

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

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. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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Preface

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

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

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

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

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated semi-annually. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

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

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

Results

The table below lists the single topic for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Ten topics in this priority area were being tracked in the system as of November 4, 2014.) This topic (indicated below with an asterisk) emerged as having high-impact potential on the basis of experts’ comments and their assessment of potential impact.

Priority Area 11: Peptic Ulcer Disease and Dyspepsia

Topic	High-Impact Potential
1. * Teduglutide (Gattex) for treatment of short bowel syndrome	Moderately high

Discussion

Teduglutide was included as the only topic with potential high impact in the June 2014 report, and it remains in the December 2014 issue as well. Compared with other priority areas, we have identified relatively few leads and topics that meet inclusion criteria for new developments related to peptic ulcer and intestinal tract diseases in the horizon scanning system, despite extensive searches. 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), and we continue tracking novel drugs and interventions such as fecal microbiota therapy for irritable bowel disease that are in clinical trials but have not yet reported phase III data.

Experts provided comments on teduglutide in May 2014 indicating its potential for high impact. 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 the parenteral nutrition (PN) that can accompany SBS.

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 after 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 intravenous nutrition delivery and PN delivered through feeding tubes. An estimated 10,000–20,000 people in the United States receive at-home PN for SBS, based on data from the early 1990s (the most recent data), at a cost of more than \$100,000 per patient per year. Long-term PN can, however, 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 transplant. Teduglutide (Gattex[®], NPS Pharmaceuticals, Inc., Bedminster, NJ) is a subcutaneously administered glucagon-like peptide 2 analog intended to induce the cells lining the intestine to regenerate and repair themselves. This, in turn, increases the size and density of intestinal villi in the intestinal epithelial layer, resulting in better nutrient absorption. Phase III trials on which U.S. Food and Drug Administration (FDA) approval was based reported that patients with SBS experienced a significantly reduced need for PN when treated with teduglutide. Additionally, a long-term extension trial demonstrated that some patients were able to completely stop PN. Because the drug is a synthetic intestinal growth factor, some clinicians have been 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 physician communication plan and prescriber training because of a potential for increased risk of patients developing one or more of the following while taking the drug: intestinal cancer and polyps, obstructions, gallbladder disease, biliary tract disease, and pancreatic disease. Daily self-injection with teduglutide at the recommended dose of 0.05 mg/kg costs about \$30,000 per month, or about \$360,000 annually. Our searches of representative third-party payers identified 10 payers that have policies covering teduglutide under certain conditions.
- **Key Expert Comments:** Overall, experts commenting on this intervention agreed that an unmet need exists for effective treatments to improve nutritional absorption in patients with SBS. Experts were optimistic that reductions in PN use could potentially improve patient health outcomes and quality of life, as well as lower the high costs of PN. However, experts noted that patients would likely be concerned about potential adverse events. Most experts who commented thought that this intervention would appeal to patients with SBS, because of the limited number of treatment options and the potential to reduce PN dependence. Experts noted that this intervention is likely to be accepted by clinicians; however, a few experts anticipated issues regarding training of both patients and clinical staff about potential risks. Experts expected to see additional scrutiny of teduglutide's safety and its impact on cost of care going forward.
- **High-Impact Potential:** Moderately high

Peptic Ulcer Disease and Dyspepsia Interventions

Teduglutide (Gattex) for Treatment of Short Bowel Syndrome

Unmet need: Short bowel syndrome (SBS) encompasses a group of health problems, related to malnutrition, that occur 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.¹ About 70% of patients with Crohn's disease require at least one surgical procedure during their lifetime to remove damaged intestine, leaving them at risk of SBS.² SBS can cause diarrhea, fatigue, abdominal pain, bloating, heartburn, and nutrient deficiencies.¹ An estimated 10,000–20,000 people in the United States receive at-home intravenous nutritional support for SBS, according to data from the early 1990s, at a cost of more than \$100,000 per patient per year.³ 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.⁴ 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. These actions include 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.² As a glucagon-like peptide 2 (GLP-2) analog, teduglutide contains a single amino-acid substitution that is reported to render it resistant to dipeptidyl peptidase-4. This characteristic has been shown to significantly increase teduglutide's biologic half-life and activity.^{5,6} As a GLP-2 agonist, it is reported to induce the cells lining the intestine to regenerate and repair themselves and to increase the size and density of intestinal villi in the intestinal epithelial layer, resulting in better nutrient absorption.^{5,6} Teduglutide is self-administered as a subcutaneous injection (0.05 mg/kg/day), once daily.⁷

Clinical trials: In a clinical trial of 52 patients, investigators reported that after 52 weeks, “68% of the 0.05-mg/kg/d and 52% of the 0.10-mg/kg/d dose group had a $\geq 20\%$ reduction in PN, with a reduction of 1 or more days of PN.” The researchers also reported that the most common adverse events “included headache (35%), nausea (31%), and abdominal pain (25%); 7 patients withdrew because of adverse events (gastrointestinal disorders in 4). Both groups had progressive reduction in PN. Four patients experienced complete independence from PN.”⁸

