Priority Area 10: Obesity

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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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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 National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

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

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

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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 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop. The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest.
(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

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

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

Results

The table below lists the three topics for which (1) preliminary phase III data for drugs or pivotal data for devices were available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Eight topics in this priority area were being tracked in the system as of May 8, 2015.) The two topics marked with asterisks emerged as having high-impact potential on the basis of experts’ comments and assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

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Discussion

According to a 2014 report from the National Center for Health Statistics (NCHS), 34.9% of adults (about 78.6 million) and 17% of youth (about 12.7 million) in the United States are obese (defined as an excess accumulation of body fat). Worldwide, obesity rates have more than doubled since 1980. According to the World Health Organization, in 2014, more than 1.9 billion adults aged 18 years or older (39%) were overweight; of these, more than 600 million (13%) were obese. Further, 42 million children under the age of 5 were overweight or obese in 2013.

According to NCHS, overweight adolescents have a 70% chance of becoming overweight adults. Non-Hispanic black adults have the highest age-adjusted rates of obesity (47.8% are obese), followed by rates for Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%). Non-Hispanic black and Mexican-American men with higher incomes are more likely to
be obese than non-Hispanic black and Mexican-American men with low incomes. Low-income women are more likely to be obese than high-income women. Prevalence of obesity in adults has increased across all income and education levels. In children, obesity is higher among children living in low-income, low-education, and higher-unemployment households.

Obesity was at one time thought to be simply the result of caloric intake that exceeded energy expenditure. However, researchers now know that other factors including genetics, metabolism, behavior, environment, culture, and socioeconomic status contribute to obesity. Obesity is associated with increased risk of mortality and comorbidities, including type 2 diabetes mellitus (T2DM), coronary artery disease, dyslipidemia, cardiometabolic syndrome, hypertension, stroke, sleep apnea, osteoarthritis, gall bladder disease, and some cancers. In June 2013, the American Medical Association adopted a policy that recognizes obesity as a disease.

Body mass index (BMI) is a measure of an individual’s weight relative to his or her height (kg/m²). BMI is significantly correlated to an individual’s body-fat percentage and is used as a measure to determine whether someone is overweight or obese. Individuals with a BMI of 25 kg/m² or higher are considered to be overweight, and those with a BMI of 30 kg/m² or higher are considered to be obese. Obesity is further classified as extreme or morbid in individuals with a BMI of 40 kg/m² or more.

Body fat distribution is also an important determinant of disease risk. Excess body fat in the abdominal area that is out of proportion to total body fat is known to be an independent predictor of morbidity and early mortality. Waist circumference positively correlates to the amount of abdominal fat, and it can be used clinically to assess disease risk in patients. A waist circumference of more than 37 inches in men and 31.5 inches in women is associated with increased cardiovascular risk. Because of even greater morbidity risk, therapeutic intervention is considered to be urgently needed in men with a waist circumference greater than 40 inches and in women with a waist circumference of more than 35 inches.

The Healthcare Horizon Scanning System is tracking interventions in development for treating obesity including a temporary-placement dual gastric balloon, an intestinal barrier to reduce food absorption, a procedure to embolize certain abdominal arteries associated with production of appetite hormones, and drugs with reportedly new mechanisms of action and therapeutic targets.

### Prior Potential High Impact Topic Archived Since Last Report

- **Vagus Nerve Blocking (Maestro System VBLOC) for Treatment of Obesity:** According to its manufacturer, the Maestro System (EnteroMedics, Inc., St. Paul, MN) uses high-frequency, low-energy electrical pulses to block vagus nerve signals in the abdomen, inhibiting gastric motility and increasing satiety. In January 2015, the U.S. Food and Drug Administration (FDA) approved the device for treating patients “aged 18 and older who have not been able to lose weight with a weight loss program, and who have a body mass index of 35 to 45 with at least one other obesity-related condition” such as T2DM. In September 2014, Ikramuddin and colleagues reported in JAMA that patients who received an implantable vagus nerve blocking system had a mean 24.4% excess weight loss (9.2% of their initial body weight loss) compared with 15.9% excess weight loss (6.0% initial body weight loss) in the sham-device group. The 8.5% mean difference in the percentage of the excess weight loss between groups (95% confidence interval [CI], 3.1% to 13.9%) did not meet the trial’s 10-point difference target (p=0.71). Trial data submitted to FDA demonstrated an overall serious adverse event rate, both related and unrelated to treatment, of 13% in the vagus nerve blocking group and 5% in the sham-control group. Several large, private, third-party payers consider vagus nerve blocking for obesity to be investigational.
and deny coverage. Experts reviewing this intervention cited the weak efficacy data, surgical risk, and high adverse event rate as severely limiting its potential to improve health outcomes for patients with obesity. In light of experts’ comments, we archived this topic in the Healthcare Horizon Scanning System in May 2015.

