Select Health Medical Policies

Gastroenterology Policies

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MEDICAL POLICY

BRAVO PH MONITORING PROBE

Policy # 200
Implementation Date: 10/10/03
Review Dates: 11/18/04, 9/7/05, 12/21/06, 12/20/07, 12/18/08, 12/16/10, 12/15/11, 4/12/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 6/24/18, 4/23/19, 4/6/20, 4/15/21, 3/18/22, 4/20/23, 4/29/24, 4/8/25
Revision Dates: 12/19/09

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1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

The Bravo System consists of a capsule (about the size of a gelcap) that is temporarily attached to the wall of the esophagus with a proprietary delivery system. Throughout the study period, the capsule transmits pH data through radiotelemetry to a pager-sized receiver worn by the patient. Data is later downloaded to Medtronic software for analysis. Within 7 to 10 days of being attached, the Bravo capsule spontaneously detaches and passes through the digestive tract.

Modalities used to diagnose gastroesophageal reflux disease (GERD) include an empiric trial of acid-suppressing medications, endoscopy, motility studies, esophagography, and pH monitoring. Of these tests, only pH monitoring provides a direct measure of the extent to which acid is refluxing into the esophagus.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health covers the Bravo pH probe for the evaluation of gastroesophageal reflux.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

There are no systematic reviews available and, to date, no published studies in the peer-reviewed literature. FDA approval was based on the "substantially equivalent" [510(k)] principal; that is substantially equivalent (SE) to another legally marketed device - in this case, conventional pH monitoring devices. While the studies submitted to the FDA by the developer of the device, Endonetics, have not been identified, it is believed that they are represented by the abstracts provided to SelectHealth by Endonetics

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(now owned by Medtronic). According to Streets, et al., "… the quantification of esophageal pH levels by each method is similar," so the primary issues would then seem to be the reliability and accuracy of the transmitter/-receiver technology and the delivery and "sloughing" of the pH capsule to the gastro-esophageal junction. In the study reported by Antoniazzi, concordance between the Bravo system and conventional pH monitoring was determined in 20 asymptomatic volunteers—there were statistically different pH values in one of the measures, but most measures were not different. Clinical scores were equivalent. In the Ours et al. abstract 4 patients with GERD seemed to be distinctly more satisfied with the Bravo as compared to the conventional pH monitoring experience. The other studies reported various facets of esophageal pH monitoring with the Bravo system, but none seemed to represent a well-conceived and conducted trial comparing the two alternatives.

The FDA has determined that the Bravo device/system is equivalent to conventional esophageal pH monitoring devices. This is supported by a retrospective analysis (Ang D et al.) of Asian patients with heartburn symptoms undergoing both Bravo and conventional pH monitoring showed no differences in the diagnostic yield of non-erosive reflux disease and functional heartburn.

Afaneh et al. conducted a review of patients who underwent Bravo testing for suspected GERD and found that it can be more cost-effective than prolonged empiric PPI trial. Other studies (de Bortoli et al.) have shown it is primarily a helpful evaluation of non-cardiac chest pain, though it suffers in its inability to detect non-acid reflux events.

It is safe and well-tolerated across different populations, especially children who would not otherwise tolerate the conventional pH probe which is usually placed through the nasal route.

The updated American College of Gastroenterology guidelines on Diagnosis and Management of GERD recommends the use of ambulatory pH monitoring for several indications as follows: patients expecting surgical management of GERD without evidence of erosive esophagitis, and reflux monitoring (off PPI) in patients who have GERD refractory to PPI therapy

In summary, these newer studies add to the knowledge of safety and efficacy of Bravo esophageal pH testing.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

91035	Esophagus, gastroesophageal reflux test; with mucosal attached telemetry pH electrode placement, recording, analysis and interpretation

HCPCS CODES

No specific codes identified

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Bravo PH Monitoring Probe, continued

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MEDICAL POLICY

COLONIC MANOMETRY

Policy # 619
Implementation Date:10/2/17
Review Dates: 10/14/18, 10/20/19, 10/15/20, 12/4/21, 9/15/22, 10/13/23, 11/1/24
Revision Dates:

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Description

Colonic motility studies including colonic manometry are used to assess the flow of intraluminal contents, the motions of the colonic wall that induce flow, and the control systems that integrate and regulate these processes. The approaches employed have consisted of manometric techniques to record colonic contractions, barostatic methods to measure colonic tone, and recordings of myoelectric signals from the colon that initiate and control muscular contractions.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover colonic manometry (colonic motility studies), as this testing is considered experimental/investigational because clinical utility has not been established.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The study of colonic motility in a clinical setting proves to be difficult. Accurate positioning of the probes via colonoscopy requires pre-procedure cleansing of the colon, which raises the possibility of altered physiology. Recording of intraluminal pressure, by means of manometric catheters inserted into the rectum, requires prior bowel cleansing, which may modify colonic motility.

In contrast to other segments of the gastrointestinal tract, contents move through the colon in hours or days, instead of seconds to minutes; thus, prolonged observations are needed. Moreover, the larger diameter of the colon hinders the accurate detection of the upper gastrointestinal tract for manometric events. Furthermore, interpretation of intraluminal pressure measurements is complicated, because many

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contractions of the colonic wall do not occlude the lumen, and therefore, are detectable by manometry only if they cause significant pressure changes.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM)'s practice guideline for small bowel and colon transit (Maurer et al., 2013) noted that: "A position paper from the American Neurogastroenterology and Gastrointestinal Motility Society and the European Society of Neurogastroenterology and Motility states that scintigraphy is recommended for 'detection of altered small-intestine transit in subjects with suspected diffuse gastrointestinal motility disorder' and that colon transit scintigraphy 'offers reproducible and accurate performance,' as it measures whole-gut and regional colon transit in patients with suspected colonic motility disorders or more diffuse disorders involving the stomach or small intestine."

