

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

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## **Priority Area 11: Peptic Ulcer Disease and Dyspepsia**

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## **Statement of Funding and Purpose**

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

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

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

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## Preface

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

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

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

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

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# Executive Summary

## Background

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

## Methods

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

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs.

No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

## Results

The table below lists the four topics for which (1) preliminary phase III data for drugs and biologics or phase II data for devices and procedures were available; (2) information was compiled before May 16, 2013, in this priority area; and (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Fourteen topics in this priority area were being tracked in the system as of May 18, 2013.) We present two summaries of topics (indicated below with an asterisk) that emerged as having higher-impact potential on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

### Priority Area 11: Peptic Ulcer Disease and Dyspepsia

Topic	High-Impact Potential
1. Helminthic therapy (pig whipworm) for treatment-resistant ulcerative colitis	No high-impact potential at this time
2. *PerOral Endoscopic Myotomy for treatment of esophageal achalasia	Moderately high
3. *Teduglutide (Gattex) for treatment of short bowel syndrome	Moderately high
4. Vedolizumab for treatment of moderate to severe ulcerative colitis	No high-impact potential at this time

## Discussion

Compared with other priority areas, this priority area provided relatively few leads and topics that meet inclusion criteria for the horizon scanning system. Most research activity in this field focuses on drugs and biologics for irritable bowel syndrome and inflammatory bowel diseases (e.g., Crohn’s disease, ulcerative colitis). The helminthic therapy (pig whipworm) intervention had been designated as having high-impact potential in earlier reports, but its availability in the United States has been halted recently, both by actions of the U.S. Food and Drug Administration and by decisions of companies to stop importing the whipworms or making them available by mail order to anyone in the United States. Accordingly, the topic will be archived in the system.

Of the three topics on which experts provided comments, two emerged as having some potential for high impact. Experts deemed endoscopic myotomy as notable because it is minimally invasive with potential to also minimize scarring, pain, and recovery time for patients with esophageal achalasia. Teduglutide was deemed as notable for its potential to restore bowel function in patients

with short bowel syndrome (SBS), potentially improving quality of life and reducing costs and complications associated with parenteral nutrition (PN).

## **PerOral Endoscopic Myotomy for Treatment of Esophageal Achalasia**

- **Key Facts:** Esophageal achalasia is characterized by prolonged occlusion of the lower esophageal sphincter (LES) and reduced peristaltic activity, making it difficult for patients to swallow food and possibly leading to complications such as regurgitation, coughing, choking, aspiration pneumonia, esophagitis, ulceration, and weight loss. Open surgical treatment for achalasia generally requires at least five abdominal incisions to access the blocked esophagus, which can result in significant recovery time, complications, and pain. Peroral endoscopic myotomy (POEM) is a novel endoscopic procedure developed by a Japanese surgeon, Haru (Haruhiro) Inoue, M.D. It uses a natural orifice as an entry point for surgical instruments, with the intention of reducing the number of incisions needed and, thus, the overall invasiveness of surgery. POEM is performed with the patient under general anesthesia. After tunneling an endoscope down the esophagus toward the esophageal gastric junction, a surgeon performs the myotomy by cutting only the inner, circular LES muscles through a submucosal tunnel created in the proximal esophageal mucosa. POEM differs from laparoscopic surgery, which involves complete division of both circular and longitudinal LES muscle layers. Cutting the dysfunctional muscle fibers that prevent the LES from opening allows food to enter the stomach more easily. In this report, we included reports of three recent case series on a total of 292 patients with achalasia treated with POEM. Treatment success with no serious complications was reported in more than 90% of patients in these studies. In a fourth study (a nonrandomized historical control study), investigators reported that the procedure resulted in shorter operative times and less blood loss than laparoscopic Heller myotomy, although myotomy lengths, complication rates, length of stay, and narcotic use were similar between surgical groups. Some investigators speculate that because it involves cutting only one LES muscle layer, POEM might be less effective than laparoscopic surgery over the long term and revisional surgery might be difficult. Seven U.S. academic medical centers initiated clinical protocols for POEM and perform the procedure under an Institutional Review Board–approved research protocol. At the 2012 meeting of the Society of American Gastrointestinal and Endoscopic Surgeons, leading researchers presented a didactic training course with reports on outcomes of cases performed to that date. The U.S. centers have performed more than 80 of an estimated 900 POEM cases reported worldwide since 2008. Sixteen active POEMs trials were registered at the National Clinical Trials database as of June 2013, with four U.S. centers currently participating in or sponsoring trials. According to one estimate, POEM costs are comparable to Heller myotomy.
- **Key Expert Comments:** Overall, experts commenting on this topic stated that POEM could provide a permanent, minimally invasive treatment option for achalasia with fewer incisions than laparoscopic surgery, leading to shorter recovery times and less pain. In the absence of randomized controlled trials or long-term outcomes data, some experts were uncertain of POEM’s true impact potential. Overall, experts assumed that if POEM remains an inpatient procedure with general anesthesia, the impact beyond scarring and pain reduction could be minimal. If POEM can be adapted to an outpatient setting, costs might be lowered and more patients might become eligible for the surgery or elect to undergo surgical treatment for achalasia rather than receiving nonsurgical treatment. POEM could also renew clinical

