransmitter in the brain, which has long been associated with epilepsy. Ezogabine is administered as an oral tablet formulation with an initial dose of 100 mg three times daily and titrated up to 200–400 mg three times daily. Ezogabine is also intended to be used as an adjunctive therapy with other antiepileptic pharmacotherapy.

French and colleagues (2011) presented results from a phase III trial assessing ezogabine’s efficacy in 306 patients with refractory epilepsy with partial-onset seizures. Authors reported, “median percent reduction in total partial-seizure frequency was 44.3% vs 17.5% (p < 0.001) for [ezogabine] and placebo, respectively, during the 18-week double blind period; responder rates (≥50% reduction in total partial-seizure frequency from baseline) were 44.4% vs 17.8% (p < 0.001).” Additionally, authors reported, “in 256 patients ([ezogabine], 119; placebo, 137) entering the 12-week maintenance phase, median percent reduction in seizure frequency for [ezogabine] vs placebo was 54.5% and 18.9% (p < 0.001), respectively; responder rates were 55.5% vs 22.6% (p < 0.001). The proportion of patients discontinuing due to treatment-emergent adverse events (TEAEs) was 26.8% [ezogabine] vs. 8.6% (placebo).” Adverse events reported by patients treated with ezogabine in this clinical trial included “dizziness, somnolence, fatigue, confusion, dysarthria, urinary tract infection, ataxia, and blurred vision.” The company also reported that in its three, phase III trials, “Ezogabine caused urinary retention in clinical trials. Urinary retention was reported as an adverse event in 29 out of 1,365 (approximately 2%) patients treated with ezogabine. In all studies of patients with partial-onset seizures, including open-label studies, five patients required catheterization (four on ezogabine and one on placebo). In three controlled clinical studies, 25% of patients receiving ezogabine (199/813) and 11% of patients receiving placebo (45/427) discontinued treatment because of treatment-emergent adverse reactions.”

In June 2011, FDA approved ezogabine for treating partial-onset seizures in adults (18 years and older). FDA conditions of approval required a Risk Evaluation and Mitigation Strategy (REMS) to inform health care professionals who prescribe the drug of the risk of urinary retention and the symptoms of acute urinary retention. Additionally, FDA published consumer information alerting patients to risks of neuropsychiatric symptoms, including confusion, hallucinations, psychotic symptoms, and suicidal thoughts. At the time of this report, retail or average wholesale pricing for the drug in the United States was not yet available.
Clinical Pathway at Point of This Intervention

According to the Epilepsy Foundation, current treatment for this disease state includes pharmacotherapy (e.g., carbamazepine, gabapentin, phenobarbital, valproate), and, for some patients unresponsive to these agents, surgical resection or vagus nerve stimulation may be indicated. Ezogabine is being investigated as an adjunct therapy to current antiepileptic medications and would likely be used in concert with these medications. If ezogabine is found to be safe and effective for this indication, it would likely displace some of the need for surgical resection or vagus nerve stimulation. Thus, ezogabine is expected to compete with these interventions as an option for patients whose epilepsy is refractory to existing pharmacotherapy.

Figure 4. Overall High Impact Potential: Ezogabine (Potiga) for treatment-resistant, partial-onset epilepsy

Overall, experts commenting on this topic were generally optimistic about this drug’s potential to meet the need for effective pharmacotherapy for adults with treatment-resistant, partial-onset epilepsy because of its promising mechanism of action and clinical trial data. As an oral drug, experts thought, it could be incorporated easily into the existing care model for epilepsy. However, if ezogabine is proven to obviate the need for invasive interventions for epilepsy, it would affect several health system parameters, especially a change in care setting (medical management rather than surgery), patient management, and treatment costs, most experts opined. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration perspectives, commented on this intervention. These experts agreed that an unmet need exists for effective, noninvasive therapies for patients with epilepsy that is refractory to pharmacotherapy. One clinical expert commented that surgical interventions have limited efficacy, thus highlighting the importance of the unmet need for new, more effective options.

Experts expressed strong opinions about the theory underlying the intended mechanism of action of ezogabine, with one expert stating that this mechanism “has the effect of stabilizing the electrical current in the brain and prevents the sudden bursts of activity that occur with seizures.” One clinical expert thought that the underlying mechanism is “actually one of the best one could imagine,” because “potassium channels have been studied for their role in epilepsy and many drug therapies for epilepsy focus on increasing GABA levels.” Another expert, however, tempered this viewpoint, stating, “The overall decrease in neuronal responsiveness may have unintended consequences.” Experts were cautiously optimistic about the drug’s potential to improve health outcomes, stating that although additional studies are needed to confirm efficacy and side-effects data, results so far suggest improvements in seizure rate. One expert with a health systems perspective believes that potential success of ezogabine could improve patient adherence, which in turn would positively affect patient health outcomes.
Because the drug is characterized by a novel mechanism of action, experts thought, ezogabine has the potential to have an impact on “basic research and our current understanding of the mechanism of the disease,” as one expert put it. They also stated that the drug may obviate the need for surgical resection or electrical stimulation, leading most experts who commented to believe that it has potential to shift current treatment models. Similarly, by potentially reducing the need for invasive interventions, the drug has potential to shift the care setting for treatment-resistant epilepsy from an inpatient to outpatient setting, they thought, which would, in turn, “reduce hospital stays for surgical treatment of epilepsy, increase patient throughput by not requiring surgery, and decrease the amount of staff required to treat epilepsy.” However, some experts thought that treatment models would remain the same, because the drug is intended to be used as an oral adjunct to current pharmacotherapies.

Experts were divided on whether this intervention would increase or decrease the cost of care. Some experts claimed that costs would be reduced, because drugs are typically less expensive than surgical interventions, while others believe that, as one expert put it, “Surgery is a one-time deal, and [medications are taken for] a lifetime.” That expert thought a long-term increase in care costs would be seen, particularly because ezogabine would be added to current oral medication regimens.

Most experts believe that both patients and clinicians would accept this intervention readily, particularly if it is shown to obviate the need for invasive procedures. One expert with a health systems perspective expressed optimism that this intervention might improve the physician-patient relationship by giving physicians another option to offer in their armamentarium.
Gastrointestinal Disorder Intervention
Biocompatible Tissue-Bulking Agent (Solesta) for Treatment of Fecal Incontinence

Available therapies for fecal incontinence include antidiarrheal, dietary, and behavioral therapies (to improve muscle control). Other treatment modalities for this condition include sacral nerve stimulation, surgical interventions, and an implantable silicone elastomer balloon and cuff pump, which was previously the only implantable device for this disease. These therapies have had limited efficacy, been invasive, and associated with adverse events, marking the need for better options.

Nasha™/Dx (Solesta®, Oceana Therapeutics, Inc., Edison, NJ), is a biocompatible tissue-bulking agent consisting of cross-linked dextran chain microspheres, with dextran biosynthesized by fermentation of the bacteria Leuconostoc mesenteroides, and stabilized sodium hyaluronate buffered in a sodium chloride solution. The microspheres and sodium hyaluronate allow the gel to become hydrophilic and swell in water, as well as swell in the sodium chloride solution. This gel, insoluble in water and organic solvents, is intended to narrow the anal canal by expanding/bulking up the submucosal layer in the canal, thereby potentially increasing a patient’s sphincter control.

Nasha/Dx can be injected on an outpatient basis in a physician’s office (dextranomer microspheres, 50 mg/mL, and stabilized sodium hyaluronate, 15 mg/mL, in phosphate buffered 0.9 % sodium chloride solution). Four injections are given in the deep submucosal layer in the proximal anal canal. The injections consist of 1 mL each (4 mL total) spaced equally and close to the anorectal junction, where pain sensory innervation is minimal.

Graf and colleagues (2011) presented results from a phase III clinical trial evaluating Nasha/Dx’s efficacy in 206 patients receiving a diagnosis of fecal incontinence, in which primary endpoints include a 50% or more reduction in fecal incontinence episodes. Authors reported “71 patients who received NASHA Dx (52%) had a 50% or more reduction in the number of incontinence episode, compared with 22 patients who received sham treatment (31%; odds ratio 2.36, 95% CI 1.24–4.47, p=0.0089). We recorded 128 treatment-related adverse events, of which two were serious (1 rectal abscess and 1 prostatic abscess).”

In May 2011, FDA approved the treatment for fecal incontinence in adult patients whose disease is refractory to conservative, traditional therapies. In September 2011, Oceana Therapeutics launched Nasha/Dx in the United States. The average wholesale price of Solesta is reported as $1,107 per 1 mL injection or $4,428 per treatment session. Re-treatment is sometimes required and is intended to occur no sooner than 4 weeks after the initial procedure.

Clinical Pathway at Point of This Intervention

First-line treatment for fecal incontinence includes adherence to a high-fiber diet to improve stool consistency and better establish bowel control. Alternative therapeutic measures may include antidiarrheal and dietary therapy, aimed to promote bulking of feces to allow patients to more readily control release of feces. Behavioral modifications, such as Kegel exercises, are alternative measures used to help patients control release of feces. Surgical interventions for treating fecal incontinence include sphincteroplasty, tissue ablation, and device implantation. These current pharmacological, dieting, and nerve-stimulating therapies may not sufficiently improve fecal incontinence, and surgical treatments can be invasive, costly, and for some patients, result in unfavorable outcomes. Nasha/Dx is positioned as second-line therapy for patients with fecal incontinence after traditional nonsurgical treatments have failed.
Overall, experts commenting on this intervention thought that there was a particular need for more effective therapies for fecal incontinence. While several experts opined this intervention will not work for all patients and may not completely resolve fecal incontinence, Nasha/Dx could help patients avoid surgical intervention. Experts see a potential shift from inpatient surgical management to outpatient setting. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention. Experts generally agreed an important unmet need exists for effective fecal incontinence treatment for this patient population, based on the current lack of effective therapies and cost and risk of adverse events associated with available therapies. One clinical expert opined that few patients seek proper care for fecal incontinence, and those patients who seek treatment often receive conservative treatment or no treatment at all. However, one expert opined that effective alternative therapies and “protective garments” are available for fecal incontinence management and the need for improved options was incremental.