Dinning and colleagues (2016) noted that the past few years have seen an increase in the number of research and clinical groups around the world using high-resolution manometry (HRM) to record contractile activity in the anorectum and colon. Yet despite the uptake and growing number of publications, the clinical utility and potential advantages over traditional manometry remain undetermined. Nearly all the publications in the field of anorectal and colonic HRM have been published within the last 3 years. These studies have included some data on normal ranges in healthy adults, and abnormalities in patient groups with constipation or fecal incontinence, anal fissure, perineal descent, rectal cancer, and Hirschsprung's disease. Most of the studies have been conducted on adults, with only 3 published studies in pediatric populations. Very few studies had attempted to show advantages of HRM over traditional manometry. The authors concluded that high-resolution anorectal and colonic manometry provided a more comprehensive characterization of motility patterns and coordinated activity; this may help to improve the understanding of the normal physiology and pathophysiology in these regions. To date, however, no published study has conclusively demonstrated a clinical, diagnostic, or interventional advantage over conventional manometry.

An UpToDate review on, "Etiology and evaluation of chronic constipation in adults" (Wald, 2017), states that: "Colonic manometry evaluates intraluminal pressure activity of the colon and rectum and provides detailed information about the qualitative aspects such as pattern of motor activity and quantitative aspects of colonic motility. It can be combined with a barostat apparatus to assess colonic tone, compliance, and sensation. Patients can be identified to have normal, myopathic, or neuropathic colon as well as sensory dysfunction. As yet, there is no evidence that such information has added value to the management of chronic constipation in clinical practice and this test is available for clinical use in only selected centers."

And finally, all these techniques, which continue to be used extensively in a research context, have not yet been standardized for routine clinical use.

Billing/Coding Information

CPT CODES

91117	Colon motility (manometric) study, minimum 6 hours continuous recording (including provocation tests, eg, meal, intracolonic balloon distension, pharmacologic agents, if performed), with interpretation and report
91132	Electrogastrography, diagnostic, transcutaneous;
91133	Electrogastrography, diagnostic, transcutaneous; with provocative testing

HCPCS CODES

No specific codes identified

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Colonic Manometry, continued

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MEDICAL POLICY

DNA ANALYSIS OF STOOL FOR COLON CANCER SCREENING (COLOGUARD)

Policy # 260
Implementation Date: 1/3/05
Review Dates: 1/13/06, 1/26/07, 2/21/08, 2/26/09, 2/18/10, 2/17/11, 2/16/12, 4/25/13, 2/20/14, 3/19/15, 2/11/16, 4/27/17, 4/11/19, 4/20/20, 4/12/21, 3/16/22, 3/31/23, 3/31/24, 3/28/25
Revision Dates: 10/15/14, 5/17/16, 5/2/2018, 8/3/18, 11/29/18, 4/1/19, 9/16/21, 12/19/23, 8/26/24

Description

Colorectal cancer is one of the most preventable cancers, yet it is the second leading cause of cancer death in the United States. In 2002, approximately 148,300 men and women in the U.S. will be diagnosed with colorectal cancer; 5,900 in Utah. Although mortality has declined over the past 20 years (25% for women and 13% for men), an estimated 56,600 deaths will be due to colorectal cancer in 2002. Without preventive measures, approximately 5%–6% of Americans will develop colorectal cancer at some point in their lives. When colorectal cancer is detected at an early, localized stage, the 5-year survival rate is 90%; however, only 37% of cases are diagnosed at this stage. Unfortunately, the current overall survival rate is about 50%, since many cancers are detected at later stages.

While many cancers are associated with a variety of exogenous risk factors (e.g., diet and environment), Vogelstein and colleagues discovered that during the pathogenesis of colorectal cancer, a cell acquires numerous genetic changes. These changes are caused by a failure of cells to repair DNA after damage from carcinogens. The function of DNA mismatch repair genes is to maintain the fidelity of DNA during replications. Mutations of these genes may result in alterations in the repeating sequences of bases, referred to as microsatellites. Microsatellite instability (MSI) refers to alterations in tumor microsatellites compared to the pattern of microsatellites found in unaffected tissues. In patients with known colorectal cancer, detection of MSI in tumor tissue has been used as a triage technique to determine which patients might benefit from further genetic testing to detect the genetic mutations associated with hereditary non-polyposis colon cancer (HNPCC). For example, it is thought that MSI is present in over 90% of colorectal cancers associated with HNPCC mutations. However, recently, there has been interest in evaluating MSI from shed colorectal cancer cells isolated from stool samples. Two general populations of patients have been studied:

- Known or suspected carriers of HNPCC mutations, considered at high risk of developing colorectal cancer. In this setting, testing of fecal samples for MSI may be used to monitor patients for development of colorectal cancer. The test may be used either in lieu of routinely scheduled surveillance colonoscopies, or during intervals between scheduled colonoscopies. Those patients testing positive for MSI may be further evaluated with colonoscopy.
- In patients at average risk of colorectal cancer. In this setting, testing of fecal samples for MSI may be offered in lieu of, or as an adjunct to, other recommended colorectal cancer screening tests, including fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, or double contrast barium enema.

On August 11, 2014, Cologuard was approved by the FDA. This is the first stool-based colorectal screening test that detects the presence of red blood cells and DNA mutations. Cologuard utilizes a multi-target approach to detect DNA and hemoglobin biomarkers associated with colorectal cancer and pre-cancer.