According to data provided in the full prescribing information, “Across all clinical studies, 595 subjects were exposed to at least one dose of GATTEx (249 patient-years of exposure; mean duration of exposure was 22 weeks). Of the 595 subjects, 173 subjects were treated in Phase 3 SBS studies (134/173 [77%] at the dose of 0.05 mg/kg/day and 39/173 [23%] at the dose of 0.10 mg/kg/day). The most commonly reported ($\geq 10\%$) adverse reactions in patients treated... across all clinical studies (n = 595) were: abdominal pain (31.3%); injection site reactions (21.8%); nausea (18.8%); headaches (16.3%); abdominal distension (14.8%); upper respiratory tract infection (11.9%). The rates of adverse reactions in subjects with SBS participating in two randomized, placebo-controlled, 24-week, double-blind clinical studies that occurred in more than 5% of patients were considered to be mild or moderate. Of subjects receiving the recommended dose of 0.05 mg/kg/day, 88.3% (n=68/77) experienced an adverse reaction compared with 83.1% (49/59) of the placebo group. Many of these adverse reactions were reported in association with the underlying disease and/or use of parenteral nutrition.”⁷ 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.⁷

In a phase III randomized controlled trial with an open-label extension, at week 24, patients who received teduglutide were reported to have an average 4.4 liter reduction in weekly parenteral

support/PN (baseline 12.9 liters) compared with support/PN in patients who received placebo and had an average 2.3 liter reduction in fluids required (baseline of 13.2 liters; $p \leq 0.001$). After 24 weeks of treatment, 53.8% of patients treated with teduglutide reduced the number of infusion days per week by 1 or more days, compared with 23.1% of patients treated with placebo experiencing such reduction ($p=0.005$).^{7,9}

Investigators from the open-label extension of this trial reported that reductions in PN volume continued to be observed, and three patients were completely weaned from PN after 6.5, 8.0, and 9.0 months of teduglutide treatment.¹⁰ In an interim analysis of the open-label extension trial of 34 patients, investigators reported that 91% of patients given teduglutide achieved a 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.¹¹

Manufacturer and regulatory status: NPS Pharmaceuticals, Inc. (Bedminster, NJ), manufactures teduglutide. In December 2012, FDA approved the drug for treating adults with SBS who require additional nutrition from PN. Approval was based on two randomized, placebo-controlled, clinical trials and two extension studies.¹² FDA required a Risk Evaluation and Mitigation Strategy (REMS) as part of the approval and informs prescribers and patients about “possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with GATTEX.” The REMS program consists of a medication guide, elements to ensure safe use (i.e., provider training), and a timetable for assessments.¹³

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—a 1-month supply.¹⁴ Our searches of representative, private third-party payers that publish their coverage policies online identified 10 major payers that cover the drug under certain conditions.¹⁵⁻²⁴ Three of these policies require patients to be dependent on PN support for 12 months, receiving it at least three times per week.^{15,16,20} The manufacturer has announced programs to assist both insured and uninsured patients cover out-of-pocket expenses and reportedly covers the full cost of teduglutide for uninsured patients with SBS.²⁵ Although an estimated 10,000–20,000 people in the United States receive at-home intravenous PN support for SBS, the manufacturer estimates the number of candidates for this therapy to be in the range of 3,000–5,000 patients.^{3,26} According to the manufacturer, anticipated global sales of teduglutide in 2014 are expected to reach at least \$100 million.²⁷

Clinical Pathway at Point of This Intervention

SBS encompasses a group of health problems, related to malnutrition, that occur in individuals who have lost at least half of their small intestines.¹ Patients with SBS do not have the surface area left in the bowel to absorb enough nutrients from food, either because of a congenital defect or after areas of the small intestine have been surgically removed.²⁸

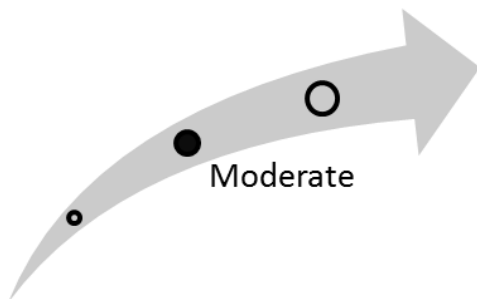
The type and extent of the health problems associated with SBS depend on the size and location of the sections of the small intestine affected.¹ In some cases, a child is born without enough intestine, but most problems associated with SBS are related to the removal of the ileum, the last section of the small intestine, which is responsible for absorbing bile acids and vitamin B₁₂.²⁹ Diseases that may require surgically removing parts of the small intestine include necrotizing enterocolitis (death of bowel tissue), meconium ileus (infant bowel obstruction), intussusception (telescoping intestine), Crohn’s disease, and certain types of cancer.¹ 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 for complications such as SBS.²