Most experts stated this intervention has potential to improve health outcomes. Although based on preliminary results, they thought the tissue-bulking agent would not always completely resolve fecal incontinence. Most experts wanted to see additional trial results. One expert with a clinical perspective found it difficult to determine this intervention’s potential to improve health outcomes, stating, “This will not work for everyone. Those with muscle disruptions will probably need surgery. Even ‘perfect’ candidates will sometimes not be successful.”

Experts generally agreed that this intervention has the potential to affect the current care model and patient management and to shift care setting from inpatient surgery to office visits. One clinical expert opined that if this treatment is proven effective, it has the potential to dramatically shift the staff needed to treat the condition, because colorectal surgeons who perform the surgical procedures would be supplanted by gastroenterologists delivering minimally invasive injections during an office visit. Another clinical expert commented on this intervention’s potential to “reduce the number of individuals needed to care for incontinent patients (decreased number of aides, LPNs, etc). It would also decrease the individual’s costs for cleaning materials and local treatments (e.g. creams and ointments).” One research expert added that this intervention would reduce the number of procedures performed in operating rooms.

Experts were divided on how this intervention would affect costs. Most experts commented that the gel polymer would be expensive. However, some experts also suggested that if the intervention improves patient outcomes, it would ultimately reduce long-term costs associated with invasive surgery and in-patient care. Experts anticipated high patient acceptance of this intervention, with one clinical expert noting a patient’s desperation for novel therapies to appropriately manage fecal incontinence. However, experts were divided on how likely clinicians would be to offer the therapy.
One clinical expert opined “I am not optimistic about adoption by gastroenterologists. They often do not want to care for anorectal diseases.” However, other experts noted that this intervention might become widely accepted because it is a noninvasive alternative to surgery that would have appeal to patients. Overall, experts agreed this tissue-bulking agent has higher potential for high impact among this patient population, particularly for those patients wishing to avoid highly invasive surgical procedures.
Genetic Disorder Intervention
Icatibant (Firazyr) for Treatment of Acute Hereditary Angioedema

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.\(^6^2\) During a serious attack, the throat may swell and cause the airway to close, resulting in asphyxiation; this is associated with a mortality rate of 15% to 33%.\(^8^3\) Abdominal attacks can also cause severe pain and disfigurement. Bouts of edema can last 3–5 days; the trigger for attacks is unknown.\(^8^2\) Icatibant (Firazyr\(^®\), Shire, plc, Dublin, Ireland) is a selective and specific synthetic polypeptide bradykinin receptor-2 (BR2) antagonist.\(^8^2,8^4\) Preclinical studies have purportedly 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.\(^8^2\) Icatibant is currently available as a subcutaneous injection administered 30 mg in 3 mL as needed.\(^8^4\) The injection can be administered in a health care setting (more likely on the initial attack) or by the patient during subsequent attacks.

In two double-blind, randomized, multicenter trials, the effects of icatibant were evaluated in patients with HAE presenting with cutaneous or abdominal attacks.\(^8^5\) In one trial (n=56), researchers reported that the primary endpoint of median time to clinically significant relief of symptoms was 2.5 hours compared with 4.6 hours with placebo, although the result did not reach statistical significance (p=0.14). In the second trial (n=74), researchers reported that the primary endpoint of median time to clinically significant relief of symptoms was 2 hours with icatibant versus 12 hours with tranexamic acid (p<0.001). No icatibant-related serious adverse events were reported.\(^8^5\) Recent data from a phase IIIb trial evaluating patients who self-administered icatibant (n=88) in response to acute HAE attacks were also reported.\(^8^6\) Icatibant significantly reduced the patient-assessed median time to onset of symptom relief (2.0 vs. 19.8 hours) and the median time to onset of primary symptom relief (1.5 vs. 18.5 hours) versus placebo (p<0.001).\(^8^7\) Icatibant also reduced the median time to almost complete symptom relief compared with placebo (8.0 vs. 36.0 hours; p=0.012). Researchers stated that patients treated with icatibant reported significantly faster initial symptom improvement compared with placebo (0.8 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 which included diarrhea, nausea, dyspepsia, headache, and injection site erythema; and no patient treated with icatibant experienced a serious adverse event.\(^8^7\) The most common adverse events associated with icatibant’s use include (in order of frequency) injection site reactions, pyrexia, increased transaminase levels, and dizziness.\(^8^4\) Patients with HAE attacks affecting the larynx are advised to seek medical attention after self-administration of icatibant.\(^8^4\)

Shire filed a new drug application with FDA in 2007.\(^8^8\) However, FDA issued a nonapprovable letter in April 2008.\(^8^9\) The company submitted a complete response letter containing additional data in February 2011.\(^9^0\) In August 2011, FDA approved icatibant for treating type I or type II acute HAE.\(^9^1\) BioRx (Cincinnati, OH), has entered a limited agreement with Shire to distribute icatibant in the United States.\(^9^2\)

According to one online pharmacy, the retail cost of one 30 mg dose of icatibant is about $8,400.\(^9^3\) The retail cost of one 30 mg dose of ecallantide (Kalbitor\(^®\)), a recently approved competitor to icatibant, was listed at about $9,500.\(^9^3\) Shire’s Quick Start program and extended OnePath Access Program were created 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.\textsuperscript{91}

Our searches of 11 representative private third-party payers that provide online medical coverage policies (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.\textsuperscript{94-103} In general, 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.\textsuperscript{94-103}

**Clinical Pathway at Point of This Intervention**

Three new drugs have been approved in the United States for treating HAE. Two are given intravenously by a medical professional. Cinryze\textsuperscript{®} and Berinert\textsuperscript{®} are plasma-derived C1INH concentrates purified from human plasma for short-term prophylaxis and acute HAE attacks; ecallantide (Kalbitor\textsuperscript{®}) is a plasma kallikrein inhibitor administered by subcutaneous injection for acute HAE attacks.\textsuperscript{82} Icatibant represents a novel mechanism for HAE treatment to reduce inflammation during acute HAE.

**Figure 6. 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 while 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 the management of 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-potential-impact range.

**Results and Discussion of Comments**

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.\textsuperscript{104-110} Overall, experts agreed that current treatment options for HAE are much less effective than desired, and a strong unmet need exists for new therapies for the disease. All experts offering comments agreed that the theory behind the mechanism of icatibant action is sound, and the available data from clinical trials showed promising results that icatibant appeared efficacious at relieving HAE symptoms within a relatively short time. Two experts with clinical perspectives and two experts with research perspectives believe the findings associated with icatibant could increase our understanding of targeting pathways involved in immunologic acute-phase responses.
Additionally, experts stated that the ability of patients to self-inject icatibant on an outpatient basis to treat acute HAE attacks was one of the main unmet needs in HAE treatment that icatibant could address. Cost was also identified as an area that may be affected by the use of icatibant; however, experts were generally unsure as to the magnitude and direction of the impact on cost, given the unavailability of cost information at the time of review. One clinical expert and one health systems expert stated that cost savings could be realized if emergency department visits could be avoided; however, another clinical expert stated that costs may increase if icatibant is used for mild cases of HAE, while cost savings may be realized if icatibant is used on an outpatient basis for more serious cases of HAE. The lack of sufficiently effective therapies and the severity of the disease inclined all experts to state that they expected few barriers to acceptance of icatibant by patients and physicians. One clinical expert stated that the high anticipated cost of the intervention and the small population of patients with HAE would prevent providers from stocking a potentially effective therapy, thereby providing a source of controversy. One clinical expert and one research expert also stated that self-injection might present a barrier to patient acceptance. Two research experts and one health systems expert also identified concerns regarding ischemia and stroke, which may be associated with the use of icatibant, as sources of controversy.

Overall, experts viewed icatibant as having significant potential to shorten the duration of symptoms and improve clinical outcomes in the small number of patients affected by HAE.
Hematologic Disorder Intervention
OBI-1 (Recombinant B-Domain Deleted Porcine Coagulation Factor VIII) for Treatment of Acquired Hemophilia

Acquired hemophilia is a rare disease occurring mostly in middle-aged individuals and rarely in children. An estimated 20,000–25,000 individuals in the United States have some type of hemophilia.\textsuperscript{111,112} Acquired hemophilia is rare and affects approximately 1–4 individuals per 1 million population.\textsuperscript{112} Current therapies, specifically human factor VIIa (NovoSeven\textsuperscript{®}, Novo Nordisk a/s (Bagsvaerd, Denmark), and factor VII Inhibitor Bypassing Activity (Feiba\textsuperscript{™}, Baxter International, Inc., Deerfield, IL) work by bypassing the coagulation cascade, producing extremely higher-than-normal levels of factor VIIa to induce coagulation.\textsuperscript{113} However, an increase in novel therapies is needed to more effectively address the underlying pathogenesis of acquired hemophilia, in which autoantibodies produced against the body’s coagulation factors result in excessive bleeding episodes. OBI-1 (Inspiration Biopharmaceuticals, Inc., Laguna Niguel, CA) therapy is purported to address the unmet need of patients receiving a diagnosis of acquired hemophilia A.

OBI-1 is an intravenous recombinant porcine factor VIII product that serves as factor VIII replacement therapy by activating the natural coagulation cascade.\textsuperscript{113} In acquired hemophilia, the production of autoantibodies in adult life inactivates factor VIII, causing hemophilia type A. This therapy purportedly has low cross reactivity with autoantibodies against factor VIII, significantly reducing immunogenicity of the antigen to recombinant porcine factor VIII. In a previous study, OBI-1 was evaluated in patients with congenital hemophilia A. Results from this study demonstrated that OBI-1 had the capacity to stop the bleeding in all study participants, which paved the way for investigation of its efficacy for acquired hemophilia A.\textsuperscript{114} In an ongoing phase II/III trial, OBI-1 is being given by intravenous infusion over a period of 2–3 hours in the trial for patients with acquired hemophilia A.