**Topics Deemed High-Impact**

**Intragastric Dual Balloon (ReShape Duo) for Treatment of Obesity**

- **Key Facts:** The ReShape Duo® dual intragastric balloon device is being studied for nonsurgical obesity treatment in patients with BMIs of 30–40 kg/m². According to the manufacturer, the ReShape Duo achieves weight loss by reducing the stomach’s capacity. An inflated dual balloon occupies space in the stomach, reportedly causing the patient to achieve satiety with less food intake. A clinician inserts the uninflated balloons into the patient’s stomach using an endoscope and guidewire. Once in the stomach, the physician inflates each balloon with equal volumes of saline. Device placement is a 15–30 minute outpatient procedure that requires only conscious sedation. The ReShape Duo is designed to be kept in the stomach for 6 months and then removed, using an endoscopic procedure similar to balloon placement. ReShape Duo has been studied in a pivotal investigational device exemption (IDE) clinical trial of patients with BMIs between 30 and 40 kg/m². The manufacturer submitted a premarket approval application to FDA in July 2014. In April 2015, the company announced that FDA would not require an advisory panel meeting for the device and that it expected an FDA decision before the end of 2015. The ReShape Duo has been CE marked since 2007 and, after some product revisions, was launched in the United Kingdom in March 2012. Anticipated U.S. costs have not been established. However, reports from Canada and the United Kingdom estimate costs for the device plus implantation in these countries would be between $7,000 and $8,000 (U.S. dollars).

- **Key Expert Comments:** Most experts acknowledged that a treatment gap exists between conservative measures and bariatric surgery for patients with BMIs between 30 and 40 kg/m². Most experts also thought that this intervention could help many patients achieve short-term weight loss. However, several experts were concerned about the paucity of data regarding long-term health outcomes and potential weight gain after the device is removed. Most experts anticipated moderate acceptance from clinicians and patients because the intervention is reversible, appears safe, and provides another therapeutic option. Overall, experts thought that the ReShape device would not substantially alter health care disparities or have a substantial effect on health care costs.

- **High-Impact Potential:** Lower end of the high-impact-potential range

**Liraglutide (Saxenda)**

- **Key Facts:** Liraglutide (Saxenda®) is a synthetic analogue of the peptide hormone glucagon-like peptide-1 (GLP-1), which is recognized (Astrup et al., 2009) for its ability to suppress appetite and energy intake, as well as delay gastric emptying. The drug is believed to induce a feeling of satiety, which can result in less caloric intake leading to weight reduction. Liraglutide is engineered to have a substantially longer half-life than endogenous GLP-1 (13 hours vs. 1–2 minutes, respectively). As an antiobesity treatment, liraglutide is self-administered once daily via subcutaneous injection using an automatic injection pen with a recommended daily dose of 3.0 mg. (Liraglutide was previously approved with a different brand name and dosing regimen for treating diabetes.) In December 2014, FDA
approved liraglutide for injection under the trade name Saxenda as a treatment for chronic weight management in addition to a reduced-calorie diet and physical activity. Saxenda’s FDA-approved labeling has a boxed warning that highlights the possibility of thyroid tumors; this risk was identified in animal studies. The FDA approval required a risk evaluation and mitigation strategy (REMS) to inform prescribers of potential risks with liraglutide use. Other approval conditions included multiple postmarketing studies to evaluate cardiovascular outcomes, potential risks of breast cancer, a form of thyroid cancer called medullary thyroid carcinoma, and liraglutide use in pediatric patients. According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, liraglutide under the name Saxenda costs up to about $1,200 per month compared to about $200 to $500 for competing obesity drugs, such as lorcaserin (Belviq®), phentermine/topiramate (Qsymia®), naltrexone/bupropion (Contrave®) and orlistat (Xenical®). However, liraglutide may also help resolve diabetes in addition to reducing weight, so may be an option for obese individuals with T2DM.

- **Key Expert Comments:** Experts generally thought that liraglutide has potential to fill an obesity treatment gap between highly invasive bariatric surgery and conservative measures. Although other obesity drugs are available, several experts cited liraglutide’s potential to improve some measures of diabetes as complementing liraglutide’s moderate potential for weight loss. Experts cited the cost, need for daily injections, and unknown long-term safety profile as potential barriers to wider acceptance from patients and physicians. Generally, experts did not expect liraglutide to substantially alter health care disparities or disrupt health care infrastructure or existing patient management procedures.