Eleven biomarkers are targeted and provide a stronger connection between colorectal cancer and precancer. Methylation, mutation, and hemoglobin results are combined in the laboratory analysis to provide a single positive or negative reportable result.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers Cologuard once every 3 years for stool for colon cancer screening when all the following criteria are met (Effective April 1, 2019):

1. Ages 45 to 75 years old
2. Patients who show no signs or symptoms of colorectal disease, including but not limited to:
    a. Lower gastrointestinal pain
    b. Blood in stool
    c. Positive fecal occult blood test or fecal immunochemical test
3. No prior history of abnormal fecal DNA test
4. Patients who are at average risk for developing colorectal cancer:
    a. No personal history of adenomatous polyps colorectal cancer or inflammatory bowel disease (Crohn's Disease and Ulcerative Colitis)
    b. No family history of colorectal cancer or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer
    c. No personal history of getting radiation to the abdomen (belly) or pelvic area to treat a prior cancer
5. Member has not had a colonoscopy after Cologuard has been performed (assumption: Cologuard had a positive result)

Select Health does not cover the Guardant Health Shield blood test in the evaluation of colorectal cancer. This test is considered not medically necessary as the clinical utility has not been determined due to a lack of evidence available in peer-reviewed literature supporting either sufficient sensitivity or specificity.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

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Summary of Medical Information

As with any diagnostic test, the key outcomes are the diagnostic performance (i.e., sensitivity, specificity, positive and negative predictive value) compared to a gold standard, and consideration of how the results of the test will be used to benefit patient management. Of the various screening options (fecal occult blood testing, flexible sigmoidoscopy, double contrast barium enema, colonoscopy), colonoscopy is considered the gold standard. For example, in patients considered at high risk for colorectal cancer, due either to a family history or HNPCC mutation, colonoscopy at varying intervals is recommended by the American Society of Colorectal Surgeons, the American Gastroenterological Society, and the American Cancer Society. Therefore, for patients at high risk of colorectal cancer with suspected or known mutations of the HNPCC gene, the diagnostic performance of DNA analysis of stool samples will be compared with colonoscopy. In addition, the role of DNA analysis in the context of the recommended colonoscopic screening must be explored. Will this test be offered in lieu of colonoscopy, such that patients with a negative test can defer a scheduled colonoscopy, or will this test be offered as an adjunct to colonoscopy screening, for example during the intervals between colonoscopies.

For patients at average risk to moderate risk for colorectal cancer, the above organizations also recommend colonoscopy starting at age 50, with an interval of 10 years, as one screening option. In addition, other screening techniques are also considered options, and the choice of screening option may be dictated in part by patient preference. Many authors have noted the low patient acceptance of current colorectal cancer screening options, particularly flexible sigmoidoscopy and colonoscopy; at the present time only about 40% of eligible patients undergo screening for colon cancer. Advocates of genetic testing of stool samples have hypothesized that the relative simplicity of collecting a stool sample might increase the overall compliance with screening recommendations. Therefore, for patients at average to moderate risk of colon cancer, genetic testing of stool samples will be compared to colonoscopy and also to fecal occult blood testing, the other entirely noninvasive technique. Patient acceptance of the different options is also a relevant outcome as a technique to increase screening compliance.

The available published, peer-reviewed data focus on the technical feasibility of genetic testing of stool samples. For example, Ahlquist and colleagues published a study focusing on the use of a multitarget assay panel for colorectal cancer screening. This retrospective study included 22 patients with known colorectal cancer, 11 with adenomas, and 28 patients with normal colonoscopy examinations. It was not reported whether these patients were considered at average, moderate, or high risk for cancer. The panel included 15 sites on the KRAS gene, p53 and adenomatous polyposis genes, analysis of BAT-26, and highly amplifiable DNA. The panel detected 20 of the 22 cancers (91%) and 9 of the 11 adenomas (82%). The same panel assay was performed on tissue samples from 19 of the 21 cancers. The presence of point mutations was concordant in tissue and stool analysis in 12 of the 19 paired specimens. The authors attributed the high neoplasm detection rate of the stool analysis to the efficient isolation of human DNA from the stool, but also commented that cancers represented in this study were large (median 4 cm in diameter) and symptomatic, and thus may shed more aberrant DNA than smaller cancers. For the 11 patients with adenomas, the results of the stool DNA testing were compared to fecal occult blood testing. While the fecal occult blood testing was negative in all these patients, genetic mutations were detected in the stool sample of all patients with adenomas.

Dong and colleagues performed a study of stool DNA isolated from 51 colorectal cancer patients. The stool DNA and tumor tissue were evaluated for the presence of mutations in the genes p53, BAT-26, and KRAS. The 3 genetic markers together detected 71% of the 51 patients. Of interest, no genetic mutations were identified in the tumor tissue of 15 patients. Other feasibility studies using a variety of markers have also focused on patients with known cancers, and thus these studies do not duplicate the targeted populations for screening. No prospective studies were found in the published literature comparing the diagnostic performance of analysis of DNA from stool samples to either colonoscopy or fecal occult blood

testing among either average to moderate risk to high-risk patients. For average risk patients, the published feasibility studies focused on the use of different panels of DNA markers. No study identified focused on the use of the single marker, BAT-26, in patients with known or suspected mutations of the HNPCC gene. No studies discussed how the use of DNA analysis in stool samples might supplant or enhance current screening options.

An updated search of the literature based on MEDLINE through October 2004 did not return any new prospective clinical trial data that addresses the issues described above. In addition, both the American Cancer Society and the American Gastroenterological Association do not recommend analysis of human DNA in stool samples for colorectal screening. The American Cancer Society's Colorectal Cancer Advisory Group concluded that there is insufficient evidence to determine whether fecal DNA testing can be recommended for average-risk individuals. The advisory group noted further studies are needed to determine the most appropriate and best combination of markers for DNA detection and results of testing in average-risk populations. These guidelines note screening for altered DNA in stools is a promising technology, however, further research is required before DNA analysis in stools can be recommended as a screening tool for colorectal cancer.

No other medical specialty society or other related health organization has issued a policy statement, practice guidelines, or position statement that endorses the use of the analysis of fecal DNA as a screening test for colorectal cancer including the American College of Physicians, the American College of Colorectal Surgeons, and the National Cancer Institute.