interest in natural orifice transluminal endoscopic surgery (known as NOTES) if it can demonstrate better outcomes than laparoscopic surgery.

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

## **Teduglutide (Gattex) for Treatment of Short Bowel Syndrome**

- **Key Facts:** SBS encompasses a group of health problems, related to malnutrition, that occur in individuals who have lost at least half of their small intestines. Frequently, SBS arises from the surgical removal of diseased bowel portions. A shortened bowel results in diarrhea, fatigue, abdominal pain, bloating, heartburn, and nutrient deficiencies. Treatment for severe SBS may involve oral rehydration solutions, intravenous nutrition delivery, and liquid food (PN) delivered through feeding tubes. An estimated 10,000–20,000 people in the United States receive at-home PN for SBS, an estimate based on data from the early 1990s, at a cost of more than \$100,000 per patient per year. Long-term PN can lead to serious side effects such as liver damage, the risk of which increases the longer a patient is PN-dependent. No effective treatments are available to improve long-term nutritional absorption other than intestinal transplantation. Teduglutide (Gattex<sup>®</sup>, NPS Pharmaceuticals, Inc., Bedminster, NJ) is a subcutaneously administered glucagon-like peptide 2 analog purported to induce repair and regeneration of the cells lining the intestine and increase nutrient absorption. Phase III trials reported that patients with SBS treated with teduglutide can significantly reduce the need for PN. Additionally, a long-term extension trial demonstrated that some patients were able to completely stop PN. Because it is a synthetic intestinal growth factor, some investigators are concerned about accelerated neoplastic growth. In December 2012, FDA approved teduglutide for treating adults with SBS who require nutritional support with PN. The approval required a Risk Evaluation and Mitigation Strategy consisting of a communication plan and prescriber training, because of a potential for increased risk of patients developing cancer and polyps in the intestine, obstructions in the intestine, gallbladder disease, biliary tract disease, and pancreatic disease while taking the drug. Daily self-injection with teduglutide at the recommended dose of 0.05 mg/kg costs about \$30,000 per month. Our searches revealed no information regarding third-party coverage or payment for teduglutide, but payer policies might not have been updated since its approval.
- **Key Expert Comments:** Experts commenting on this drug believe that reductions in PN use could potentially improve patient health outcomes and quality of life, as well as lower the high costs of PN. If teduglutide proves to be generally tolerable in patients with SBS over the long term, reductions in PN could be sufficient motivation for patients to self administer the drug's daily injections, because treatment options for SBS are limited. Additional scrutiny of teduglutide's safety and its impact on cost of care is likely going forward.
- **Potential for High Impact:** Moderately high