- **High-Impact Potential:** Moderate
Obesity Interventions
Intragastric Dual Balloon (ReShape Duo) for Treatment of Obesity

**Unmet need:** Bariatric surgery in the form of gastric bypass, sleeve gastrectomy, or laparoscopic banding is considered to be effective in many patients for treating obesity; however, some of these procedures are very invasive with serious risks and side effects, and some permanently alter the anatomy. These procedures are indicated only for morbidly obese patients (body mass index [BMI] of more than 40 kg/m²) or for obese patients with BMIs of 35–40 kg/m² who have related comorbidities. However, morbidly obese patients who are at high surgical risk (e.g., unstable angina, acute heart failure) are typically precluded from such surgery. Therefore, minimally invasive treatments are needed that could enable these patients to lose weight and that could help super-obese patients who want to undergo bariatric surgery lose enough weight to be eligible for it, thereby reducing surgical risk.

**Intervention:** The ReShape Duo® is a dual intragastric balloon device being developed for nonsurgical obesity treatment in patients with BMIs of 30–40 kg/m². Weight loss with the Reshape Duo is intended to be achieved by reducing the stomach’s capacity: the inflated dual balloon occupies space in the stomach, purportedly causing the patient to feel full with less food intake. Placement of the ReShape Duo is reportedly a 15–30 minute outpatient procedure requiring only conscious sedation. The clinician delivers two uninflated balloons to the patient’s stomach through the patient’s mouth via an endoscope and guidewire. Once in the stomach, a physician inflates each balloon in turn with equal volumes of saline (450 cc each balloon). Compared to single intragastric balloons, which are inflated with 400–700 cc of saline, the dual-balloon design of ReShape Duo purportedly allows for a greater stomach volume to be occupied without overdistention. The company states that the dual balloon is also designed to conform with the stomach’s natural curvature and reduce the risk of balloon migration and obstruction that has been seen with single intragastric balloons.

The Reshape Duo is designed to be kept in the stomach for no longer than 6 months. After that, clinicians remove the balloons using an endoscopic procedure similar to the balloon placement. During this procedure, a clinician places the endoscope in the patient’s stomach while the patient is under conscious sedation. The endoscope is fitted with a “proprietary suction cap” to drain the saline from the balloons individually in a controlled manner. Once the balloons are drained, the clinician secures the deflated dual balloon’s tip with a snare on the endoscope and removes the device through the patient’s mouth.

In a pivotal clinical trial conducted for the premarket approval application, the ReShape Duo was tested in patients with BMIs of between 30 and 40 kg/m². In May 2015, Lopez-Nava and colleagues reported on total body weight loss (TBWL), percentage of baseline total body weight loss (%TBWL), percentage of excess body weight loss (%EWL), and adverse events in 60 patients who received a ReShape Duo device. Patients had balloons in place for at least 6 months and also received regular counseling from a multidisciplinary team. Investigators reported that initial BMI of 38.8 kg/m² decreased by 6.1 units, with the following mean results: 16.6 kg TBWL, 15.4% TBWL, and 47.1% EWL. Investigators observed no difference in %TBWL between grade of obesity, age, or sex. However, morbidly obese patients were reported to have achieved greater TBWL, and women and less-obese subjects reportedly obtained higher %EWL. Patients were reported to have generally tolerated the balloon well, with one early removal for patient intolerance, one early deflation without migration, and one gastric perforation. Fourteen patients were reported to have developed small, clinically insignificant ulcers or erosions noted at the time of balloon retrieval.
In December 2014, Ponce and colleagues reported on %EWL and ReShape Duo treatment responder rate among 326 patients with BMI 30–40 kg/m² who were randomly assigned to endoscopic ReShape Duo treatment plus diet and exercise (DUO, n=187) or sham endoscopy plus diet and exercise alone (DIET, n=139) for 24 weeks. Both primary endpoints were met in the study. The DUO group was reported to have achieved significantly greater %EWL at 24 weeks (25.1% intent-to-treat [ITT], 27.9% completed cases [CC, n=167]) than the DIET group (11.3% ITT, p=0.004, 12.3% CC, n=126). Investigators found that the DUO group significantly exceeded a prespecified 35% response rate (49.1% ITT, p<0.001, 54.5% CC) for weight loss dichotomized at 25% EWL. Accommodative symptoms abated rapidly with support and medication. Balloon deflation without migration occurred in 6% of the DUO group. Investigators retrieved the device early for nonulcer intolerance in 9% of patients. Gastric ulcers occurred in 10% of the DUO group. Investigators noted that a minor device change significantly reduced the size and frequency of ulcers.\(^{8}\)