An updated review of the published literature completed in May 2016, identified one systematic review and 5 primary studies which met inclusion criteria for review. Most prominent of the articles were those by Imperale et al. and Redwood et al. both related to Cologuard. The systematic review was based primarily on the Imperiale et al. article and concluded that the test is most likely to reduce CRC-related death than FIT but with higher resource utilization. However, this assumption is based on annual, not triennial, administration of the test.

Notably, the study by Imperiale et al., was a non-randomized, cross-sectional, multicenter trial of 9,989 patients who were included in the primary analysis. Results from a single, albeit large, study show that Cologuard has better sensitivity and worse specificity than FIT across various clinical manifestations. The other 2 included studies are 1) a model that is based on incorrect pricing information and 2) a study unique to a specific population no relevant in a broad sense. Though the test has a recommended use of once every 3 years, 1 systematic review illustrated its benefit is best if used annually. This may impact its cost effectiveness in real world settings.

Billing/Coding Information

CPT CODES

81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

Not covered when billed for the indications listed above

81479	Unlisted molecular pathology procedure

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Revision History

Revision Date	Summary of Changes
12/19/23	For Commercial Plan Policy, added criterion #4c: "No personal history of getting radiation to the abdomen (belly) or pelvic area to treat a prior cancer" to align with updated societal guidelines.
8/26/24	For Commercial Plan Policy, added an exclusion for the Guardant Health Shield blood test.

Select Health

Select Health

MEDICAL POLICY

DRUG MONITORING FOR MONOCLONAL ANTIBODY THERAPY IN INFLAMMATORY BOWEL DISEASE AND OTHER DISORDERS

Policy # 532
Implementation Date: 7/31/13
Review Dates: 6/19/14, 6/11/15, 6/16/16, 6/15/17, 6/21/18, 6/25/19, 6/10/20, 6/17/21, 5/21/22, 6/15/23, 6/20/24, 6/22/25
Revision Dates: 5/27/14, 5/15/19, 2/26/20, 6/2/22, 6/19/25

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description
Monoclonal antibodies are biologic substances with unique mechanisms of action directed towards specific target cells. Their use has become widespread in a variety of disorders including inflammatory bowel disease (IBD), rheumatologic and vasculitis disorders, skin conditions, and cancer.

IBD refers to ulcerative colitis (UC) and Crohn's disease, as well as idiopathic diseases affecting the gastrointestinal (GI) tract. Although the clinical course of IBD is chronic and often relapsing and remitting, mortality is generally not greater than in the general population. Patients may require monoclonal antibody therapy for remission in these diseases.

Monoclonal antibodies are also used in rheumatologic disorders, vasculitis disorders, and skin disorders as disease-modifying therapy. Patients with these disorders usually have a broad range of medications available, so antibody testing is less utilized because a patient can be switched to another drug if the current drug is not maintaining disease remission and the data on antibody testing in this subset of patients is limited.

Patients who are treated with infliximab, adalimumab, ustekinumab, vedolizumab, or certolizumab, may have varying serum levels of the drug, even among equally-dosed patients. Patients may develop antibodies to these biological agents, and this is postulated to reduce the efficacy of these treatments. Measuring serum levels may aid physicians in correctly dosing their patients undergoing these therapies for any of the indicated disorders.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health commercial plans cover drug and antibody level monitoring in tumor necrosis factor (TNF) medications used in the treatment of IBD. The clinical utility of these tests is supported by AGA guidelines*. One of the following criteria must be met:

- Patient has active symptoms related to IBD that are confirmed with objective findings from biochemical markers, endoscopic, or radiologic findings of active inflammation.

Select Health

OR

- Patients are asymptomatic, clinically, but have findings of objective inflammation on endoscopy, radiologic findings, and/or biochemical markers.

Select Health commercial plans do not cover drug and antibody level monitoring for all other disorders (e.g., rheumatologic disorders, vasculitis, skin disorders) due to inadequate literature; this meets the plan's definition of experimental/investigational.

Select Health commercial plans do not cover the Prometheus Anser ADA test, the Prometheus Anser IFX test, the Prometheus Anser VZD test, the Prometheus Anser UST test, and the Prometheus Anser RZB test. Other equivalent laboratory tests are covered when one of the medical necessity criteria have been met.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Antibodies to infliximab, adalimumab, ustekinumab, vedolizumab, or certolizumab, are present in a substantial number of patients treated with these drugs for IBD, and there may be a correlation between the level of these antibodies and clinical response. However, the clinical utility of measuring antidrug antibody concentrations has not been established, as it is not known how patient management would change based on test results. In addition, there are technical factors relating to the use of different assay methods across studies—it has not yet been established whether the use of threshold levels aids in the discrimination of treatment response—nor has the optimal timing of when to measure antibody levels been established. Regardless, consensus statements have supported the use of therapeutic drug monitoring, or "TDM", in patients diagnosed with IBD and on monoclonal antibody therapy.

It is clinically unproven whether low serum concentrations of these drugs cause clinical non-responses in individuals and/or at what serum concentration levels are non-responses seen for these drugs. Clinical trials are lacking in whether these concentrations make a clinical difference in response to treatment. However, for IBD, there are recommendations from the AGA for testing if disease remains active. Similar recommendations do not exist for monoclonal therapy for other disorders, but this testing may be useful if a patient has limited remaining drug choices with a decreasing response while on a monoclonal antibody. A supported strategy for incorporating serum concentration testing is utilizing this test instead of empirically dose optimizing monoclonal antibody therapy.