## **Peptic Ulcer Disease and Dyspepsia Interventions**

# PerOral Endoscopic Myotomy for Treatment of Esophageal Achalasia

**Unmet need:** Achalasia is characterized by prolonged occlusion of the lower esophageal sphincter (LES) and reduced peristaltic activity, making it difficult to swallow food. It can lead to complications such as regurgitation, coughing, choking, aspiration pneumonia, esophagitis, ulceration, and weight loss.<sup>1</sup> About 3,000 esophageal achalasia cases are diagnosed annually.<sup>2</sup> Traditional laparoscopic surgery for esophageal achalasia generally requires at least five abdominal incisions to access the blocked esophagus, which can result in significant recovery time and complications.<sup>2,3</sup>

**Intervention:** Peroral endoscopic myotomy (POEM) is a novel endoscopic procedure that uses a natural orifice as an entry point for surgical instruments, with the intention of reducing the total number of incisions needed and, thus, the overall invasiveness of surgery.<sup>2</sup> POEM is performed with the patient under general anesthesia.<sup>3</sup> A surgeon inserts an endoscope into the patient's mouth and tunnels it down the esophagus toward the esophageal gastric junction. Then the myotomy is performed by cutting only the inner, circular LES muscles<sup>4</sup> through a submucosal tunnel created in the proximal esophageal mucosa.<sup>5</sup> This differs from current surgical technique, which involves complete division of both circular and longitudinal LES muscle layers.<sup>5</sup> Cutting the dysfunctional muscle fibers that prevent the LES from opening is intended to allow food to more easily enter the stomach.<sup>2</sup> Gastrointestinal and endoscopic surgeons perform POEM. It is purportedly an extremely sophisticated and demanding technique, even for experienced endoscopists.<sup>5</sup> The appropriate treatment option for esophageal achalasia must be carefully selected, with the decision based on a patient's disease severity and surgical risk status. However, a minimally invasive procedure such as POEM might offer potential benefits including greater surgical precision, a shorter recovery time, shorter hospital stay, less pain, and a lower incidence of reflux after the procedure.<sup>2</sup>

**Clinical trials:** In a published case series of patients with achalasia treated with POEM (n=56), in all cases, dysphagia symptoms were significantly reduced or disappeared.<sup>6</sup> The average myotomy length was 11.2 cm (range 5–22 cm). Resting LES manometric pressure changed from 52.5 mm Hg before POEM to 19.8 mm Hg after the procedure. No specific complications related to the surgery were experienced. During the followup period, one patient required 20 mm balloon dilatation 1 month after POEM, which was successful in treating mild dysphasia. In this study, three patients had received surgical myotomy before undergoing POEM (2 laparoscopic Heller myotomy [LHM], 1 thoracoscopic myotomy). These patients gained symptomatic control following POEM. During the followup period (up to 25 months), no patient reported dysphagia recurrence, but some patients reported mild chest pain. Four patients had endoscopically visible gastroesophageal reflux disease (GERD). In three patients, GERD symptoms were controlled with proton pump inhibitors.<sup>6</sup>

In results of another retrospective study of patients with achalasia (n=205) treated with POEM, investigators reported that 98.5% of patients were successfully treated. POEM was ineffective in three patients because of severe submucosal fibrosis attributed to previous therapies. The mean operation time was 68.5 minutes (range 10–180 minutes), and the average myotomy length of the inner circular muscle was 9.5 cm (range 7–13 cm). No serious complications resulted from POEM.<sup>7</sup>

In a third report of patients with achalasia (n=31) treated with POEM, the success rate was 94%. Two patients had recurrent symptoms at 3 months and both responded to pneumatic dilation. Mean myotomy length was 8.6 cm (range 3–14 cm), mean procedure time was 145 minutes (43–240 minutes), and mean length of stay was 2.2 days (1–5 days). Mean postprocedure followup was 8.4 months. Significant reductions in Eckardt score (1.1–7.5,  $p<0.0001$ ) and LES pressure (19–49 mm Hg,  $p<0.0001$ ) were observed. No complications occurred requiring intensive care, hospital stays longer than 5 days, surgical or interventional radiology interventions, blood transfusions,

surgical conversion, or POEM-related readmissions. Eighty-seven percent of patients treated with POEM reportedly did not require posttreatment analgesia.<sup>8</sup>