**Manufacturer and regulatory status:** ReShape Medical, Inc. (San Clemente, CA), is developing the ReShape Duo device. The company submitted a premarket approval (PMA) application to the U.S. Food and Drug Administration (FDA) in July 2014 after the pivotal trial met its primary efficacy endpoints.\(^9,10\) The company is positioning its device for use in patients with a BMI of 30–40 kg/m², for whom surgery is not an option and for whom diet and exercise alone have failed to produce adequate weight loss.\(^11\) ReShape Medical has reported that FDA will not require an advisory panel meeting for the device. With that waiver, the company anticipates receiving an FDA decision before the end of 2015.\(^12\) The device has been CE marked since 2007, allowing marketing in Europe; after product revisions, it was launched in the United Kingdom in March 2012.\(^13\)

**Diffusion:** If ReShape Duo is approved for treating obesity and third-party coverage and reimbursement become available, moderate diffusion could be expected in the eligible morbidly obese population as an adjunct to lifestyle modifications. However, the experience with other gastric balloons might influence perceptions of the ReShape Duo device. An early generation, single intragastric balloon (Garren-Edwards Gastric Bubble, American Edwards Laboratories [now part of Edwards Lifesciences, Irvine, CA]) was introduced in 1985 and withdrawn from the U.S. market in 1992 because of concerns about safety and efficacy due to frequent complications.\(^14\) A 2007 review by the Cochrane Metabolic and Endocrine Disorders Group concluded that “Compared with conventional management, IGB [intragastric balloons] did not show convincing evidence of a greater weight loss. The relative risks for minor complications, for example gastric ulcers and erosions were significantly raised.”\(^15\) In 1987, the U.S. Centers for Medicare & Medicaid Services established a national coverage determination (NCD) regarding gastric balloons. The NCD indicated that “the use of the gastric balloon is not covered under Medicare, since the long term safety and efficacy of the device in the treatment of obesity has not been established.”\(^16\) A subsequent NCD for bariatric surgery for treating morbid obesity issued in 2013 notes that CMS’s previous noncoverage policy for intragastric balloons for obesity remains unchanged and in force.\(^17\)

Because of this NCD, intragastric balloons coming to the U.S. market would have to undergo a new formal national coverage analysis to establish coverage under Medicare; if Medicare were to cover the balloons, other third-party payers might follow suit. Anticipated U.S. costs for the technology have not been established. Reported costs of the ReShape Duo device and implantation procedure in the United Kingdom and Canada range between $7,000 and $8,000 (U.S. dollars), which might make it more appealing than surgical procedures for some patients.\(^14,18\) However, diffusion is likely to be hampered if payers choose not to reimburse for its use.

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield of Alabama, Blue Cross/Blue Shield of
Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified no payers that provide coverage for intragastric balloons to treat obesity. Generally, these payers consider intragastric balloons to be investigational and deny coverage for the technology for treating obesity. Furthermore, searches found no major payers with policies covering bariatric surgery for patients with BMIs of less than 35 kg/m². The policies on obesity surgery indicate that for plans that provide coverage, a patient must have a BMI of more than 40 kg/m² or more than 35 kg/m² with a comorbidity.¹⁹-²⁹ For patients with BMIs between 30 and 40 kg/m², ReShape Duo could compete with recently approved pharmacotherapies for obesity (e.g., liraglutide [Saxenda®], lorcaserin [Belviq®], naltrexone/bupropion [Contrave®], phentermine/topiramate [Qsymia®]).³⁰,³¹ Weight-loss surgery is indicated for patients only after other therapies have failed or in cases in which patients are experiencing complications related to their obesity.³² Therefore, ReShape Duo will likely compete with these surgeries only in patients with BMIs of 35 kg/m² or more and obesity-related comorbidities. ReShape Duo also could complement weight-loss surgeries in some patients. Bariatric surgery in patients with BMIs higher than 40 kg/m² can present high surgical risk and technical challenges, and these patients may benefit from preoperative weight loss.³²,³³ If the indications for ReShape Duo include patients with BMIs this high, the device could serve as a noninvasive means for weight loss before bariatric surgery.

ReShape Duo may also compete with other minimally invasive endoluminal treatments that are in development, such as the Orbera™ single intragastric balloon, the EndoBarrier® endoluminal sleeve, and vagus nerve blocking.³⁴,³⁵

**Clinical Pathway at Point of This Intervention**

The National Heart, Lung and Blood Institute’s Panel on Weight Loss recommends that patients who are morbidly obese lose 10% of their excess body weight before bariatric surgery to help reduce both surgical risks and postoperative complications.³⁶ Losing weight through diet and exercise alone has often been unsuccessful in this patient population. Therefore, physicians may also recommend weight-loss medication.³⁶ If goals are not achieved with medications, patients may opt for new, minimally invasive options (in development), such as intragastric balloons, including the one discussed here, should they become available in the United States. The manufacturer reportedly intends to position the Reshape Duo balloon for use in patients with a BMI of 30–40 kg/m², for whom surgery is not an option and for whom diet and exercise alone have failed to reduce weight adequately.¹¹