In July 2011, Inspiration Biopharmaceuticals announced results from its pivotal trial in the OBI-1 Accur8 clinical trial program. OBI-1 treatment was given to three patients with acquired hemophilia who had experienced severe bleeds uncontrolled by other therapeutic agents. Bleeding stopped in all three patients treated with OBI-1 therapy. A larger phase III trial was planned to begin in 2011.\textsuperscript{115} FDA granted OBI-1 orphan drug status in March 2004. The European Commission also granted orphan drug status.\textsuperscript{114} A U.S. regulatory submission for marketing approval is not expected until 2014.

Clinical Pathway at Point of This Intervention

Patients with acquired hemophilia A present a different pattern of bleeding (extensive purpura) when compared with common congenital forms of the disease (bleeding into joints).\textsuperscript{112} Primary care providers may be the first to encounter the patient, who is then referred for a hematology consultation, ideally at a comprehensive hemophilia treatment center. These centers provide a multidisciplinary approach that includes a team consisting of hematologists, nurses, social workers, physical therapists, and other health care providers.\textsuperscript{111} According to the U.S. Centers for Disease Control and Prevention, treatment involves replacing the missing clotting factor through plasma-derived concentrate or genetically engineered recombinant factors (i.e., not from plasma) of the missing factor, cryoprecipitate for acute bleeding episodes, or other medications intended to induce clotting, such as DDAVP (desmopressin acetate) and Amicar\textsuperscript{®} (epsilon aminocaproic acid).\textsuperscript{111} For acquired hemophilia, treatment also targets production of the antibody inhibitors.\textsuperscript{112} OBI-1 is proposed as a treatment for acute bleeding episodes in patients with acquired hemophilia A who have developed inhibitors to human factor VIII.
Overall, experts expressed optimism about OBI-1’s potential to address the need for effective first-line treatment for acquired hemophilia, highlighting its sound mechanism of action and limited side effects. Experts thought that it would likely change the treatment model for this condition. However, experts also opined that further studies evaluating efficacy and safety are needed to confirm its promise. Experts remained divided on per-patient costs with OBI-1 therapy, but thought clinicians and patients would be very accepting of this therapy because of the lack of other effective treatments, marking its potential for high impact. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.116-122 Experts agreed that an unmet need exists for more effective therapy aimed at stimulating the natural coagulation cascade and countering inhibition of clotting factors by autoantibodies. One expert with a clinical perspective indicated that recombinant porcine factor VIII therapy may be a significant upgrade over current therapies, most notably human factor VIIa, which may induce problems related to hypercoagulation.

Experts agreed that the underlying mechanism of action of OBI-1 therapy is quite sound. One expert with a research background stated, “Recombinant factor VIII is supplied to counter the effects of antibodies to endogenous factor VIII. Since the recombinant factor VIII is porcine based, the antibodies that are interfering with endogenous human factor VIII will not attack the porcine factor VIII.”119 Another expert with a research perspective believes the underlying mechanism shows “great potential to work on acquired hemophilia A” based on results from a previous clinical study.116 Another expert indicated that the underlying mechanism for OBI-1 therapy seems sound and appears to offer a low risk of adverse events to this patient population. Experts were cautiously optimistic about OBI-1’s potential to improve health outcomes, stating that additional studies are needed to confirm efficacy. One clinical expert remained highly optimistic about this therapy’s potential to improve several components of a patient’s life. This expert stated that with early intervention with OBI-1, “the patient’s life can be improved dramatically by decreasing the time and money currently spent on existing infusion treatments that stand a marginal chance of treating this disorder.” This same expert also described how a patient’s quality of life can be increased by avoiding the complications seen with existing treatments, such as hypercoagulation effects seen with use of human factor VIIa.

Experts’ comments were generally mixed regarding whether OBI-1 therapy has the potential to inform current understanding of acquired hemophilia. One expert with a health systems perspective indicated that increased understanding of this therapy’s mechanism of action “could change the direction by which other factors could be used for activating the normal hemostatic pathways.”116 An expert with a clinical perspective wrote, “Clinical focus has always been on arresting the bleeding by initiating any intrinsic means available,” which results in numerous transfusions and
resultant hypercoagulation. This expert added “OBI-1 infusions deliver precisely [factor VIII], which acquired hemophilia type A patients are missing, and this allows us to study and treat this disorder with increased specificity.” Most experts believe that this therapy has potential to significantly disrupt current care models for this patient population, indicating that OBI-1 may serve as first-line therapy for treating acquired hemophilia. These experts claimed that not only does OBI-1 therapy incorporation into the current care model have the potential to replace existing therapies, but it may also offer a new perspective on future treatment modalities for treating acquired hemophilia. However, two experts believe that the current care system would not be disrupted by incorporation of OBI-1 therapy and that it might be used as an adjunctive therapy.

Four of seven experts believe that per-patient cost of care with OBI-1 therapy would rise. The other three contended that per-patient costs would decrease, with one expert citing that there might be the potential to shift care for hemophilia A from the inpatient to outpatient setting. Another expert believes that this shift from inpatient to outpatient could also reduce costs to third-party payers. Experts generally agreed that patient acceptance for OBI-1 therapy would be high and that if proven efficacious, this recombinant porcine coagulation factor VIII product has the potential for high impact.
Pain Intervention
Orally Inhaled Dihydroergotamine (Levadex) Treatment for Migraine Headache

Migraine headache is one of the most common chronic pain disorders, affecting an estimated 28 million people each year in the United States. Many patients are not satisfied with their current migraine treatment because of inconsistent response to the medication, high migraine recurrence rates after treatment, and/or slow onset of action of the medication. Therefore, new treatments for migraine headache are highly desired.

One commonly employed migraine treatment is the ergot alkaloid dihydroergotamine mesylate (DHE). While the exact mechanism of action of DHE is unclear, it is proposed to act as an agonist of various 5-hydroxytryptamine 1 (5-HT1 [serotonin]) receptors, and could mitigate migraine symptoms by causing meningeal vasoconstriction and trigeminal inhibition of proinflammatory neuropeptide release. DHE is available as an injectable solution and as a nasal spray.

Levadex® (MAP-004, MAP Pharmaceuticals, Inc., Mountain View, CA) is a novel, orally inhaled formulation of DHE that is delivered by its developer’s proprietary Tempo™ breath-activated metered dose inhaler. Compared with currently available injectable DHE, Levadex is purported to be more convenient and faster-acting, with fewer side effects for patients who are known to respond to DHE. Preliminary data suggest that patients treated with Levadex might not experience nausea and vomiting as often as patients treated with intravenous DHE. The developer claims that, compared with the currently available nasal spray DHE, inhaled Levadex would avoid nasal irritation and inconsistent absorption often observed with nasal spray delivery.

In April 2011, results were published from a randomized, double-blind, phase III trial comparing Levadex to placebo for treating 903 patients who experience migraines. Of the 903 patients, 792 had a qualifying migraine during the trial (395 patients in the Levadex arm and 397 patients in the placebo arm), and researchers reported that Levadex met its primary endpoints of superiority to placebo in the percentage of patients who reported pain relief (58.7% vs. 34.5%; p<0.0001), freedom from heightened auditory sensitivity (52.9% vs. 33.8%; p<0.0001), freedom from heightened light sensitivity (46.6% vs. 27.2%; p<0.0001), and no nausea (67.1% vs. 58.7%; p=0.0210). In August 2011, MAP Pharmaceuticals filed a new drug application for Levadex for treating migraine headache and FDA accepted the submission for review. In March 2012, FDA issued a complete response letter requesting that the manufacturer address issues relating to chemistry, manufacturing, controls, and a facility inspection at a third-party manufacturer. FDA was also unable to complete a review of inhaler usability information it had requested late in the review cycle. FDA did not cite any clinical safety or efficacy issues or request any additional clinical studies for approval. The manufacturer planned to meet with FDA to address issues raised in the complete response letter.

Clinical Pathway at Point of This Intervention

Patients with mild to moderate migraine headaches are typically treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Patients experiencing more severe symptoms and those who do not respond to NSAIDs may be treated with migraine-specific drugs such as triptans or DHE. Several existing formulations are available for triptans and DHE, and patients’ use of one treatment over another is based mainly on delivery method preference and response to treatment. Levadex would represent another delivery option for DHE treatment of acute migraine headache.
Overall, experts providing comments on this topic believe that a significant unmet need exists for an improved formulation of DHE that could allow fast, easy, and effective self-administration. However, this improvement is largely incremental and experts were unsure whether Levadex would truly improve outcomes compared with current DHE formulations. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention. Experts were divided on the significance of an orally inhaled DHE formulation to address the unmet need of better migraine treatments, noting that Levadex provides only an alternative delivery method for an existing drug. Some experts suggested that this was significant; one expert with a clinical background expressed the opinion that DHE was the best available treatment for acute chronic migraine and that an orally inhaled delivery method had the potential for more consistent dosing than the nasal spray formulation and offered more convenience than injected formulations. Conversely, one expert with a research perspective noted that, given the availability of a nasal spray formulation of DHE that could be used in the home setting, Levadex does not really address a gap in treatment.

Most experts agreed that the scientific rationale behind the treatment is sound, largely based on successful historical use of DHE to treat migraine and the successful creation of orally inhaled medications for other conditions. However, one expert with a clinical perspective argued that patients might experience some degree of variability in intraoral absorption, ultimately decreasing efficacy. This expert also questioned whether mucosal irritation in the lower airway might occur, because studies involving intranasal DHE have reported irritation to the nasal mucosa. Additionally, several experts had concerns regarding the delivery method and suggested that patient training would be needed to ensure accurate dosing. However, one clinical expert who had observed use of the device suggested that it seemed easy to master and convenient. While multiple experts noted that clinical trial results demonstrated efficacy of Levadex, two experts offering research and clinical perspectives suggested that a head-to-head comparison with an alternate DHE formulation would be more meaningful than comparison with placebo and noted the lack of data supporting increased patient satisfaction relative to use of the nasal spray formulation.

As a formulation change to an existing treatment, Levadex would not cause significant changes to migraine treatment models, health care staffing, or health care infrastructure, experts believe. However, multiple experts noted that Levadex has the potential to reduce visits to the emergency department for migraine treatment where intravenous infusion would likely be administered. The change from emergency department intravenous infusion to at-home self-administration figured prominently experts’ estimates of Levadex’s impact on health care costs. One clinical expert noted that if Levadex replaces intravenous administration of DHE, it has the potential to reduce costs;
however, if patients currently using established alternatives such as oral triptans switch to use of Levadex, it could increase costs.