In a nonrandomized, historical control trial, investigators reported that patients with achalasia were treated with POEM (n=18) or LHM (n=55).<sup>9</sup> Operative times were shorter for POEM than for LHM (113 and 125 minutes, respectively,  $p<0.05$ ). Additionally, estimated blood loss was less in patients treated with POEM ( $\leq 10$  mL in all POEM cases vs. 50 mL for LHM,  $p<0.001$ ). Myotomy lengths, complication rates, and length of stay were similar between groups. Pain scores were similar upon postanesthesia care and postoperatively on day 1, but were higher at 2 hours for POEM patients (3.5 vs. 2.0,  $p=0.03$ ).<sup>9</sup> Narcotic use was similar between groups, although fewer patients treated with POEM received ketorolac.<sup>9</sup>

POEM has been generally well tolerated according to reports from studies thus far.<sup>10</sup> However, the procedure carries the usual risks associated with surgery—such as those associated with general anesthesia and infection—and risks of other natural-orifice transluminal endoscopic surgery (NOTES) procedures. Because POEM involves cutting only one LES muscle layer, some speculate that it may not be as effective long term as laparoscopic surgery and that revisional surgery might be difficult, involving extensive procedures such as esophagectomy.<sup>5</sup>

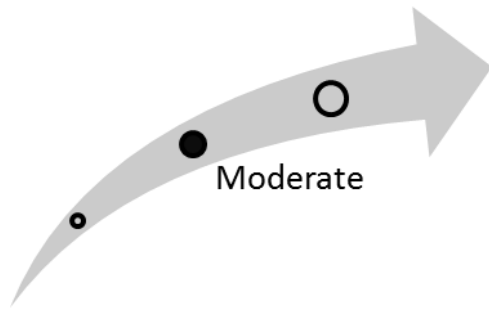
**Regulatory status and diffusion:** POEM uses available laparoscopic instrumentation and, as a surgical procedure, is not subject to regulation by the U.S. Food and Drug Administration (FDA). In the United States, the surgery is being performed by at least seven academic teaching hospitals through Institutional Review Board-approved clinical trial protocols. Sixteen active POEMs trials were registered in the National Clinical Trials database as of June 2013, with four U.S. centers currently participating in or sponsoring trials.<sup>7,8,10-12</sup> U.S. centers have performed more than 80 of the estimated 900 POEM cases reported worldwide since 2008.<sup>13,14</sup> At the 2012 meeting of the Society of American Gastrointestinal and Endoscopic Surgeons, leading researchers presented a didactic training course with reports on outcomes of cases performed to that date.<sup>15</sup>

The costs of POEM are similar to Heller myotomy, according to one published commentary.<sup>14</sup> According to one participant in an online forum, the total cost of POEM is about \$35,000, of which their insurance provider purportedly covered most of the costs.<sup>16</sup> The U.S. Centers for Medicare & Medicaid Services has no national coverage determination for POEM, and we identified no private third-party payers that publish their medical coverage policies and mention POEM coverage.

## Clinical Pathway at Point of This Intervention

Esophageal achalasia is typically diagnosed by the manometric detection of elevated LES resting pressure, incomplete relaxation of the LES after swallowing, and abnormal smooth muscle contractility within the tubular esophagus.<sup>5</sup> The American College of Gastroenterology recommends surgery as the primary therapy in patients with a low risk of complications from undergoing surgery. Laparoscopic myotomy with fundoplication is considered the gold standard therapy for achalasia, and it has replaced open Heller myotomy.<sup>5,17</sup> The standard surgical technique involves complete division of both circular and longitudinal muscle layers.<sup>5</sup> Other treatment options include endoscopic balloon dilation and endoscopic botulin toxin injection.<sup>3</sup> Pharmacologic options include using nitrates and calcium channel blockers.<sup>1</sup> POEM is intended to be less invasive than laparoscopic techniques, possibly reducing complications and pain.