**Figure 1. Overall high-impact potential: intragastric dual balloon (ReShape Duo) for treatment of obesity**

Most experts commenting on this intervention thought that a treatment gap exists between conservative measures and bariatric surgery for patients with BMI between 30 and 40 kg/m². Experts generally thought that this intervention could help some morbidly obese patients with short-term weight loss. However, they also were concerned that data are unclear about long-term health
outcomes and potential weight gain after device removal. Most experts anticipated moderate acceptance from clinicians and eligible patients because the intervention is reversible and provides another therapeutic option. Overall, experts thought that the ReShape device would not have a large impact on health care costs or changing health care disparities. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.37-42 One clinical expert reported consulting relationships with other manufacturers of anti-obesity medical devices.37 This conflict of interest is counterbalanced by views of the other experts, who reported no potential conflict of interest. We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts thought that an unmet need exists for patients with BMIs between 30 and 40 kg/m², because available therapies are often inadequate.37-39,41,42 One clinical expert noted, “There is a need for effective and safe treatments for patients with BMI under 35, i.e. those who would not qualify for bariatric surgery. The ReShape Duo would fit into this category as a procedure. These patients could reduce their risk for obesity-related complications with treatments that lead to weight loss and maintenance over time.”38 Likewise, a research expert stated, “Bariatric surgeries are so invasive that they’re a really tough sell to patients until they get truly morbidly obese, and many of these patients are too sick to be candidates for surgery. This leaves a huge population of people who are too large for diet and exercise alone but not yet ready for…more invasive bariatric surgery.”41 Generally, the experts agreed that the intervention has potential for health improvement as demonstrated by some short-term weight loss, but they would prefer to see longer-term data to analyze how well patients maintained that weight loss long after the balloons were removed. Some experts believe the intervention has potential fulfill the unmet need,37,38,41 while other experts were less convinced that the ReShape Duo could fill the therapeutic gap between conservative measures and invasive bariatric surgery.39,40,42

Acceptance and adoption: Experts were divided evenly about the likelihood of clinician adoption of the ReShape Duo balloon. One clinical expert positively stated, “The procedure appears to be safe. I would think that clinicians in the obesity field would have moderate to wide acceptance. For those outside of the field, acceptance is likely to be lower until the procedure is done frequently and is demonstrated to be safe in large numbers of patients.”38 Another clinical expert was less optimistic, stating, “Acceptance/ adoption is likely to be minimal, particularly if not reimbursed. Could reach moderate acceptance if reimbursed.”37 Several experts thought that patients might be more receptive to the technology than clinicians.38-41 One research expert stated, “Maybe a little scary compared to diet and exercise, but MUCH less scary than bariatric surgery.”41 Another research expert had tempered optimism: “Patients would like the fact that it’s nonsurgical and is only for 6 months. They can hope that they’d be able to maintain the weight loss afterwards, but that probably would be very difficult.”39 One clinical expert stated, “It appears that nausea/vomiting are the main adverse effects early on. Quality of life measures improved in the REDUCE pivotal trial. It is difficult to predict which patients might prefer the balloon to using an effective medication.”38 However, two experts anticipated lower patient acceptance.37,42 One clinical expert stated, “Patients may be eager to try it in the short term. However when the lack of durability of weight loss is considered, usage may decrease over time.”37

Health care delivery infrastructure and patient management: Experts concurred that the ReShape Duo balloon would likely have a small impact on health care infrastructure, with the exception of initial training on device implantation and patient followup. Likewise, most experts
anticipated a small disruption to the way most patients are managed.\textsuperscript{37-40,42} One clinical expert stated, “There would need to be patient education about the procedure and how to identify problems such as balloon deflation. Patients would still need to work on lifestyle changes and should be part of a multidisciplinary program with behavioral, nutritional and medical/surgical providers.”\textsuperscript{38} Another clinical expert noted, “If gastrointestinal physicians use the device, they will need to have ancillary providers (registered dieticians and nurses) available to assist with care.”\textsuperscript{37} However, one research expert stated, “If you can keep patients away from bariatric surgery and resolve their comorbidities, this will be a moderate change.”\textsuperscript{41}