Aside from the concerns regarding the need to train patients in the use of the Levadex inhaler to ensure proper dosing, most of the experts thought there would not be barriers to acceptance of Levadex by patients or physicians. However, one expert with a clinical perspective noted that potential side effects of intraoral DHE, when compared with triptans, could affect patient acceptance. Several experts noted that the ability to easily treat oneself on location wherever the migraine occurred would allow patients who respond to DHE increased access to rapid migraine treatment and likely spur rapid adoption.
Sensory Disorder Interventions
Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

Diabetic macular edema (DME) is a thickening or swelling of the retina caused by fluid leaking from blood vessels within the macula in patients with diabetes mellitus. The swelling that occurs as a result of fluid build-up distorts central vision, mainly affecting an individual’s ability to see form, color, and detail. Patients gradually lose their ability to focus on objects in their central field of vision over a period of months or years as the disease progresses. According to the World Health Organization, people with diabetes who go untreated for eye care have a 25% to 30% chance of developing clinically significant macular edema with moderate vision loss. Currently, the main treatment modality is macular focal/grid laser photocoagulation, because there are no other FDA-approved devices or pharmacotherapies for DME treatment.

Iluvien (Alimera Sciences, Inc., Alpharetta, GA) is a tiny tube containing 190 mcg of fluocinolone acetonide that is injected into the back of the eye with a 25-gauge needle in a single, in-office procedure. Over a period of 2–3 years, the tube releases a constant, low flow of medication. The estimated daily dosage dispensed by the implant was 0.23 mcg. The exact mechanism by which fluocinolone acetonide functions in DME treatment is unknown, but it is thought to be due to the combined vasoconstrictive, anti-inflammatory, and antipruritic qualities inherent to corticosteroids such as fluocinolone. Whereas current FDA-approved management and treatment options are designed to slow or halt damage, clinical trials with Iluvien have demonstrated that damage can be reversed, and in many cases patients can regain a portion of the vision lost due to DME.

Alimera Sciences (2011) reported results from a 2-year, phase III trial assessing the efficacy and safety of 0.23 and 0.45 mcg of fluocinolone in 956 patients with DME. Authors reported, “Trial A and B data combined demonstrated a statistically significant effect at week three. This effect was maintained throughout the 36 months, with 28.7% of Iluvien [low dose] patients and 16.2% of control patients (p=0.002) having an improvement in BCVA [best corrected visual acuity] of 15 letters or greater over baseline at month 24, 31.4% versus 15.1% at month 30 (p=<0.001), 29% versus 17.3% at month 33 (p=0.004) and 28.7% versus 18.9% at month 36 (p=0.018).”

Clinical Pathway at Point of This Intervention

A patient who presents with DME undergoes a history and physical examination including an assessment of the individual’s history of vision and eye disease, and risk factors for DME including diabetic history (type 1 at higher risk), older age, poor glucose control, pregnancy, hypertension, and increased lipid levels. Using a high magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. Treatment for DME is focused on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Laser photocoagulation reduces the risk of moderate visual loss but some patients experience permanent visual loss even after intensive treatment. New advances in devices, pharmacotherapy and surgical techniques have shown promise in treating DME.
Overall, experts thought this intervention could offer an alternative to laser photoacoagulation for treating DME, for which no FDA approved treatments exist to restore vision. While some experts believe risk of adverse events could minimize clinician adoption of this intravitreal implant, experts opined patients would be willing to accept this intervention if restoring vision to any degree was the end result. Experts expected reduced per-patient costs to be associated with this intervention, compared with laser photoacoagulation. Experts thought costs would be significantly greater with this intervention when compared with off-label use of other anti-VEGF (vascular endothelial growth factor) agents. However, its potential to significantly restore vision or slow progression of disease suggests that this intervention has moderate potential impact. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on the fluocinolone acetonide implant. Most experts agreed that treatment options for DME are limited, with laser photoacoagulation being an invasive intervention that can slow progression of disease. One expert stated there are no FDA-approved treatments available to improve vision in these patients. However, one clinical expert explained there are already available treatments that slow progression of DME and there is relative uncertainty as to whether this intervention could improve visual acuity.

Most experts agreed the fluocinolone acetonide implant has potential to significantly improve patient health outcomes, with one health systems expert stating “once vision has been lost, any treatment that can return some sight is important.” However, this same clinical expert remained skeptical based on results of clinical trials, which the expert believes is a reason the FDA did not approve the new drug application for this intervention. Another clinical expert also remained skeptical of this intervention’s potential to improve health outcomes, mentioning “in its present form, the small benefits provided by Iluvien in the reported clinical trials are superceded by the adverse effects in terms of a significantly increased risk of cataracts and increased intra-ocular pressures (glaucoma).” Most experts suggested this intervention will not affect health disparities, particularly due to costs and third-party payers’ unwillingness to cover the implant.

Experts generally agreed this intervention’s potential to disrupt the current health care delivery infrastructure would be minimal, citing that intravitreal injections are becoming more commonplace in the physician’s office. One research expert noted this intervention could obviate the need for more invasive surgical intervention, moving treatment setting from the operating room to the physician’s office. While some experts opine this intervention would minimally disrupt current patient management, others believe this intervention could become the standard of care if proven effective and safe, thus increasing patient management in the retinal specialists’ office. However,
one research expert states, “…given the incidence of side-effects with this intervention the
treatment of these symptoms would involve a moderate disruption of long-term treatment of these
patients.”

Expert opinions were mixed regarding clinician and patient acceptance. Several experts opined
that provided the fluocinolone acetonide implant is deemed safe and effective, clinicians would
willingly adopt this intervention and patients would eagerly accept an implant capable of restoring
their vision. However, in terms of clinician acceptance, a health systems expert opines adoption
could be less given the severity of adverse events associated with this intervention. In terms of
patient acceptance, this same expert conceded patients could be willing to accept the risk of adverse
events for the chance of restoring vision. Experts commenting on potential financial impacts of the
intervention believe per patient cost will be increased when compared to off-label drugs, including
triamcinolone and bevacizumab, but think costs could be reduced when compared to laser
photocoagulation. Overall, experts believe that given there are no FDA approved treatments aimed
to improve vision in patients with progressive DME, the fluocinolone acetonide treatment has
moderate potential for high impact in this patient population.
Implantable Miniature Telescope (IMT) for Treatment of End-Stage, Age-Related Macular Degeneration

While several treatments are available to slow progression of age-related macular degeneration and even restore some vision in some patients, many patients stop responding to treatment and progress to blindness. More effective interventions are needed to restore vision and improve quality of life in patients with end-stage, wet, age-related macular degeneration (AMD). The implantable miniature telescope (IMT, VisionCare Ophthalmic Technologies, Inc., Saratoga, CA) is intended to improve vision in patients 75 years of age or older with stable, severe to profound vision impairment caused by end-stage AMD.

The IMT is a miniature telescopic device surgically implanted in one eye that replaces the anatomical lens, magnifying an image more than two times. The non-implanted eye aids in peripheral vision. This device combines wide-angle micro-optics with the optics of the cornea. Its telephoto system magnifies images in front of the eye about 2.2 or 2.7 times their normal size. The magnification is projected onto perimacular areas of the retina instead of the macula alone, where breakdown of photoreceptors and loss of vision may have occurred as a result of wet AMD. The intraocular telescope is surgically implanted in the capsular bag (containing the lens) and is held in place by two loops. The IMT includes a fused silica capsule in which the optical elements are contained, a clear polymethylmethacrylate (PMMA) carrier and a blue PMMA light restrictor. Before the device is implanted, potential candidates are evaluated and trained with external telescopes (2.2 and 3.0 times magnification) to simulate what they could expect if the implantation with the IMT is successful. Implantation is performed via limbal or scleral tunneling procedures. A viscoelastic material (to protect eye structures) is injected into the anterior chamber and a circular tear of 6.5 mm in the anterior eye capsule is made. According to the IMT clinical trials data, larger incisions (e.g., 12 mm) were associated with a significant loss of corneal endothelial cells at a level exceeding the targeted endpoint levels. Topical antibiotics and nonsteroidal anti-inflammatory medications are usually given for at least 2 days after surgery. Postsurgery steroid treatment lasting approximately 3 months was given in a clinical trial conducted for premarket approval.

Brown and colleagues (2011) presented results from a phase III clinical trial evaluating 3X model IMT implantation procedure in 76 patients with end-stage AMD and severe vision loss whose disease is refractory to medications. Following the 2-year trial, authors reported, “vision improved from 20/326 to 20/141 (mean values) in 76 patients who received the 3X model IMT. Most patients could once again see people's faces rather than just blurry outlines, and could get around the market or their backyard on their own. Overall, these IMT patients' lives improved substantially and at a reasonable cost. Quality of life was measured using a system called human value gain, with standards based on the actual experiences of people with vision loss.” The FDA Center for Devices and Radiological Health approved the IMT for end-stage AMD treatment in July 2010. IMT implantation does not cure macular degeneration, rather, it is intended as an aid to improve vision. In October 2011, the U.S. Centers for Medicare & Medicaid Services determined that the device met criteria for pass-through payment, making reimbursement possible. Medicare has no national coverage determination, leaving coverage decisions to the discretion of local Medicare carriers. In November 2011, the company announced the first IMT device implantation post-approval. “CentraSight” is the company’s name for the combination of procedural and rehabilitation services for the IMT. It also has a Conformité Européene (CE) mark in the European Union and Israel Ministry of Health approval.
Clinical Pathway at Point of This Intervention

The IMT is intended to be used when first-line medications are no longer effective in patients with severe to profound vision impairment due to end-stage AMD. A retina specialist is required to perform the surgical implantation of the IMT.\textsuperscript{156}

Figure 10. Overall High Impact Potential: Implantable Miniature Telescope (IMT) for treatment of end-stage, age-related macular degeneration

Experts thought the IMT could offer an alternative for a condition for which no current treatment is available to restore some degree of vision. Experts thought the demand for specialists in retinal surgery would increase as the technology diffuses; however, its applicability is limited to individuals of a specific age cohort at this time. Experts expected significant costs to be associated with the device and surgery, because it has no competing intervention and would be a new addition to the care paradigm for AMD. Experts thought that third-party coverage would be likely if the device provides significant benefits in terms of independence and quality of life and has a low rate of complications. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.\textsuperscript{157-163} Most experts agreed that treatment options for end-stage AMD are limited, and available medications do not provide improvement for some patients at all or for others after a time. Experts also agreed that no treatments are available to improve vision in these patients. The IMT concept of sending images to areas of the retina not affected by AMD was considered novel by most experts. One expert with a clinical perspective agreed with the IMT concept provided it is deemed compatible with the cornea and intraocular pressure. One expert with a health administration perspective questioned how the brain will adapt to and interpret the images sent by the IMT to the retina. Another expert with research experience thought this benefit was unsatisfactory because it does not address the underlying cause of AMD.