**Figure 1. Overall high-impact potential: PerOral Endoscopic Myotomy for treatment of esophageal achalasia**



POEM is a novel procedure that has potential to provide a permanent, minimally invasive surgical option with shorter recovery time and less pain than current surgical options for achalasia. In the absence of results from randomized or long-term trials, some experts are unsure about the true potential of POEM, although the increase in number of registered clinical trials in 2012 (at the time of expert comment) signals marked interest in the procedure. Experts who commented generally assumed that if POEM remains an inpatient procedure, the impacts beyond scarring, pain, and shortened hospital stay could be modest. If the procedure becomes an outpatient procedure performed under twilight sedation (more commonly known as conscious sedation), as one clinical expert from a facility with POEMs experience noted, the care-setting change could represent a paradigm shift in treatment, costs savings might be achieved, and more patients could become eligible for, or elect surgical treatment. Additionally, POEM could renew interest in NOTES procedures and instrumentation if ongoing trials demonstrate better outcomes than other surgical options. 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, and health systems backgrounds, offered comments on this intervention.<sup>18-24</sup> We organized the following discussion of expert comments by the parameters on which they commented.

**Unmet need:** A significant unmet exists need for a less-invasive, less-painful, less-expensive treatment option with a shorter recovery time and faster return to normal activity, said all of the experts except two representing health systems and research perspectives. One clinical expert stated that POEM could satisfy all of these unmet needs. But most experts who commented were less certain of POEM's efficacy because of a lack of randomized controlled trials. They stated that current treatment options for achalasia have benefits and risks associated with each respective option.

**Acceptance and adoption:** Some of the experts stated the steep learning curve and lack of data from randomized trials could be a barrier to clinician acceptance. Patients, on the other hand, are likely to accept a less-invasive procedure, the experts stated. One clinical expert stated that some patients will still prefer quick outpatient procedures such as balloon dilation or Botox<sup>®</sup> injections.

One clinical expert stated that in his facility, the procedure is performed by surgeons. This expert said that clinicians are eager to learn the procedure, and no patients have rejected the opportunity to enroll in an ongoing POEM trial. The expert stated that after the procedure, patients have been highly satisfied with results. The expert stated the facility required the surgeon to perform 20 procedures to be considered proficient in POEM and that the ideal practitioner would be experienced in LHM and proficient in flexible endoscopy.

The experts stated that POEM is not likely to affect the cost of care much, unless it can significantly shorten length of patient stay. If POEM can eventually be performed on an outpatient basis, significant cost savings could be realized. One clinical expert stated that POEM has reinvigorated interest in NOTES procedures and instrumentation because it is the only procedure demonstrating potential to have better outcomes than laparoscopic alternatives.

**Health care delivery infrastructure and patient management:** POEM lacks features that would significantly change many aspects of health care infrastructure and patient management because no new infrastructure is needed, other than surgeon training in how to perform the procedure, most of the experts thought. They expected achalasia's relative rarity to minimize the impact on infrastructure and staffing, if the procedure were to become standard of care. However, one clinical expert stated that POEM has a large disruptive potential based on this expert's clinical experience. The expert thought that POEM could be performed in an endoscopy suite under moderate sedation and could eventually be performed on an outpatient basis. This expert thought that eventually gastroenterologists could provide "one-stop shopping for achalasia care," which differs from the current care model. Additionally, this expert stated that patients valued the lack of postoperative restrictions and lack of visible incisions. Additionally, 75% of patients reported no pain after POEM, based on experience at the expert's facility.