**Health disparities:** Overall, experts did not expect the intervention to reduce disparities because many insurers seem unlikely to cover the technology and less-affluent patients, who represent a greater share of the overweight population, are unlikely to be able to afford the expected out-of-pocket costs. One clinical expert noted, “The device only has potential to impact health disparities in a profound way if third party payers, particularly public plans, will provide reimbursement for it. I am not particularly optimistic that they will.”\textsuperscript{37} Experts generally thought it difficult to predict the intervention’s cost impact because short-term savings from improved health with the device could diminish or disappear if weight is regained over the long term. One clinical expert noted, “There may be short term decreases in health care costs for patients, who, while losing weight, show improvements in weight-related health problems. However, these are likely to remit over time with weight regain once the device is removed at 6 months.”\textsuperscript{37} Another clinical expert noted, “The procedure is less expensive than bariatric surgery but is more expensive than 6 months of medication (including new medications). If weight loss is sustainable, healthcare costs could be saved. If not, costs would increase to an extent. One would expect that weight loss would not be sustainable in most people after the balloon is removed, though medication could be used to help with this.”\textsuperscript{38}
Liraglutide (Saxenda) for Treatment of Obesity

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a need for novel pharmacologic therapies aimed at weight reduction when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly elevated FDA’s regulatory bar for gaining approval, with developers required to provide long-term safety data with new drug applications and commit to long-term postmarket studies. Until mid-2012, orlistat, a pancreatic lipase inhibitor that blocks about one-third of daily fat absorption, was the only FDA-approved antiobesity drug available for long-term use in the United States, and remains the only one approved for adolescent use. FDA approved three other drugs—phentermine/topiramate, lorcaserin, and naltrexone/bupropion—between 2012 and the end of 2014. Because these drugs may not provide dramatic weight loss for many patients, more effective pharmacotherapies are needed that can offer more options to patients who are not yet candidates for invasive bariatric surgery.

Intervention: Liraglutide is a synthetic analogue of the peptide hormone glucagon-like peptide-1 (GLP-1) that has been shown to suppress appetite and energy intake and delay gastric emptying, which may induce a feeling of satiety. GLP-1 is a naturally occurring incretin hormone that stimulates insulin production in the presence of hyperglycemia and blocks the effects of glucagon, a hormone produced in the pancreas that signals the liver to release stored sugar into the bloodstream.

Endogenous human GLP-1 has a short half-life (1–2 minutes); however, liraglutide has been modified to allow binding to serum albumin, which increases its half-life to about 13 hours. It has been demonstrated to help blood glucose control by stimulating insulin release and lowering glucagon secretion in response to high blood glucose levels.

As an antiobesity treatment, liraglutide is self-administered, once daily, by subcutaneous injection using an automatic injection pen with recommended daily dose of 3.0 mg. That is roughly twice the dose used for treating T2DM. The dose range for treating T2DM is 1.2–1.8 mg liraglutide daily. In practice, given that many patients with diabetes are also obese, the drug may fulfill a dual role of managing both diabetes and obesity. Nonetheless, the manufacturer pursued a separate labeled indication for treating overweight and obesity.

Clinical trials: In March 2015, Wilding and colleagues reported on weight loss and adverse events in 3,652 patients in the phase III, randomized, controlled SCALE™ trial (Satiety and Clinical Adiposity-Liraglutide Evidence in Non-Diabetic and Diabetic people). The trial randomly assigned patients who were overweight (BMI of 27 kg/m² or greater with comorbidities) or obese (BMI of 30 kg/m² or greater) to receive once-daily liraglutide or placebo injections plus diet and exercise. The liraglutide group (n=2,432) had 8% mean weight loss compared with 2.6% mean weight loss in the placebo group (n=1,220) after 56 weeks (estimated treatment difference, 5.4%; p<0.0001). Mild to moderate nausea and diarrhea were the most common adverse events in the liraglutide group. Incidence of serious adverse events was not statistically different: 6.3% in the liraglutide group and 5.0% in the placebo group. Liraglutide use was not associated with increased risk of depression or suicidal thoughts. Liraglutide use showed higher incidence than placebo for gallbladder-related adverse events (3.1 vs. 1.4 events per patient-year of exposure) and acute pancreatitis (0.4 vs. <0.1 events per 100 patient-years at risk). Liraglutide use also showed increased lipase activity, but most elevations were transient and not predictive of pancreatitis. Liraglutide reduced mean systolic and diastolic blood pressure versus placebo (estimated treatment difference [ETD] -2.8 and -0.9 mm Hg; p<0.001) but increased mean pulse (ETD 2.4 beats/minute; p<0.0001). Cardiovascular events were not statistically different with liraglutide and placebo (8.7% vs. 9.9%, respectively). Investigators noted that the safety profile of liraglutide 3.0 mg injection was
consistent with known effects of GLP-1 receptor agonists. Investigators also reported that liraglutide injection improved fasting and post-load glycemia level compared with placebo (ETD: fasting plasma glucose -0.38 mmol/L, plasma glucose [oral glucose tolerance test, area under the curve] -2.0 mmol/L, glycated hemoglobin [HbA1c] -0.23%; p<0.0001 for all). More individuals with prediabetes had reverted to normal glycemic levels on liraglutide 3.0 mg than on placebo (69.7% vs. 32.1%; p<0.0001), while more individuals with normal glycemic levels had progressed to prediabetes on placebo than on liraglutide (19.9% vs. 6.9%; p<0.0001). Further, more individuals taking placebo developed T2DM than individuals taking liraglutide (14 vs. 4 individuals; p=0.0003).