Concerning IMT’s impact on health outcomes (i.e., improved visual acuity), experts agreed that IMT has potential to improve visual acuity, although its impact over the long term is not yet known. An expert with research perspective indicated that the different photoreceptors on the retina (primarily rods at the periphery and primarily cones at the center) process images differently, and this could affect quality of vision in some patients. However, the same expert also thought that these detriments would likely be outweighed by the benefits of having a larger portion of the visual field available for sight. An expert with a health administration perspective suggested the age of the intervention’s targeted population (people aged 75 years and older) might decrease as IMT technology is diffused and more data on its real-world effectiveness emerge. However, this expert also indicated that low risk for complications and payer acceptance would affect how quickly the target age for the intervention would be lowered. An expert with a clinical perspective expressed
concern over a patient’s difficulty to adapt to an IMT given previous inability to adjust to wearable telescopes. This may ultimately lead to removal of the IMT for that patient population.

All experts agreed that the IMT would increase per-patient costs and would increase the demand for retinal specialists. Patient acceptance, excluding costs, was not perceived as a detriment to adoption according to most experts commenting on this parameter. An expert with a clinical perspective noted the potential for unequal refractive power (anisometropia) if the IMT is implanted in one eye, leading to decrease in patient acceptance in a small number of this patient population. Most experts thought the IMT would have little impact on improving health disparities.
Ranibizumab (Lucentis) for Treatment of Diabetic Macular Edema

Diabetic macular edema (DME) is a thickening or swelling of the retina caused by fluid leaking from blood vessels within the macula in patients with diabetes mellitus. The swelling that occurs as a result of fluid build-up distorts central vision, mainly affecting an individual’s ability to see form, color, and detail. Patients gradually lose their ability to focus on objects in their central field of vision over a period of months or years as the disease progresses. According to the World Health Organization, people with diabetes who go untreated for eye care have a 25% to 30% chance of developing clinically significant macular edema with moderate vision loss. Currently, the main treatment modality is macular focal/grid laser photocoagulation, because there are no pharmacotherapies approved by FDA for treating DME.

Ranibizumab (Lucentis, Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and Novartis International AG, Basel, Switzerland) is a humanized, recombinant immunoglobulin G1, kappa isotope, monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A), FDA-approved for wet AMD and macular edema with retinal vein occlusion treatment. Ranibizumab’s mechanism of action allows it to bind to multiple subtypes of VEGF-A, causing an inhibiting effect, which prevents the growth of new blood vessels under the macula. This prevention reduces the likelihood of vascular leakage and neovascularization; thus, vision loss as a result of fluid and protein buildup under the macula is also reduced. In pivotal phase III clinical trials, ranibizumab is administered as a 0.5, 1.0, or 2.0 mg intravitreal injection given once every 4–5 weeks. Treatment is often required indefinitely or until reversal of vision loss.

Boyer and colleagues (2011) presented results from the combined RIDE and RISE clinical trials evaluating ranibizumab in 759 patients receiving a diagnosis of DME with baseline visual acuity of 20/40 to 20/320. Authors reported 62.2% to 63.2% of patients receiving intravitreal ranibizumab improved visual acuity to the 20/40 baseline for driving in the RIDE and RISE trials, respectively. In terms of achieving the primary endpoint of a gain of at least 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale over baseline, 33.6% and 44.8% of patients receiving a 0.3 mg dose of ranibizumab and 45.7% and 39.2% of patients receiving a 0.5 mg dose of ranibizumab achieved endpoints compared with 12.3% and 18.1% treated with sham. The percentage of patients receiving a 0.5 mg dose of ranibizumab who gained at least 10 letters (two lines on the eye chart) was 65.6%. In terms of eyesight deterioration (loss of three lines on the eye chart), fewer than 4% of patients treated with ranibizumab were reported compared with 8.5% to 10.2% of patients treated with sham.

Ferrone and colleagues (2011) presented results from a clinical trial evaluating ranibizumab dose response in 50 patients with clinically significant DME. Authors reported “at Month 24, significant visual acuity gains from baseline were observed in both 0.5mg and 1.0mg groups. There was a significant mean decrease in central foveal thickness in both the 0.5mg and 1.0mg groups. In the 0.5mg group, a smaller proportion of patients gained 15 or more ETDRS letters compared to patients in the 1.0mg group. The average number of injections in the 0.5mg group was similar as compared to the 1.0mg group. Fifteen patients received 2.0mg ranibizumab starting at or after Month 24. In this subset, visual and anatomic outcomes were maintained through follow-up. When compared to the 6 months preceding the transition to the 2.0mg dose, the average time (days) between treatments increased in both groups (0.5mg vs 2.0mg: 49 vs 66; and, 1.0mg vs 2.0mg: 45 vs 56).”
Ranibizumab has been approved by FDA since 2006 for treating wet AMD. In June 2010, ranibizumab was approved in the United States for patients with macular degeneration following retinal vein occlusion. Investigators from phase III trials (RISE and RIDE trials) reported positive preliminary results in June 2011, and Genentech filed for the extended labeling; FDA is expected to make a decision in August 2012.

**Clinical Pathway at Point of This Intervention**

A patient who presents with DME receives a history and physical including an assessment of the individual’s history of vision and eye disease, and risk factors for DME including diabetic history (type 1 at higher risk), older age, poor glucose control, pregnancy, hypertension, and increased lipid levels. Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. Treatment for DME is focused on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Laser photocoagulation reduces the risk of moderate visual loss but some patients experience permanent visual loss even after intensive treatment. New advances in pharmacotherapy and surgical techniques have shown promise in treating DME.

![Figure 11. Overall High Impact Potential: Ranibizumab (Lucentis) for treatment of diabetic macular edema](image)

Experts thought ranibizumab could offer an alternative to laser photocoagulation for treating DME, for which no FDA approved pharmacotherapy exists to restore vision. Some experts thought that the frequency of intravitreal administration of ranibizumab might pose a barrier to patient adherence to treatment recommendations, limiting its ability to significantly improve patient outcomes and potentially affecting patient acceptance. Experts expected significant costs to be associated with this intervention, particularly if it is used as an adjunctive therapy to laser photocoagulation. Experts thought that the existence and off-label use of other anti-VEGF agents, significant per-patient costs, and potential patient nonadherence because of intravitreal injection frequency may serve as barriers to ranibizumab’s impact. However, its potential to significantly restore vision or slow progression of disease suggests that this intervention has moderate potential impact. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

**Results and Discussion of Comments**

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention. All experts agreed that treatment options for DME are limited, with laser photocoagulation being an invasive intervention with a variable degree of efficacy. One research expert stated that with regards to photocoagulation, “some treated patients experience permanent vision loss after laser treatment.” This expert also believes the increasing number of people being diagnosed with diabetes will warrant more effective therapy for treating
DME. Experts also agreed that no FDA-approved treatments are available to improve vision in these patients. Regarding ranibizumab’s potential to fulfill the unmet need in this patient population, one clinical expert stated, “The burden of loss of vision to the individual has far reaching consequences and thus any therapy that improves vision or slows down vision loss [is] important and addresses an important unmet need.”

Experts also agreed that ranibizumab for treating DME has the potential to significantly improve patient health outcomes, with one clinical expert stating that ranibizumab has been shown to improve visual acuity more effectively than laser photocoagulation and steroids. Some experts believe in the potential of ranibizumab to improve patient outcomes, but would like more published clinical results to more competently evaluate this therapy’s efficacy and safety. In terms of this intervention’s potential to impact health disparities, opinions were mixed among experts, with several experts arguing that the frequency of physician visits needed for intravitreal injection would increase nonadherence among patients in rural and low socioeconomic areas, increasing disparities. One research expert thought the pricing of ranibizumab in terms of dollars per quality-adjusted life-year would be significantly more expensive compared with laser photocoagulation, therefore widening the barrier for the economically disadvantaged. One expert believes ranibizumab has the ability to improve health disparities on the basis that African Americans and Hispanics are most affected by DME, with access still likely to remain a barrier.

Experts remained mixed on this intervention’s potential to disrupt the current health care delivery infrastructure, with some experts suggesting that an effective intravitreal drug would not significantly affect current settings, while other experts argued repeated physician visits for intravitreal injection compared with the outpatient procedure with standard laser photocoagulation could significantly change the current infrastructure. One research expert stated that this intervention’s potential to disrupt the current delivery infrastructure “would depend on whether [ranibizumab] emerges as a monotherapy or an adjunct to laser therapy.” Expert opinions were also mixed regarding the potential for ranibizumab to disrupt how patients are currently managed, with some experts believing the change from laser therapy to intravitreal injection is significantly disruptive. One research expert stated, “Current standard of treatment with laser has longer lasting effect and requires an extended interval between treatments (4 months). With ranibizumab, patients will require more frequent follow-up visits and more frequent injections/treatments (monthly).” One clinical expert did not expect much disruption, since “retina specialists already use anti-VEGF therapy for DME (Avastin).”