**Health disparities:** Two experts stated that POEM could reduce health disparities because of shorter inpatient stays, which would limit lost work days and costs. But another expert representing a health systems perspective stated that POEM could increase health disparities because the procedure would be performed only in specialty centers.

## Teduglutide (Gattex) for Treatment of Short Bowel Syndrome

**Unmet need:** Short bowel syndrome (SBS) encompasses a group of health problems related to malnutrition that occurs in individuals who have lost at least half of their small intestines. The primary cause of SBS is surgical removal of more than half of the small intestine because of disease, injury, or birth defects.<sup>25</sup> About 70% of patients with Crohn's disease require at least one surgical procedure during their lifetimes to remove damaged intestine, leaving them at risk of complications such as SBS.<sup>26</sup> SBS can cause diarrhea, fatigue, abdominal pain, bloating, heartburn, and nutrient deficiencies.<sup>25</sup> An estimated 10,000–20,000 people in the United States receive at-home intravenous nutritional support for SBS indicated by data from the early 1990s, at a cost of more than \$100,000 per patient per year.<sup>27</sup> Long-term parenteral nutrition (PN) can lead to serious side effects such as liver damage, the risk of which increases the longer a patient is PN-dependent.<sup>28</sup> No effective long-term treatments are available to improve nutritional absorption other than intestinal transplant.

**Intervention:** Teduglutide (rDNA origin [Gattex®]) is intended to provide several critical actions throughout the gastrointestinal tract for treating SBS, including suppressing gastric motility; stimulating intestinal nutrient transport, intestinal blood flow, and crypt cell proliferation; inhibiting crypt cell apoptosis (programmed cell death); and enhancing gut barrier function.<sup>26</sup> Teduglutide is a glucagon-like peptide 2 (GLP-2) analog, containing a single amino-acid substitution that is purported to render it resistant to dipeptidyl peptidase-4, thus significantly increasing the biologic half-life and activity of teduglutide.<sup>29,30</sup> As a GLP-2 agonist, teduglutide is purported to induce repair and regeneration of the cells lining the intestine and increase the size and density of intestinal villi in the intestinal epithelial layer, resulting in better absorption of nutrients.<sup>29,30</sup> Teduglutide is administered as a subcutaneous injection (0.05 mg/kg/day) once daily.<sup>31</sup>

**Clinical trials:** In results of a randomized, double-blind, placebo-controlled, phase III trial, investigators reported that 63% of patients (n=43) given teduglutide (subcutaneous injections 0.05 mg/kg, daily) responded to treatment ( $\geq 20\%$  reduction from baseline in weekly PN and/or intravenous fluid volumes) versus 30% of patients (n=43) given placebo ( $p=0.002$ ).<sup>31</sup> At week 24, patients who received teduglutide experienced an average 4.4 liter reduction in weekly parenteral support/PN (baseline 12.9 liters) compared with patients who received placebo, who experienced an average 2.3 liter reduction in fluids required (baseline of 13.2 liters;  $p\leq 0.001$ ). After 24 weeks of treatment, 54% of patients treated with teduglutide were able to reduce the number of infusion days per week by 1 or more days, compared with 23% of patients treated with placebo experiencing such reduction ( $p=0.005$ ).<sup>31,32</sup>

In an open-label extension trial, reductions in PN volume continued to be observed in patients treated with teduglutide and three patients were completely weaned from PN after 6.5, 8.0, and 9.0 months of teduglutide treatment.<sup>33</sup> In an interim analysis of the open-label extension trial enrolling patients with SBS who were treated with either teduglutide (n=34) or placebo for 12 months, investigators reported that 91% of patients given teduglutide were responders (achieved 20% to 100% reduction in PN and/or intravenous volume from baseline). Additionally, after 12 months of teduglutide treatment, 53% of patients reduced their infusion days per week, and 24% of patients reduced their infusion days per week by 3 or more days. The mean reduction in PN volume and/or intravenous fluids was 5.2 liters per week from pretreatment baseline.<sup>34</sup> As of October 2012, the manufacturer reported, 12 patients (14%) had achieved independence from PN or intravenous support while using teduglutide.<sup>35</sup>