**Manufacturer and regulatory status:** Novo Nordisk a/s (Bagsvaerd, Denmark) manufactures liraglutide. In December 2014, FDA approved the drug for injection under the trade name Saxenda® for chronic weight management in addition to a reduced-calorie diet and physical activity. According to FDA, Saxenda’s labeling has a boxed warning that highlights rodent studies linking liraglutide to C-cell tumors of the thyroid gland. However, no link between liraglutide and thyroid C-cell tumors, including a thyroid cancer called medullary thyroid carcinoma (MTC), has been identified in humans. FDA advises that liraglutide should not be used in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (a disease in which patients have tumors in more than 1 gland in their body, which predisposes them to MTC). FDA required a risk evaluation and mitigation strategy (REMS) for approval to inform prescribers of potential risks from liraglutide use. The company must also conduct multiple postmarketing studies for liraglutide: trials to evaluate dosing, safety, and efficacy in pediatric patients; an animal study to evaluate potential effects on growth, sexual maturation, and central nervous system development and function; an MTC case registry of at least 15 years duration to identify any increase in MTC incidence; and an evaluation of the potential risk of breast cancer in ongoing clinical trials. The company is also conducting a cardiovascular outcomes trial. FDA had approved liraglutide injection in January 2010 under the trade name Victoza® as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. In January 2015, liraglutide received approval from the European Commission for weight management in overweight or obese adults in addition to a reduced-calorie diet and physical activity.

**Diffusion:** Since receiving FDA approval to treat obesity in December 2014, Novo Nordisk has announced plans to assign about 500 of its 3,000 U.S. sales representatives to heavily promote Saxenda for obesity treatment in the United States. The company reportedly anticipates reaching “blockbuster” status for the drug with $1 billion in annual sales worldwide, despite other competitors in the obesity drug market. Time will tell the accuracy of the company’s sales projections. A U.S.-based, online aggregator of prescription-drug prices, GoodRx, lists the price of a carton of liraglutide containing five 3 mL pens at a dose of 3 mg/0.5 mL ranging from $1,087 to $1,175 at various pharmacies, with most requiring the use of a coupon. Based on recommended dosing, after the 5-week dose-escalation schedule, one carton of liraglutide represents about a 1-month supply of the drug. Other weight-loss drugs are priced between $200 and $500 (lorcaserin, naltrexone/bupropion, orlistat, phentermine/topiramate) for a 1-month supply.

We searched 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield of Alabama, Blue Cross/Blue Shield of Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) to identify policies that mention Saxenda or liraglutide injection for treating obesity. The following payers address Saxenda in their coverage policies or formularies. Depending on plan language, Aetna may cover liraglutide (Saxenda) for obesity when selection criteria are met; however, “many Aetna plan benefit descriptions specifically exclude services and supplies for or related to treatment of obesity or for diet and weight control.” CIGNA requires prior authorization for Saxenda
prescriptions for obesity. Medica considers Saxenda a tier 3 drug with step-therapy requirements.

Clinical Pathway at Point of This Intervention

Endocrine Society clinical guidelines on using pharmacology to manage obesity suggest using FDA-approved weight-loss medications (over no medication therapy) to improve comorbidities and adherence to behavior changes, which they state may improve physical functioning and enable more physical activity in individuals with BMIs of 30 kg/m² or more or in individuals with BMIs of 27 kg/m² or more and at least one obesity-related comorbid condition. The guidelines further recommend that clinicians monitor obesity drug safety and efficacy at least monthly for the first 3 months, then at least every 3 months in all patients prescribed weight-loss medications. If clinicians determine drug therapy is safe and effective, defined as weight loss of 5% or greater of body weight at 3 months, the guidelines recommend continuing the medication, and stopping if ineffective or unsafe. Further, the Endocrine Society guidelines state, “In patients with T2DM who are overweight or obese, we suggest the use of antidiabetic medications that have additional actions to promote weight loss (such as glucagon-like peptide-1 [GLP-1] analogs or sodium-glucose-linked transporter-2 [SGLT-2] inhibitors), in addition to the first-line agent for T2DM and obesity, metformin.” Thus, liraglutide injection would be used as adjunctive therapy to diet and lifestyle/behavior modification for patients with obesity.