Billing/Coding Information

CPT CODES

84999	Unlisted chemistry procedure
80299	Quantitation of therapeutic drug, not elsewhere specified

82397	Chemiluminescent assay
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

HCPCS CODES

J1745	Injection, infliximab, excludes biosimilar, 10mg
J0135	Injection, adalimumab, 20 mg
J0717	Injection, certolizumab pegol, 1 mg
J2323	Injection, natalizumab, 1 mg
J3357	Ustekinumab, for subcutaneous injection, 1 mg
J3358	Ustekinumab, for intravenous injection, 1 mg
J3380	Injection, vedolizumab, 1 mg
S9359	Home infusion therapy, anti-tumor factor intravenous therapy; (e.g. infliximab); administrative services, professional pharmacy service, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
Q5103	Injection, infliximab-dyyb, biosimilar (inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar (renflexis), 10 mg
Q5109	Injection, infliximab-qbtx, biosimilar (ixifi), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar (avsola), 10 mg

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Revision History

Revision Date	Summary of Changes
6/19/25	For Commercial Plan Policy, added clarifying language regarding TNF medications used in the treatment of IBD, and added an exclusion for the Prometheus Anser RZB test.

Select Health

Drug Monitoring in Inflammatory Bowel Disease, continued

Select Health

MEDICAL POLICY

ENDOSCOPIC ABLATIVE THERAPIES IN THE TREATMENT OF BARRETT'S ESOPHAGUS

Policy # 322

Implementation Date:10/31/06

Review Dates: 5/17/07, 4/24/08, 8/16/11, 8/16/12, 8/15/13, 6/19/14, 2/16/17, 2/15/18, 2/10/19, 2/17/20, 2/18/21, 1/20/22, 2/16/23, 2/4/24, 2/4/25

Revision Dates: 4/23/09, 4/22/10, 9/8/15, 2/26/24

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Barrett's esophagus is a condition in which an abnormal, intestinal-type epithelium, called specialized intestinal metaplasia (columnar epithelia), replaces the stratified squamous (flat, fish-shaped epithelial cells) epithelium that normally lines the distal esophagus.

Individuals with Barrett's esophagus are at elevated risk for esophageal adenocarcinoma and the primary reason for managing Barrett's esophagus is cancer prevention. Cancers in Barrett's esophagus evolve through a sequence of DNA alterations that cause morphological changes to esophageal tissue that produce dysplasia. Dysplasia is a constellation of histological abnormalities suggesting that one or more clones of cells have acquired genetic damage rendering them neoplastic and predisposed to malignancy. Dysplasia is graded as low- or high-grade based upon the severity of architectural and cytologic features. The rate at which low-grade dysplasia progresses to high-grade dysplasia is unclear. Cumulative incidence estimates range from 5%–28%. These uncertainties make prediction of cancer occurrence in patients with Barrett's more difficult.

The length of the abnormal mucosa and the degree of dysplasia are the primary risk factors for development of cancer. While most esophageal adenocarcinomas arise from Barrett's esophagus, the annual incidence of adenocarcinoma in all patients with Barrett's esophagus ranges from 0.2%–2.0%. Data from multiple prospective studies suggest that the mean annual incidence of esophageal cancer in this condition is approximately 1%. However, this estimate may be influenced by publication bias among studies reporting the incidence of cancer in Barrett's esophagus. An annual incidence of approximately 0.5% may be more accurate after adjusting for this effect. The risk of developing esophageal cancer is increased at least 30 times above that of the general population. High-grade dysplasia is the stage immediately preceding cancer, and these individuals are at higher risk for esophageal adenocarcinoma (annual estimates range between 2%–62%).

Most patients with Barrett's esophagus will never go on to develop this cancer and esophageal adenocarcinoma is a rare cause of death in Barrett's esophagus patients. Most of these patients die from other causes. Many Barrett's patients are elderly and succumb to common diseases such as coronary artery disease before developing adenocarcinoma in their esophagus. Furthermore, some studies demonstrate that the overall survival of patients with Barrett's esophagus is no different than that of the general population. Even in those studies that reported lower survival in patients with Barrett's, the authors indicated that the elevated death rate was not due to esophageal adenocarcinoma.

There are several different procedures used to treat Barrett's esophagus. Photodynamic therapy (PDT) uses an intravenous drug called porfimer sodium (Photofrin) that makes Barrett's cells sensitive to light. A few days later, the clinician activates the drug inside the esophagus with a laser light inserted through an endoscope. The interaction between light and the drug create energy that is transmitted to surrounding

Select Health

tissue, killing the targeted cells. Radiofrequency ablation (RFA) uses controlled bursts of radiofrequency energy to burn away thin layers of esophageal tissue; the Halo 360 System from BARRX Medical is just one of several radiofrequency systems available.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers radiofrequency ablation (RFA) or cryoablation for the treatment of Barrett's esophagus for patients with high-grade or low-grade dysplasia.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For this policy, specifically, there are no CMS criteria available; therefore, the Select Health Commercial policy or InterQual criteria apply. Select Health applies these requirements after careful review of the evidence that supports the clinical benefits outweigh the clinical risks. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The research literature on endoscopic ablative therapies for Barrett's is most extensive for photodynamic and argon plasma coagulation therapies. The literature on cryoablation (1 study), multipolar electrocoagulation (5 studies), laser (5 studies), and radiofrequency therapies (4 studies) is comparatively sparse and conclusions about these treatments are extremely limited.

High-Grade Dysplasia: In 2002, Hayes gave PDT for Barrett's esophagus with high-grade dysplasia a 'C' (investigational/experimental), reflecting inconclusive evidence regarding long-term efficacy. The report concluded that while preliminary data were encouraging, the small sample sizes and short follow-up prevented a determination about whether PDT prevents early-stage esophageal cancer. A more recent report from the California Technology Assessment Forum (2005) similarly concluded that the available research evidence was insufficient to conclude that PDT was any more effective than surveillance at preventing esophageal cancer.