A second randomized, double-blind, placebo-controlled, trial comparing teduglutide with placebo was conducted. Adult patients with SBS dependent on PN or intravenous fluids for at least 12 months and who required PN at least 3 times per week were treated with daily injections of

either teduglutide 0.05 mg/kg (n=35), teduglutide 0.10 mg/kg/day (n=33), or placebo (n=16). The primary efficacy endpoint was a graded categorical score that did not achieve statistical significance for high-dose teduglutide. Treatment response (defined as least 20% reduction in PN or intravenous volume from baseline to weeks 20 and 24) was achieved in 46% of patients given teduglutide 0.05 mg/kg/day versus 6% of patients given placebo. Patients given teduglutide at both dosages experienced a 2.5 liter per week reduction in PN support versus a 0.9 liter per week reduction for patients given placebo at 24 weeks. Two patients treated with teduglutide 0.05 mg/kg/day were weaned from PN support by week 24.<sup>31</sup>

In a blinded, uncontrolled extension of the second trial, patients (n=65) received teduglutide for up to an additional 28 weeks. Seventy-five percent of those who responded to therapy in the first part of the study had a sustained response after 1 year of treatment.<sup>31</sup> Patients treated continuously with teduglutide had a 52% reduction from baseline in PN support required after 1 year. Patients who were completely weaned from PN or intravenous fluid support in the first part of the trial remained off PN support through the extension, and an additional patient from the first part of the study was weaned from PN support.<sup>31</sup>

The prescribing information states that the most commonly reported adverse events occurring in more than 10% of patients taking teduglutide were: abdominal distension, abdominal pain, fluid overload, headaches, injection site reactions, nausea, upper respiratory tract infection, and vomiting.<sup>31</sup> The manufacturer warns that patients taking teduglutide may be at increased risk of developing accelerated neoplastic growth, biliary and pancreatic disease, fluid overload, or intestinal obstruction.<sup>31</sup>

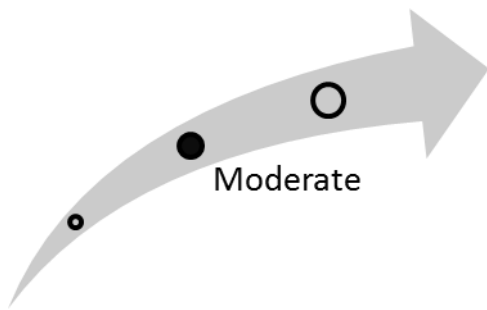
**Manufacturer and regulatory status:** NPS Pharmaceuticals, Inc., of Bedminster, NJ, makes teduglutide. In December 2012, FDA approved teduglutide for treating adults with SBS who require additional nutrition from PN.<sup>36</sup> Approval was based on two randomized, placebo-controlled, clinical trials and two extension studies.<sup>36</sup>

**Diffusion:** A query of a U.S.-based, online pharmacy identified a retail cost of about \$30,000 for 30 single-injection vials of teduglutide.<sup>37</sup> Our searches revealed no information regarding third-party coverage or payment for teduglutide, but payers may not have yet updated their policies, given the recency of the FDA approval.

## Clinical Pathway at Point of This Intervention

Mild SBS can be treated by eating small and frequent meals, taking nutritional supplements, and using medication to manage diarrhea. Moderate SBS may also require using intravenous electrolyte and fluid supplements. Treatment for severe SBS may involve oral rehydration solutions, intravenous nutrition delivery, and liquid food delivered through feeding tubes. In very severe cases, intravenous nutrition can be required indefinitely.<sup>25</sup> In cases in which an obstruction in the intestine or extreme shortening of the small intestine exists, surgical options can enhance the surface area of the intestine or lengthen the time food spends in the intestines, which increases nutrient absorption.<sup>38</sup> Recombinant human somatropin (Zorbtive®) can also be used to increase nutrient absorption; however, somatropin has not been evaluated for longer than 4 weeks in patients with SBS.<sup>39</sup> Teduglutide is intended to treat adults with SBS who require additional nutrition from PN.<sup>36</sup> Patients with SBS who cannot be maintained on PN are potential candidates for intestine transplantation.<sup>28</sup>