Figure 2. Overall high-impact potential: liraglutide (Saxenda) for treatment of obesity

Overall, experts thought that liraglutide has potential to fulfill an unmet need for new alternatives to highly invasive bariatric surgery. Several experts noted that the moderate weight loss that liraglutide offers would be complemented by the potential to improve some measures of comorbid diabetes. Experts cited the cost, need for daily injections, and unknown long-term safety profile as potential barriers to wider acceptance from patients and physicians. Generally, experts did not expect liraglutide use to substantially alter health care disparities or disrupt health care infrastructure or existing patient management procedures. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on liraglutide. One clinical expert reported consulting relationships with other manufacturers of antiobesity medical devices. This conflict of interest is counterbalanced by views of the other experts, who reported no potential conflict of interest. We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts cited a moderate to large unmet need for new obesity treatments, especially pharmacotherapies, that could be options in a treatment continuum...
between highly invasive bariatric surgery and diet and lifestyle modifications to improve patient outcomes and address the needs of an increasing population with obesity and comorbid conditions. However, two experts with research and health systems backgrounds thought that the availability of several other treatment options for obesity minimizes the potential unmet need. Most experts believe that liraglutide has good potential to improve patient outcomes as adjunctive treatment to aid in weight loss. One clinical expert noted, “Weight loss, more than the specific properties of the medication, has great potential to improve health. Liraglutide also may have added benefits related to the treatment of type 2 diabetes.” However, another clinical expert and a research expert anticipated that liraglutide would have smaller potential to improve patient health, although they thought liraglutide has good potential to fulfill an unmet need. One clinical expert stated, “Despite the limitations and concerns, this is a novel agent in the overall paucity of antiobesity medications. Particularly for the low BMI category that may not be amenable to surgical options, being provided with a new option that may also prevent secondary metabolic disease states or help correct obesity-associated T2DM as an adjunct benefit, it fulfills a moderate unmet need. Separately, newer similar agents brought to market will likely serve as a natural source of market competition that may help reduce the anticipated cost burden to the patient. Studies better defining the potential long-term risks (breast cancer and cardiovascular risks) need to be determined before likely seeing wider acceptance.” However, four experts anticipated that liraglutide is less likely to fulfill the unmet need. One clinical expert and one research expert cited the drug’s safety concerns, cost, and need for daily injections as reducing its appeal to many patients and therefore, lowering its potential to fulfill the unmet need.

Acceptance and adoption: Experts were divided on how patients and physicians would accept liraglutide for weight loss. Three experts with research and clinical backgrounds thought that health care providers would be more accepting of the drug, because of its potential for weight loss and diabetes improvement, than patients, who might be less willing to undergo daily injections. One clinical expert stated, “Providers are frequently looking for new weight loss treatments. The previous acceptance, usage, and safety profile of liraglutide will promote acceptance among providers. However, the cost may discourage some providers from recommending it to those from lower socioeconomic status groups and without insurance coverage for the medication.” Most experts thought that liraglutide would likely have a moderate effect on health care costs. They suggested that liraglutide’s higher treatment cost compared with some other obesity drugs would be offset by its potential to reduce costs for treating obesity-related complications over the long term.

Two research experts thought that the drug would likely have a larger potential impact on out-of-pocket treatment costs for patients and on costs for payers that provide coverage for the drug.

Health care delivery infrastructure and patient management: Experts agreed that the use of liraglutide is unlikely to disrupt health care infrastructure because it is a self-injectable drug. Similarly, most experts thought that the drug would have a limited disruption on the way most patients with obesity are managed. The new drug would likely be added to other drugs and counseling used by clinicians to help patients manage their conditions. Two research experts thought that the need to train patients to administer a self-injected drug could represent a somewhat bigger change to the way patients are managed. One clinical expert and one health systems expert anticipated that patients might more widely accept liraglutide than physicians, because of its potential health benefits. One health systems expert noted, “Patients are likely to moderately accept liraglutide, mostly due to its success in clinical trials. Ultimately patients are more likely to be persuaded by successful clinical trials, albeit not enough evidence, and are more likely to continue trialing new interventions until the problem (obesity) is resolved.” One research expert expected low adoption from both patients and clinicians due to liraglutide’s long-term safety concerns, cost, and need for daily injections that could deter continued use.
**Health disparities:** Generally, experts did not expect liraglutide to substantially change health care disparities, although the cost could decrease access to the drug for less-affluent populations that might be more affected by obesity. One clinical expert noted, “There are significant health disparities issues in obesity and a great need for affordable medications to help those with obesity and from lower socioeconomic groups. Unfortunately, the projected price point makes it unlikely that it will impact the health disparities gap.”\(^7\)
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