All experts agreed that this intervention’s potential for clinician and patient acceptance is high, because the need for more effective therapy to treat DME is acknowledged. In terms of per-patient costs for ranibizumab, experts opined that costs would significantly increase, with one research expert stating “costs have been calculated for quality adjusted life year as $5,862 for Laser, $23,000 for Ranibizumab and approximately $3,000 for Avastin (which has recently been shown to be as effective as Ranibizumab for AMD in a head-to-head CATT trial).” This research expert also believes that there is controversy surrounding the cost of ranibizumab and the financial burden it may place on patients and the health care provider, with benefits of this intervention having to be exceptional to justify the financial responsibility. Overall, experts believe that while financial implications for this therapy may serve as a barrier to widespread diffusion, the potential efficacy and safety of ranibizumab for treating DME has them thinking this is an intervention of high potential impact.
Recombinant Human Microplasmin (Ocriplasmin) Injection for Treatment of Focal Vitreomacular Adhesion

Current treatment options for symptomatic vitreomacular adhesion are 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. Therefore, clinicians have significant interest in nonsurgical methods that could replace or complement surgical treatments for vitreoretinal conditions such as vitreomacular adhesion. Ocriplasmin (formerly microplasmin) is an enzymatic vitreolysis agent that is under study as an intravitreal injection for treating symptomatic vitreomacular adhesion.

Focal vitreomacular adhesions are characterized by a vitreous gel with an abnormally strong bond to the retina; the adhesions have an effect on the development and progression of numerous back-of-the-eye conditions and have been associated with a poor prognosis in diabetic retinopathy and AMD. A nonsurgical approach for treating vitreomacular adhesion being pursued is the intravitreal injection of agents that could both induce liquefaction of the vitreous and disrupt adhesion between the vitreous and the retina, leading to completion of posterior vitreous detachment (PVD). 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. Ocriplasmin is a truncated form of plasmin produced using recombinant methods in the yeast (Pichia pastoris) expression system. Recombinant ocriplasmin (ThromboGenics NV, Heverlee, Belgium) retains the catalytic characteristics of human plasmin and is purported to have 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. Preclinical studies in animal models indicated that ocriplasmin could induce complete PVD following a 7–21 day intravitreal exposure. Late-stage clinical trials of ocriplasmin for treating symptomatic vitreomacular adhesion used an intravitreal injection of 125 mcg. 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.

ThromboGenics (2010) reported pooled results from TG-MV-006 and TG-MV-007 phase III trials conducted on 652 patients at 48 centers in Europe and the United States. It reported that 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 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 placebo treated patients (p=0.000003). The pooled results, stated the investigators, confirmed that ocriplasmin was generally safe and well tolerated. There was no evidence of an increased risk of retinal tear or detachment. The company submitted a biologics license application (BLA) for ocriplasmin to FDA in December 2011. However, in February 2012, ThromboGenics announced that the original BLA had been withdrawn following an indication from FDA that the agency would grant ocriplasmin priority review status. ThromboGenics intended to resubmit a new BLA in the first half of 2012 that would allow it to meet deadlines associated with the anticipated priority review.
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 assist in making 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). Intraocular injection with ocriplasmin may provide a nonsurgical method to resolve vitreomacular adhesion.

Figure 12. Overall High Impact Potential: Recombinant human microplasmin (Ocriplasmin) injection for treatment of focal vitreomacular adhesion

Experts commenting on this intervention thought recombinant microplasmin injection therapy could offer an alternative for a condition in which invasive surgical intervention is the primary standard of treatment for patients most affected by focal vitreomacular adhesion. Some experts believe that microplasmin injection could potentially serve as first-line therapy for patients, while others thought that surgical intervention might ultimately be needed for some patients, particularly in the case of the intervention’s ineffectiveness. A potential shift in care setting and management could occur, transitioning to more outpatient care with care potentially being provided by a retinal specialist. In general, experts believe that an alternative therapy to surgical intervention would decrease cost of treatment, although one expert expressed concern that costs of injection might offset surgical costs. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention. Most of 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 clinical perspective expressed that surgical interventions present risk, including “optic disk, foveal, and extra-foveal damage” and that “less invasive or pharmacological approaches will reduce these risks.” However, one expert with a research perspective questioned the significance of the unmet need, believing that only a small percentage of the patient population continues to require surgery, regardless of intervention with microplasmin injection.

All experts agreed that the underlying mechanism for recombinant microplasmin injection appears sound and promising, with several experts citing efficacy in clinical studies as quantitative proof of the intervention’s concept. Concerning microplasmin 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. However, one expert with a research perspective would like to see more data to determine to what degree the resolution of focal vitreomacular adhesions improves the patients’ quality of life.

There were mixed comments regarding the intervention’s potential to disrupt the current care model for this patient population. Several experts believe that integration of microplasmin injection therapy would affect the current intervention model for patients with focal vitreomacular adhesion, with one clinical expert stating that “this intervention has the potential to be a first-line non-invasive approach for the treatment of vitreomacular adhesion and may eliminate the need for vitreomacular surgery.” Other experts believe that the current model of care would be minimally affected, stating that existing interventions would not be completely eliminated and that surgery would ultimately be available for patients not responding to microplasmin injection therapy. Regarding potential shift in patient management, most experts believed recombinant human microplasmin injection may reduce or eliminate the need for vitreomacular surgery. One expert believes this treatment could shift patient management to outpatient care “by a retinal specialist.” One expert with a health systems perspective believes that there would not be any change to patient management for this disease.

Most experts agreed that per-patient cost would decrease with reduction of surgical interventions for this patient population. However, one clinical expert believes that while “less surgical costs” may be incurred, “total cost may be offset by the cost of the medicine.” Most of the experts agreed that patients would accept this intervention, because microplasmin injection can provide an effective alternative to surgical intervention. One clinical expert thought that while success of this intervention might lead to patient acceptance and physician adoption, there are concerns regarding “percent success rate and potential side-effects” of microplasmin injection therapy. Overall, although one expert had reservations regarding how many patients would actually need this intervention, the remainder believe that the therapy has potential for high impact to provide a sound alternative to current treatment for patients with focal vitreomacular adhesion.
Sleep Disorder Intervention
Neurostimulation (remedē System) for Treatment of Central Sleep Apnea in Patients With Heart Failure

Many patients with heart failure have a comorbid condition called Cheyne-Stokes respiration, a type of central sleep apnea (CSA) that affects up to two-thirds of heart failure patients and is associated with increased mortality. The cascade of events from this disordered breathing can trigger many types of events, including atrial fibrillation, inflammation, intrathoracic pressure changes, myocardial ischemia, and release of oxygen radicals. Currently, there are no commonly accepted treatments for CSA in these patients. Pharmacotherapy is sometimes used, but is often ineffective or predisposes a patient to cardiac conditions, prompting some clinicians to suggest the use of continuous positive airway pressure (CPAP), which is associated with low patient adherence. Therefore, effective treatments for CSA are needed.

The remedē™ System (Respicardia, Inc., Minnetonka, MN) is an implantable stimulator being investigated for treating CSA in patients with heart failure. According to the manufacturer, the system is intended to deliver electrical pulses via a transvenous stimulator lead positioned within a vein near one of the phrenic nerves. The phrenic nerve stimulation is intended to restore natural breathing to enable better oxygenation, less activation of the sympathetic nervous system, and improved sleep. According to the manufacturer, the system consists of three implantable components: a pulse generator comprising electronic circuitry and a battery, which are sealed in a titanium case; a stimulation lead; and a sensing lead that detects respiration. The system also includes an external programmer, which is used to change the pulse generator settings or to review diagnostic data via telemetry. The pulse generator, which appears to be similar to a pacemaker, is implanted under the skin below the clavicle. The manufacturer has not released the details of the implantation procedure.

Abraham and colleagues (2010) reported results from a clinical trial assessing the RespiCardia stimulator implantation for 1 month, with an overnight sleep evaluation followup in three patients with a history of episodic breathing. Authors reported, “The RespiCardia system improved respiratory parameters (AHI [apnea-hypopnea index] and CAI [CSA index]), sleep architecture (arousal index) and oxygenation (ODI5). Observed changes were similar in magnitude to those achieved during the acute study without reports of adverse events.”

Ponikowski and colleagues reported results from a multicenter (five centers in the United States and Europe), 2-night, 13-patient feasibility study at the European Society of Cardiology Heart Failure meeting in May 2010. Patients served as their own controls with 1 night of no intervention and 1 night of unilateral phrenic nerve stimulation. The endpoint was a 50% reduction in CSA. The authors reported “no deleterious effect on sleep or airway tone, no stimulation-related arrhythmias, and one thrombus in azygos vein on review of the cine: lead was removed after anticoagulation without sequelae.” On sleep apnea indices, the authors reported a “49% (p = 0.0006) decrease on the apnea-hypopnea index,” a “91% decrease on the central apnea index (p <0.0001),” and a “51% (p = 0.0005) decrease in arousals.”

Two phase II clinical trials are ongoing under FDA investigational device exemption status. The device received Conformité Européenne (CE) mark for marketing in Europe in August 2010.

Clinical Pathway at Point of This Intervention

According to the American Heart Association, first-line treatment for CSA can include diuretics to lower cardiac-filling pressure and angiotensin-converting enzyme inhibitors and beta blockers to lessen CSA severity. In some patients, however, these agents can actually predispose a patient to CSA. If CSA persists, clinicians may prescribe nighttime supplemental oxygen, although its
effectiveness in improving heart function, mortality, and quality of life has also been questioned. CPAP and other kinds of pressure support intended to improve breathing are sometimes used. The respiratory stimulant theophylline is not typically used long term because of its potential adverse consequences in heart failure patients (i.e., inotropic and arrhythmia-inducing effects). If the remedē system is approved for marketing, it would likely displace the use of CPAP in CSA, which is associated with low patient adherence.