Clinicians diagnose SBS after obtaining a detailed medical history, performing a physical examination, and evaluating diagnostic tests.²⁹ These tests may include blood tests to measure nutrient levels in the bloodstream, abdominal x-rays or ultrasound to provide images of the abdomen, stool-sample tests to detect infection or unabsorbed sugar and protein, endoscopy or colonoscopy to examine the inside of the intestine, and other tests that measure nutritional needs and carbohydrate absorption.²⁹

The primary treatment goal for SBS is symptomatic relief through nutritional status maintenance. Treatment may include a high-calorie diet with vitamins, minerals, and certain types of carbohydrate, protein, and fat. Furthermore, some vitamins and minerals may be given by injection. Anemia may be treated with vitamin B₁₂, folic acid, and increased dietary iron. Medications may be given to slow the movement of nutrients through the intestine. PN is required if normal feeding is not delivering enough nutrients.²⁸ 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.²⁹ 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.³⁰ Teduglutide is intended to treat adults with SBS who require additional nutrition from PN.¹² Patients with SBS who cannot be maintained on PN are potential candidates for intestine transplant.⁴

Figure 1. Overall high-impact potential: teduglutide (Gattex) for treatment of short bowel syndrome



Most experts who commented on this intervention were optimistic about teduglutide's potential to reduce the frequency of PN administration in patients with SBS. PN reduction might significantly improve patient outcomes and quality of life. Experts listed cost as a barrier to adoption but also noted the potential to reduce home-care costs and complications associated with PN. SBS affects a relatively small number of patients, but those affected have few treatment options. Although teduglutide is unlikely to obviate completely the need for PN in most patients with SBS, experts commented that this the drug could reduce the amount of health care resources required for treating SBS. Most experts who commented on this intervention anticipated minor disruptions to patient management and health care infrastructure. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.³¹⁻³⁶ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: The experts noted that 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. One expert representing a clinical perspective stated, “Since all treatment for SBS is supportive, an option that may lessen the need to total parenteral nutrition (TPN) in these patients is huge. Even short term TPN use is extremely dangerous and I try to avoid it in practice as much as possible, having patients be able to receive fewer PN is a significant achievement.”³⁶

Overall, experts were optimistic about teduglutide’s ability to reduce the need for PN, an important outcome. One expert representing a research perspective commented, “Studies indicate that teduglutide can reduce the majority of patients’ dependency on PN.”³⁴ Some experts were also unsure whether reductions in PN in patients taking teduglutide would be enough to outweigh adverse events observed; one expert representing a research perspective stated that although teduglutide “shows some promising results in the clinical trials, there’s also a significant number of patients who had to withdraw from the studies due to adverse effects. It is uncertain how widely this treatment can be used.”³⁵

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. One expert representing a research perspective opined, “If effective, I would expect moderate acceptance by clinicians as a means to reduce dependence on parenteral nutrition in patients with short bowel syndrome.”³¹ Patients, who are significantly affected by the disease and have few treatment options, also are expected to easily and widely adopt teduglutide. One expert representing a clinical perspective noted, “Patients with SBS are used to frequent contact with the health care system and thus a daily injection or medication administration is likely to be accepted.”³³ Another expert representing a research perspective commented, “Some patients may not be amenable to receiving a daily injection however most patients should look forward to less reliance on PN which in the long run will help reduce liver damage.”³²

Health care delivery infrastructure and patient management: The disruption to patient management would be minimal, most experts generally agreed. One expert representing a research perspective commented, “Patients or home caregivers will need to be trained on how to administer the daily subcutaneous injection.”³¹ However, a greater disruption to patient management was anticipated by some experts. One expert representing a clinical perspective noted, “Patients may definitely be started on teduglutide first, prior to TPN initiation in order to attempt to avoid TPN adverse events.”³⁶

Disruption to health care infrastructure and staffing are less likely, the experts thought, because of the relatively small patient population. One expert representing a research prospective opined, “This treatment may reduce the need for patients to receive PN administration which may result in less staff. However, the number of patients with SBS only number in the tens of thousands.”³⁴ However, some experts believe that teduglutide administration would cause a greater disruption to health care infrastructure and staffing. One expert with a clinical perspective stated, “Patients with SBS consume a large amount of health care resources and if teduglutide is effective this would potentially lead to a decreased need for such resources, therefore the disruption would be helpful.”³³

Most experts generally agreed that teduglutide administration would have a minor impact to cost of care. One expert representing a research perspective opined, “The cost of this medication is relatively low, considering the secondary costs resulting from the inadequacies of current treatment options.”³⁵ One clinical expert commented, “Although teduglutide has the potential to decrease PN use, the cost of the medication, monitoring and resources associated with it may render the potential impact on healthcare costs negligible.”³³ However, one research expert offered an alternative opinion, “Very costly- \$1,000/dose plus costs of disposables for injection.”³¹

Health disparities: Most experts commenting on this intervention agreed on the potential to adversely affect health disparities. One research expert commented, “Due to the high cost of teduglutide (\$30,000 for 30 vials), I foresee a high potential for affecting health disparities for patients not covered by their insurance and for the uninsured.”³² Another expert representing a clinical perspective stated, “\$30,000 per 30 injections is significant for low income families where Medicaid may not be covering this medicine.”³⁶

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