We identified an additional 17 studies on PDT published since the 2002 Hayes report; 14 studies on APC met criteria for inclusion in this report. The studies on PDT evaluated a variety of treatment schedules and photosensitizers including (porfimer sodium m-tetrahydroxyphenyl chlorin, delta-ALA, and 5-aminolevulinic acid). The median follow-up period of the clinical studies was 31.5 months (range = 1–51) and the median sample size was 48.5 (range = 12–208). The median follow-up period for APC studies was 14 months (range = 9–84) with a median sample size of 33 (range = 7–70). These studies frequently combined results of patients with metaplasia, low- and high-grade dysplasia, and early adenocarcinoma, which complicate interpretation of study results.

These studies generally conclude that PDT and APC are both effective at eliminating or reducing the intestinal metaplasia associated with Barrett's esophagus. For example, a 2005 randomized controlled trial by Overholt et al. involved 208 Barrett's patients with high-grade dysplasia from 30 clinical centers.

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These patients were randomized to either PDT with porfimer plus omeprazole, or to omeprazole alone. Combination therapy produced complete ablation of dysplasia more frequently than did omeprazole alone (77% vs. 39% of cases). At 2 years, 13% of the PDT patients had developed adenocarcinoma compared with 28% of patients treated for GERD symptoms.

In a 2004 randomized trial, Ackroyd et al. randomly assigned 40 patients with histologically proven Barrett's and previous fundoplication for GERD were to either APC or endoscopic surveillance. In the 20 APC patients, complete ablation of Barrett's epithelium was observed in 12 patients, with a 95% reduction in the remaining 8 patients. At 1 year, 1 of these partially cleared patients experienced complete regression. One patient relapsed after failure of fundoplication surgery. Interestingly, partial regression spontaneously occurred in 11 of the 20 endoscopically-monitored patients and 3 short-segment patients regressed completely. The authors concluded that APC was safe and effective in ablating Barrett's metaplasia, but that long-term follow-up is needed to determine whether APC would have any impact on the incidence of esophageal adenocarcinoma.

The remaining studies were primarily level 2 case series of patients treated with PDT or APC as part of a clinical protocol for Barrett's. Two studies were cost-effectiveness analyses of PDT and are discussed later in this report. One study was a patient satisfaction survey that concluded that PDT with porfimer sodium produces satisfactory results in treated patients. Again, these studies generally concluded that PDT and APC are effective treatments for Barrett's.

Results from the 3 randomized controlled trials that compared these 2 treatments head-to-head suggest that the treatment effects from either modality do not consistently differ. For example, in the 26 patients with low or high-grade dysplasia studied by Ragunath et al., APC and PDT were equally effective at eliminating Barrett's mucosa. However, PDT was more effective with dysplastic tissue. In Kelty et al.'s trial of 68 patients, PDT and APC were again judged to be efficacious at treating Barrett's mucosa at 24 months. However, reduction in area was greatest for patients treated with APC (97% vs. 50%). Hage et al. evaluated APC and PDT under 2 different dosing schedules in 40 Barrett's patients; 32 without evident dysplasia, and 8 with low-grade dysplasia. At 12 months, 82–90% of PDT patients had experienced complete eradication of Barrett's mucosa compared with 67% of APC patients.

While the results of these studies suggest that APC and PDT are potential alternatives to surveillance and esophagectomy for managing Barrett's, the primary weakness of this literature continues to be a lack of randomized controlled trials comparing these newer alternatives to standard care. While it is fairly clear from the literature that either therapy is effective at reducing or eliminating dysplasia, there are insufficient data to determine the long-term impact of these therapies on incidence and mortality from esophageal cancer, particularly over longer time intervals. Some long-term cancer data have been published:

- Attwood et al. reported that 4 of 22 patients with high-grade dysplasia developed esophageal cancer within 84 months of completing APC treatment.
- Familiari et al. did not observe any cases of esophageal cancer in 35 patients in the 49.5 months after APC.
- Madisch et al. followed 66 patients treated with APC over a median follow-up period of 51 months and found no cases of esophageal adenocarcinoma.
- In Overholt et al., 3 of 65 (4.6%) patients with high-grade dysplasia treated with PDT developed adenocarcinoma during the 50.65-month average follow-up.

Without comparative data, however, it is difficult to determine whether similar rates would be observed with endoscopic surveillance. These limited data do suggest, however, that esophageal adenocarcinoma remains a significant risk in patients with high-grade dysplasia, even after ablative therapy has been completed, thus, the need for surveillance endoscopy may not be eliminated in treated patients.

Of equal concern, is the uncertainty in the medical literature regarding the predictive value of Barrett's esophagus for future esophageal cancer. The literature assembled for this review offer several conclusions regarding the transformation from Barrett's to cancer:

- Barrett's Esophagus is the primary risk factor for esophageal adenocarcinoma;
- Patients with Barrett's are at significantly higher risk for adenocarcinoma than the general population or patients with other disorders of the esophagus;

- The overall incidence and mortality rates for esophageal adenocarcinoma in Barrett's patients are relatively low. Several studies state that previous figures overestimate actual risk to Barrett's patients;
- Overall mortality is not substantially higher in patients with Barrett's, relative to the population; and
- Risk for esophageal cancer varies according to the progression of Barrett's mucosa.

While the risk for cancer is clearly higher in persons with dysplasia, a number of these studies focused on patients with intestinal metaplasia and at least 1 treatment strategy (Balloon Radiofrequency Ablation; Halo 360, BARRX) is being marketed as a therapy for patients with metaplasia. Yet, the above epidemiological studies raise questions about the cost-effectiveness of routine endoscopic ablation in all Barrett's cases as a strategy for cancer risk-reduction. Furthermore, the fact that many Barrett's cases are diagnosed after adenocarcinoma has developed suggests that mortality from esophageal cancer may be more greatly impacted through improved strategies for detection, risk stratification, and surveillance for Barrett's, rather than through routine mucosal ablation.