Figure 13. Overall High Impact Potential: Neurostimulation (remedē System) for treatment of central sleep apnea in patients with heart failure

Overall, experts commenting on this intervention thought that it could have an important impact on many aspects of the health care system, particularly treatment and care models, by offering a very different treatment approach, requiring different staffing to implant the device, and requiring infrastructure to accommodate a new surgical procedure for this patient population. Additionally, the stimulation parameters would need programming and adjusting. While experts wanted to see more data to determine whether this intervention is safe and effective, they were nonetheless optimistic about the technology’s potential to address this unmet need. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered their perspectives on this intervention. Experts generally agreed that there is an important unmet need for effective CSA treatment for heart failure patients, based on the current lack of available therapies, the prevalence of the condition, and the negative outcomes associated with CSA secondary to heart failure.

Most experts stated that it was difficult to determine whether this intervention has the potential to improve health outcomes, given the very preliminary data, although they believe that the underlying theory of the technology is sound. One expert with a clinical perspective stated, “Whether this would improve heart failure outcomes is much less certain. The question remains as to where on the causal pathway of adverse outcomes in CHF [congestive heart failure] sleep disordered breathing lies.” One expert with a research perspective stated, “Phrenic nerve stimulation as a means to restore normal breathing and improve sleep has a reasonable theoretical basis, but the degree of improvement that could be expected is unclear.”

Experts generally agreed that this intervention has the potential to affect the current care model and patient management and to shift the care setting, changing the focus from oxygen-based therapies to neurostimulation. If this treatment is proven effective, it has the potential, as one expert said, to “become the de facto treatment for patients with CSA and heart failure,” which represents an important change, because optimal medical care for CSA is so highly debated and largely ineffective. The intervention would also shift care from the outpatient setting of at-home medical therapy or CPAP therapy to inpatient surgery and cardiac electrophysiology laboratories.
Because the intervention requires surgery, it would require a moderate learning curve on the part of physicians and would have a notable impact on costs, experts thought. Although clinicians are already familiar with placement of similar technology such as implantable cardioverter-defibrillators and pacemakers, surgeons would need to learn how to place this particular device. One expert with a clinical perspective pointed out that there are “not too many cardiac electrophysiologists available for such a large patient population,” which might prove to be an obstacle for diffusion.¹⁹⁷

Experts were divided on how this intervention would impact costs. Most experts suggested that the device and the surgical procedure to implant it would be expensive, especially when compared with current CSA interventions. However, some experts also suggested that if the intervention is shown to improve patient outcomes, it would ultimately reduce the long-term costs associated with CSA and heart failure. Experts were divided on whether third-party payers would reimburse the use of the device, stating on one hand that the device would “likely be covered,” but on the other hand that “reimbursement will be limited until the intervention analytics can be established and public and private payers understand the increased costs of this intervention and its patient benefits.” ²⁰⁰

Experts anticipated high patient and clinical acceptance of this intervention, citing that “similar available technologies have gained support and wide acceptability.”¹⁹⁷ Although a couple of experts noted that the invasiveness of the implantation procedure might cause some reluctance to accept it, one expert noted that the invasiveness of other devices on the market to which heart failure patients have already been exposed limits this as a barrier.
Spinal Cord Injury Rehabilitation Interventions
Computerized Walking Systems (ReWalk and Ekso) for Patients With Paraplegia From Spinal Cord Injury

Currently, conventional manual and powered wheelchairs are the primary assistive devices 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 system (Argo Medical Technologies, Ltd., Yokneam Ilit, Israel) and the Ekso system (Ekso Bionics, Berkeley, CA) may provide greater mobility and freedom to persons 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 to walk 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 with the use of 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 approximately 35 lb.\textsuperscript{203}

The Ekso (formerly eLegs) system is another powered exoskeleton device for patients with paraplegia or lower-extremity paresis due to neurologic diseases, including spinal cord injuries, multiple sclerosis, amyotrophic lateral sclerosis, or Guillain-Barré syndrome. It incorporates technology similar to that in the ReWalk system. The 45-lb Ekso system is based on the Human Universal Load Carrier, a motorized exoskeleton designed to allow users to carry up to 200 lb continuously for several hours over any terrain that the U.S. military uses. The manufacturer’s clinical testing of the Ekso system was carried out in 12 U.S. rehabilitation hospitals in 2011 and early 2012.\textsuperscript{204} The manufacturer states transfer to and from a patient’s wheelchair and this powered exoskeleton device takes less than 5 minutes and the user requires little to no assistance.\textsuperscript{205} The company estimates the battery life for this device to be 3 hours.\textsuperscript{205}

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 premarking approval application procedures.\textsuperscript{206} Such products require only FDA device registration and listing. As of November 2011, the ReWalk-I system was FDA-listed for institutional use only, reportedly costing about $105,000 per system. The company expects to soon register ReWalk-P, for personal use for those who qualify for its use upon medical examination and rehabilitation training, costing about $20,000, although this has not been confirmed with the manufacturer.\textsuperscript{207} According to the Ekso system’s manufacturer, the system became available to the Craig Hospital (Denver, CO) in February 2012, the company’s first commercial health care participant, for institutional use.\textsuperscript{204} The cost of the Ekso institutional system is about $130,000, with anticipated costs for personalized Ekso exoskeletons to be $50,000–$75,000.\textsuperscript{208}

Clinical Pathway at Point of This Intervention

Occupational and physical therapists work with patients after acute treatment of spinal cord injury to evaluate their 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.\textsuperscript{209} 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, improving their quality of life by increasing their mobility and independence.

Figure 14. Overall High Impact Potential: Computerized walking systems (ReWalk and Ekso) for patients with paraplegia from spinal cord injury

Experts thought that the high cost and complexity of this technology could limit its introduction and diffusion into the mainstream of rehabilitative services and centers treating patients with paraplegia from spinal cord injury. They expected that staffing models would be affected by the need for clinical and software engineers and technicians to maintain and adjust the equipment. Also, they thought that the equipment would likely be appropriate only for patients whose health was robust enough to use it. Experts indicated that lessons learned from users of this type of intervention may pave the way for future similar interventions capable of addressing the needs of many more patients with this condition. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention. Two of seven experts thought that a major benefit of this intervention would be psychological, allowing patients to have improved social interactions. Three experts (clinical and nonclinical) reported that this intervention could increase the time of rehabilitation because more sessions would be needed to train patients in using these new devices. Clinical experts also indicated that muscle atrophy, tone, and spasms could affect the response to these devices and require constant adjustments, especially during the first year after spinal cord injury.

Cost was a limiting factor mentioned by the experts in terms of access and diffusion, especially to populations affected by health disparities and by limited access to rehabilitative services. The estimated device cost ranges 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.

Two experts with research perspectives indicated that this type of device would work only in patients with significant upper body strength. For example, those who retain use of their hands and shoulders, can stand with the aid of crutches, and have good bone density and good cardiovascular health might be the appropriate population that could benefit from these devices.

Six experts reported that staffing patterns in rehabilitation centers would likely change with introduction of these devices. Three experts thought there would be a need for additional technical staff (clinical and software engineers) to address computer hardware and software issues needed to maintain the equipment.
Magnetic Pierced-Tongue Aid for Directing Mobile Wheelchair

While conventional manual and powered-assisted devices exist that attempt to improve quality of life for individuals with paraplegia, efficacy and safety issues remain a primary concern. Specifically, regarding 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. Use of the magnetic pierced-tongue aid system, a tongue-operated assistive neurotechnology for managing spinal cord paralysis, would represent a novel device that might enhance patient mobility and allow patients to perform more daily tasks in a safer, less invasive, and more effective manner.

The Tongue Drive System (TDS, Georgia Institute of Technology, Atlanta) is a tongue-operated assistive neurotechnology that consists of a lentil-sized magnetic tracer/stud that is affixed to the tongue, most commonly by piercing. The magnetic tracer/stud creates a magnetic field around the pierced glossal area, where magnetic sensors located on a wireless headset and headphones communicate with a wheelchair. Since the tongue is a durable muscle that does not tire easily and is generally spared in spinal cord injuries and neuromuscular diseases, it was designated an ideal target for this neuroassistive technology. 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). This system can be recharged via USB after 2 days of continuous use. There is a standby mechanism for the TDS, allowing patients to perform daily tasks, such as eating, sleeping, and conversing, without unnecessary use of the TDS. Patients must undergo computer training with the TDS for the computer program to appropriately interpret and calibrate tongue movement, allowing proper control of the wheelchair and computer device.

Ghovanloo and colleagues (2009) reported results from a trial of five patients with tetraplegia to determine the usability of the TDS for patients with spinal cord injury. “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.” As of May 2012, the TDS had not been approved by FDA, and no additional manufacturer or regulatory status information was available. No cost information about the device was identified.

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. 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 a tongue-mounted magnetic tracer, magnetic sensors, smartphones, computers, and wheelchairs.
Experts commenting on this intervention thought that the magnetic tongue-directed aid could be a viable alternative to existing technologies. While experts thought the unmet need was not significant, others who have worked directly with patients using assistive devices to control powered wheelchairs believe this intervention could significantly improve patient health outcomes and quality of life, allowing patients to perform daily activities in a quicker and less exhausting manner. Several experts thought safety concerns could be a barrier to clinician acceptance, because device malfunction might cause harm to the user. Overall, this device’s perceived complex nature, the existence of comparators, and limited safety and efficacy data thus far have 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-potential-impact range.

Results and Discussion of Comments

Nine experts, with clinical, research, health systems, and health administration backgrounds, provided comments on this intervention. Generally, experts opined that there is a significant need to introduce new assistive technology aimed at restoring mobility in patients with spinal cord injury. Several experts reported the magnetic tongue-directed neuroassistive device could become a viable alternative technology to conventional manual and powered devices for this patient population. One research expert mentioned the potential efficiency of this device in terms of control and communication, stating, “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.” 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.” However, several experts thought this device might not significantly impact this patient population, suggesting the availability of numerous alternatives believed to effectively restore mobility, including sip-and-puff, chin-control, head-control, and speech-control assistive devices.