**Figure 2. Overall high-impact potential: teduglutide (Gattex) for treatment of short bowel syndrome**



Teduglutide has been evaluated in a relatively small number of patients, yet most experts who commented were optimistic about its potential to reduce the frequency of PN administration in patients with SBS. A reduction in PN might significantly improve patient outcomes and quality of life. It might also reduce home-care costs and complications associated with PN. SBS affects a relatively small number of patients, but those with SBS are significantly affected and have few treatment options. However, teduglutide is unlikely to obviate completely the need for PN in most SBS patients. Based on our opinion on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

## Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.<sup>40-45</sup> We organized the following discussion of expert comments by the parameters on which they commented.

**Unmet need and health outcomes:** The experts noted an important unmet need exists, because although SBS affects only a small patient population, limited treatment options are available, and the main treatment, PN, leads to worsening quality of life and is costly. Additionally, medical advances are now allowing children with conditions that put them at risk of SBS to lead longer lives, resulting in a greater need for improved long-term treatment options for SBS. Finally, one expert representing a clinical perspective stated that no therapies are available to promote growth of villi in the intestine; thus, approval of teduglutide would mark a major advance in SBS therapy.

Overall, experts were optimistic regarding the ability of teduglutide to reduce the need for PN, an important outcome. However, whether teduglutide would lead to more significant improvements in health outcomes—such as weight gain, improvements in lean muscle mass, general well-being, and other quality-of-life measures—was a matter of diverging opinion. Some experts were also unsure if reductions in PN in patients taking teduglutide would be enough to outweigh adverse events observed, although one expert representing a clinical perspective stated that decreasing PN has been directly correlated with improving health outcomes by reducing morbidity and mortality from central line catheter–related infections and thrombosis.

**Acceptance and adoption:** In general, the experts expected wide acceptance among clinicians if the drug continues to show favorable efficacy and acceptable long-term tolerability. Patients, who are significantly affected by the disease and have few treatment options, also are expected to easily and widely adopt teduglutide, the experts thought: Two experts representing a clinical perspective stated that patients with SBS are usually quite savvy regarding treatment options, frequently have a home-care team in place, and are already capable of administering subcutaneous injections. Reductions in PN alone could be enough to spur acceptance by patients if tolerability is acceptable, one expert representing a clinical perspective stated. But another expert representing a clinical perspective stated that patient acceptance for teduglutide could be limited because of the need for daily injections and potential adverse events contrasted against the modest reductions in PN.



**Health care delivery infrastructure and patient management:** Disruptions might been seen in models of patient management with teduglutide, the experts stated. Because the drug is self administered, its use could reduce the frequency of home-care visits for PN and reduce the number of inpatient or outpatient admissions linked to PN complications. Patients or caregivers would need to learn how to administer injections, but one clinical expert stated that many SBS patients already take injectable blood thinners. Disruption to health care infrastructure and staffing are less likely, the experts thought, because the population of patients is relatively small.

How teduglutide would affect costs of care was not clear to the experts because information about its expected cost was not available at the time of expert review. Some experts stated the drug could reduce the cost of care if it could significantly reduce PN use, but others stated that any changes to the health care system would be minimal because of the relatively small patient population with SBS. One clinical expert stated that controversy could arise as the potential cost-effectiveness of teduglutide and third-party coverage become known.

**Health disparities:** Two experts representing clinical perspectives stated that PN is difficult to administer to patients who have poor access to care and that the number of medical centers performing small bowel transplants is limited. Thus, a daily self-administered injection of teduglutide, prescribed by a gastroenterologist, could help patients with poor access to care better self manage SBS, possibly reducing health disparities.

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