A literature review in April 2010 identified a trial on radiofrequency ablation with dysplasia. Shaheen et al. performed a multicenter, sham-controlled trial. Primary outcomes at 12 months included complete eradication of dysplasia. In the intention-to-treat analyses, among patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of those in the ablation group, as compared with 22.7% of those in the control group ($p < 0.001$). Among patients with high-grade dysplasia, complete eradication occurred in 81.0% of those in the ablation group, as compared with 19.0% of those in the control group ($p < 0.001$). Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, as compared with 2.3% of those in the control group ($p < 0.001$). Patients in the ablation group had less disease progression (3.6% vs. 16.3%, $p = 0.03$) and fewer cancers (1.2% vs. 9.3%, $p = 0.045$). Patients reported having more chest pain after the ablation procedure than after the sham procedure. In the ablation group, 1 patient had upper gastrointestinal hemorrhage and 5 patients (6.0%) had esophageal stricture.

Low-Grade Dysplasia: A literature review completed in September 2015 to evaluate endoscopic ablation for low-grade dysplasia (LGD) in Barrett's esophagus, identified four systematic reviews; and 27 primary studies were identified which met inclusion criteria for review. Studies dated from 2008 to 2015 included outcomes on > 4,597 patients. All but three of the studies specifically addressed treatment for LGD. Many of the studies had follow-up periods extending past 5 years.

A key principle identified in many studies relates to the difficulty in firmly establishing the diagnosis of low-grade dysplasia histopathologically. Both Curvers et al. and Duits et al. noted 85% and 73% of patients respectively initially identified as having dysplastic disease are down-staged after expert histopathological review. This suggests that patients who are not sent on for expert review may be unnecessarily treated.

Notably, the systematic reviews included for review provided conflicting conclusions as to the outcomes from the use of radiofrequency ablation (RFA) for the treatment of LGD in Barrett's esophagus. Two of the 4 (BCBS TEC and Almond et al.) reviews stated the use of RFA in patients with diagnosed LGD does not inhibit the progression to esophageal adenocarcinoma, whereas the 2 other systematic reviews (Wani et al. and Bennett et al.), state the therapy does inhibit disease progression. None of the 4 reviews show that RFA for LGD decreases symptoms.

The body of literature demonstrates significant heterogeneity in terms of patient inclusion criteria, follow-up periods, primary endpoints, and study types. However, findings from these studies can be summarized to show:

- LGD may be over-diagnosed because of poor histopathology;
- No consensus has been reached regarding proper surveillance or treatment of LGD;
- RFA is > 90% effective in completely eradicating LGD; and
- RFA may considerably decrease the progression to HGD.

Notably, two papers, Caygill et.al. and Rubenstein et.al., published evidence on the number needed to treat (NNT) with RFA for LGD for the following endpoints:

- NNT to prevent 1 progression to HGD: 4

- NNT to prevent 1 adenocarcinoma: 13.6
- NNT to prevent 1 esophagectomy: 211

Based on the available published evidence, it appears RFA may play a role in the treatment of patients with histopathologically, not endoscopically confirmed, LGD. How RFA compares to outcomes from the use of PPIs or other conservative therapy as a long-term treatment for patients with LGD has not been adequately addressed. RFA for LGD appears to be a safe and effective therapy for the treatment of LGD.

Billing/Coding Information
Covered: For the indications outlined above
CPT CODES

Photodynamic Therapy, Laser Therapy, Cryoablation

43270 Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)

43229 Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)

Photodynamic Therapy Only

96570 Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)

96571 ; each additional 15 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)

Balloon Radiofrequency Ablation, Multipolar Electrocoagulation, Argon Plasma Coagulation

43216 Esophagoscopy, flexible, transoral; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps

43250 Esophagogastroduodenoscopy, flexible, transoral; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps

HCPCS CODES

A4270 Disposable endoscope sheath, each

Photodynamic Therapy

J9600 Injection, porfimer sodium, 75 mg

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Revision History

Revision Date	Summary of Changes
2/26/24	For Commercial Plan Policy, modified criteria to allow treatment with either radiofrequency ablation (RFA) or cryoablation when criteria are met.

Select Health

Select Health

MEDICAL POLICY

GASTRIC PACING/GASTRIC ELECTRICAL STIMULATION (GES)

Policy # 585

Implementation Date:5/23/16
Review Dates: 4/17/19, 4/15/20, 4/15/21, 3/18/22, 4/20/23, 6/6/24, 3/31/25
Revision Dates: 3/13/17, 7/10/23

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Gastroparesis is a chronic gastric motility disorder of diabetic (both type 1 and type 2 diabetes) or idiopathic etiology. It is characterized by delayed gastric emptying of solid meals. Patients with gastroparesis exhibit bloating, distension, nausea, and/or vomiting. In severe and chronic cases, patients may suffer dehydration, poor nutritional status, and poor glycemic control (in diabetics). Although gastroparesis is often associated with diabetes, it is also found in chronic pseudo-obstruction, connective tissue disorders, Parkinson's disease, and psychological pathology. Therapeutic options of gastroparesis include prokinetic agents such as metoclopramide, and anti-emetic agents such as metoclopramide, granisetron, or odansetron. Patients with severe gastroparesis may require enteral or total parenteral nutrition.

Gastric stimulation (GES), also referred to as gastric pacing, has been proposed for patients with gastroparesis who are refractory to conservative therapy including medical management. This device reduces the symptoms of gastroparesis such as nausea and vomiting and fosters improved gastric emptying. A gastric pacemaker utilizes an external programmer and implanted electrical leads to the stomach. It transmits low-frequency, high-energy electrical stimulation to the stomach to entrain and pace the gastric slow waves to foster satiety. It has also been proposed for use in patients with morbid obesity.