Experts were divided on this intervention’s potential to improve patient health outcomes. Experts expressed concerns over limited efficacy and safety studies available for this device. A research expert stated while this device could improve mobility and increase patient quality of life, concerns over potential device malfunction and collision remain. Several experts affirmed the need for comparative studies with currently available assistive devices to determine whether a clear benefit to using the TDS exists. One clinical expert expressed skepticism over its ability to improve health outcomes, because this device does not directly impact a patient’s health. However, one
health systems expert opined the technology seems usable based on available studies and would allow patients to communicate at “normal or near-normal” speed. It seems likely to prove significant mobility improvement over conventional assistive devices, allowing for more patient participation in daily societal activities.220 Another expert stated this intervention could allow patients to perform daily activities with a greater degree of ease over 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, and this writeup seems to be more thoughtful in its considerations of weaknesses that exist.”226

Experts generally agreed this neuroassistive device would not significantly impact health disparities, although one clinical expert opined the anticipated cost of this device could increase health disparities. Most experts shared opinions that this device would not significantly disrupt the current health care delivery infrastructure or how patients are managed, stating the current system in place is readily equipped for this device’s implementation and adoption. Several experts conceded adoption of this device might require an increase in hiring of rehabilitation specialists, computer specialists, and biomedical hardware specialists, to train patients and ensure proper functioning of this device. One expert believes that the anticipated increase in specialists for this device in combination with the device’s potential complexities may increase time in patient management.

Experts generally agreed TDS’s potential acceptance by both clinicians and patients would be high. Most experts generally agreed that provided this device proves safe and effective, the TDS would be easily accepted by clinicians and physical therapists. Three of these experts believe the potential of this device to improve patient dependence 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. In terms of patient acceptance, a health systems expert questioned, “How does it affect speech? Does this offend culturally? Religiously? Infection?”226 Negative perceptions regarding the required tongue piercing for this device seems to be a predominating issue for adoption by elderly patients, according to several experts. One research expert opined that elderly patients may have more reservation than the younger patient population, stating “the elderly patients had already been trained to use other assistive devices and did not want theirs to be replaced.”221

Overall, experts believe this novel neuroassistive device has potential to address an unmet need of this patient population, 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.”221
Vascular Abnormality Intervention
Off-Label Propranolol for Treatment of Life-Threatening Infantile Hemangioma

Infantile hemangiomas (IHs) are vascular anomalies that manifest as benign soft tissue tumors, affecting up to 10% of the infant population. Although 85% to 90% of IHs regress on their own without treatment, the remainder may become problematic if they “ulcerate, have massive growth, cause disfigurement, or impact normal function or cosmetic development.” These problematic IHs are commonly located in the face, ear, orbit, and airway, and complications may include obstruction of airways and vision, cardiac insufficiency, hypothyroidism, painful ulcerations, and hemorrhage. Currently, there are no FDA-approved pharmacotherapies for treating IHs. Although corticosteroids, interferon alfa, and vincristine are treatment measures used for IHs, limited efficacy, safety concerns, and intolerable adverse events associated with these therapies have prompted a search for novel therapies with more efficacious and safer profiles. Propranolol is a beta blocker that may replace or serve as an adjunct therapy to corticosteroids for treating life-threatening IHs.

Propranolol (off-patent, multiple manufacturers) is a nonselective beta adrenergic receptor antagonist (beta blocker) that has been widely used for cardiovascular indications (e.g., hypertension, angina pectoris). The drug exerts its cardiovascular effects by blocking the action of endogenous catecholamines (e.g., epinephrine and norepinephrine) on beta-adrenergic receptors. Researchers have suggested that propranolol’s early, intermediate, and long-term effects on IHs are the result of three different mechanisms of action. Specifically, the early effects, which manifest as a “brightening” of the IH’s surface, can be attributed to propranolol’s vasoconstrictive qualities. Intermediate effects (i.e., growth arrest) are thought to be a result of propranolol’s blocking of proangiogenic signals (e.g., vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinase 2/9). Finally, long-term effects are characterized by IH regression, due to apoptosis (programmed cell death) in proliferating endothelial cells. Several clinical trials report varying administration doses for propranolol. Addenbrooke’s Hospital (Cambridge, UK) has identified a protocol for administering propranolol: administer 1 mg of propranolol orally (in suspension form; divided in three doses) per kilogram of body weight per day in week 1, double the dose in week 2, and adjust propranolol dose according to patient weight gain thereafter. Some protocols recommend initial hospitalization for dose titration.

Kunzi-Rapp and colleagues (2012) reported results from a clinical trial evaluating propranolol’s efficacy in 45 children with IHs. Before the start of treatment and at each visit, clinical photographs were taken. If ultrasound did not confirm occult deeper components, children were included in the study. Result showed “treatment in the proliferative phase within the first 6 months of life (including seven preterm infants) induced regression in 59% and cessation of growth in 26% of the hemangiomas. No response or proliferation of subcutaneous components was observed in 15%. Clinically, no side effects caused by the beta-receptor blocker were noticed.” Additionally, authors reported “treatment of two ulcerated hemangiomas of the perineal region twice using a flash lamp pulsed-dye laser and propranolol ointment in the surrounding lesion led to healing of the ulcers in 3 and 6 weeks, respectively. In six patients, topical therapy was started between the ages of 7 and 33 months. Even in these hemangiomas, improvement was obvious after 2 or 3 months.”

Propranolol is not labeled as treatment for IHs under any circumstances, and its intended use by current institutions for this purpose would be considered off-label. A retrospective study published August 2011 in Archives of Dermatology’s Online First (Price et al., University of Miami) compared propranolol to oral corticosteroids, and investigators reported that propranolol therapy was more effective in treating IHs with minimal side effects and cost about $205 per treatment, about half the cost of corticosteroids.
The Pierre Fabre Group (Paris, France) is currently investigating propranolol specifically for this indication in an ongoing phase II/phase III clinical trial, with an estimated primary completion date of May 2012 and estimated study completion date of December 2013.

Clinical Pathway at Point of This Intervention

Currently, no well-defined or FDA-approved treatments for life-threatening IH exist. Although corticosteroids (e.g., prednisone) are typically used as first-line treatment, these systemic drugs are associated with variable efficacy and safety concerns, including growth disturbances, immune system dysfunction, and severe tissue loss. Second-line therapeutic options include interferon alfa and vincristine, which are not labeled for IH and are associated with undesirable side effects and toxicity. Surgical intervention is typically reserved for IHs that have disfiguring or life-threatening potential. Because these treatments are all associated with limitations, clinicians have investigated propranolol for treating IHs.

Figure 16. Overall High Impact Potential: Off-label propranolol for treatment of life-threatening infantile hemangiomas

Experts expressed optimism about propranolol’s ability to meet the need of young patients who experience complications from infantile hemangiomas, highlighting promising results from early efficacy studies. Experts generally indicated that both patient and clinician acceptance would be high for this intervention, because providing a more efficacious and safe therapy for treating IHs is of critical importance. However, experts opined that frequency of treatment and a potential increase in hospital stays might serve as barriers to acceptance for some clinicians and parents of patients. Experts also opined that further studies evaluating efficacy and safety must be performed. Overall, experts agreed that contingent on results of ongoing clinical trials, propranolol has the potential to replace corticosteroids as first-line therapy for treating IHs, marking its potential for high impact. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered their perspectives on this intervention. Experts agreed that an unmet need exists for more effective therapy aimed at reducing and treating life-threatening infantile hemangiomas. One clinical expert stated, “Existing treatment regimens have an unsatisfactory balance between treatment efficacy (low) and treatment side effects (high) that are potentially serious. The use of propranolol to treat IH has the potential to change that balance, creating high rates of treatment success with a low risk of serious adverse treatment side effects.”

Five experts agreed that propranolol has the ability to improve patient outcomes, with one research expert indicating results from early efficacy studies are “promising, with over 95% of patients in two separate studies responding positively to the therapy.” One clinical expert thought...
the existing data and literature combined with general belief among various clinicians support propranolol’s ability to effectively and safely treat IHs when compared with current standards of therapy. Two experts were skeptical of propranolol’s ability to improve patient health outcomes, citing insufficient evidence displaying efficacy of propranolol in addition to a lack of understanding of this therapy’s underlying mechanism in treating IHs. One research expert stated, “The three initial studies have mixed results…good, but not overwhelming (regrowth, side effects, etc.).”

Most of the experts did not expect this therapy to impact health disparities, although one clinical expert opined that this therapy might be more accessible to economically disparate populations than other available treatment options.

Experts generally agreed this therapy would not significantly disrupt the current health care delivery infrastructure for this patient population. Three experts noted this therapy would require inpatient hospitalization for the very first treatment, leading to slightly increased inpatient volume. Most experts also agreed this therapy would minimally affect the manner with which patients who have IHs would be managed, with one clinical expert noting propranolol administration would most likely require “more inpatient stays from the beginning of the therapy. There will be a switch from surgical to medical service management.”

One research expert cited propranolol’s potential to mitigate management of this disease’s complications including “hemangiomas that affect the airways, vision, cardiovascular system, thyroid, or [IHs] that hemorrhage or are painful.” Experts agreed on propranolol’s potential acceptance by clinicians and families of this patient population, indicating that clinicians would readily adopt a more efficacious and safe therapy for treating IHs, while parents would be ready to adopt a therapy that would improve their child’s patient health outcomes and quality of life. One research expert opined that frequency of administration may serve as a barrier to parent acceptance, given the therapy may be applied three times daily for a 6-to-9 month span in certain propranolol protocols. One expert opined that parents may have a negative perception about the use of “off-label” products, and might be more willing to accept this therapy if it had FDA approval. Most experts believe that, given propranolol’s current low cost and purported high efficacy with minimal adverse events, it has potential to significantly reduce the per-patient cost of care overall for this patient population. One clinical expert cautioned that initial costs of care might increase, given the hospitalization for initial treatment and frequency of physician visits to monitor progress over the treatment period. However, this expert opines that this therapy’s efficacy, reduction in surgical intervention, and lessened need for treatment for adverse events from current standards of therapy will significantly reduce long-term costs of care.

Overall, experts indicated that propranolol has potential to significantly fulfill the unmet need for this patient population, citing propranolol’s potential to effectively treat IHs while reducing risk of adverse events at a significantly lower cost when compared with other treatment modalities. Provided further efficacy and safety studies validate the use of propranolol for treating IHs, experts believe this therapy could replace corticosteroids as first-line therapy.
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