The Enterra Therapy System was the first device to receive FDA Humanitarian Device Exemption (HDE) approval. Electrodes are implanted in the serosa of the stomach laparoscopically, or during a laparotomy, and are connected to the pulse generator that is implanted in a subcutaneous pocket. An updated model, the Enterra II system with some enhanced functionality was subsequently approved in 2015, also with an HDE label.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers gastric pacing or gastric electrical stimulation (GES) for intractable nausea and vomiting secondary to gastroparesis when the following criteria are met:

Coverage Criteria:

1. Patient has a diagnosis of diabetic gastroparesis or idiopathic gastroparesis
2. Gastroparesis has been confirmed > 60% retention at two hours and > 10% retention at four hours, as measure by standardized gastric emptying testing while on therapy

Select Health

Gastric Pacing/Gastric Electrical Stimulation (GES), continued

3. Patient has persistent severe nausea and/or vomiting as evidenced by failure of all the following:
    a. Failure or intolerance to prokinetic agents: metoclopramide and erythromycin, serially, or in combination
    b. Failure or intolerance to at least 2 different antiemetic categories
    c. Documentation of dietary modification
    d. If diabetic, documentation at efforts to optimize glycemic control
    e. If diabetic, patient has NOT taken any of the following meds for at least 6 months prior to request:
        i. Pramlintide (Symlin)
        ii. GLP1 analogues

Select Health does NOT cover gastric pacing or gastric electrical stimulation (GES) for any other indication, including obesity, as it is considered experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For this policy, specifically, there are no CMS criteria available; therefore, the Select Health Commercial policy or InterQual criteria apply. Select Health applies these requirements after careful review of the evidence that supports the clinical benefits outweigh the clinical risks.. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Gastroparesis: The concept of stimulating the stomach to empty using electrical stimulation has been attractive for some time. The Enterra System presented data to the FDA documenting the "probable benefit" of GES (Gastric Electrical Stimulation System) based on a multi-center double-blind crossover study (FDA, 2000), which included 33 patients with intractable idiopathic or diabetic gastroparesis. In the initial phase of the study, all patients underwent implantation of the stimulator and were randomly assigned to stimulation-ON or stimulation-OFF for the first month, with cross-over to OFF and ON during the second month. The baseline vomiting frequency was 47 episodes per month, which significantly declined in both ON and OFF groups to 23 to 29 episodes, respectively. However, there were no significant differences in the number of vomiting episodes between the two groups, suggesting a placebo effect. It was concluded that long-term results of GES must be validated in longer-term randomized studies. It is important to note that GES did not return gastric emptying to normal in most of the treated patients.

A review of the literature in March 2017 revealed nine systematic reviews and 25 primary studies that have been subsequently published between 2001 and 2016. The follow-up periods after implantation extended out to 11 years, though, most studies followed patients 1 year or less.

In the 25 primary studies, the ages ranged from as low as 2 years of age in the study by Islam et al. in 2016, to 4 years of age in Teich et al. from 2013, to 77 years old in Abell et al. from 2011, and to 87 years

old by Shah et al. in 2016. The mean or median age studied from all these studies was 38.5. The systematic reviews appear divided pertaining to favorable/unfavorable conclusions of the technology. Most illustrate improved outcomes while concluding that benefits are only realized for appropriately selected patients.

The primary studies well-define the outcomes expected from GES treatment for gastroparesis, despite the fact that some studies were of poor quality (heterogeneity of patient populations, not controlled, short duration follow-up). Important results of the studies include some degree of resolution of symptoms associated with gastroparesis, but not all studies showed the same degree of resolution or resolution of the same symptoms. Also, nine of the 25 studies (36%) investigated GES in patients who were either presently on medical therapy, or in those who had previously failed medical therapy. Improvements in symptom resolutions were observed in patients who had failed medical therapy. Twelve of the 25 studies (48%) included patients with diabetes or diabetic gastroparesis. A common finding was that better outcomes were observed for patients with diabetic gastroparesis than for idiopathic gastroparesis.

- Twelve of the 25 studies (48%) noted that the explantation rate of the device was between 0% and 15.2% (average = 8.6%). Infection and lead dislodgement were among the most common reasons for explantation. The follow-up periods do not correlate with explantation rate. The studies that reported explantation rates followed patients for between 1 and 11 years.

In conclusion, a relatively large number of studies illustrated some level, even statistically significant levels of symptom relief in patients with gastroparesis. The treatment effect was most noticeable in patients with diabetes/diabetic gastroparesis, but symptom resolution was identified in some measure in most patients. Explantation of the device was substantial at 8.6%, which will add to the cost of the overall cost of the procedure, in any period of time. Short-term and long-term outcomes have been reported with data extending to 11 years. Appropriate patient selection was a common theme throughout the body of literature and must be considered of primary importance.

Weight Loss: Obesity is a major health problem among adults in the United States. It is also an increasing health concern among American children as well as adolescents. Various methods are employed in the management of obesity. One of the new approaches is gastric pacing, which is intended to induce early satiety through electrical stimulation of the gastric wall. However, the effectiveness of this technique in treating obesity has not been established. Buchwald and Buchwald (2002) considered gastric pacing as an experimental procedure for the management of morbid obesity.

Cha and colleagues (2014) evaluated the current state-of-the-art of GES to treat obesity. These investigators performed systematic reviews of all studies to evaluate the effect of different types of GES on obesity. A total of 31 studies consisting of a total of 33 different trials were included in the systematic review for data analysis. Weight loss was achieved in most studies, especially during the first 12 months, but only very few studies had a follow-up period longer than 1 year. Among those that had a longer follow-up period, many were from the Transcend (Implantable Gastric Stimulation) device group and maintained significant weight loss. Other significant results included changes in appetite/satiety, gastric emptying rate, blood pressure, and neuro-hormone levels (or biochemical markers) such as ghrelin and HbA1c. The authors concluded that GES holds great promises to be an effective obesity treatment. Moreover, they stated that stronger evidence is needed through more studies with a standardized way of carrying out trials and reporting outcomes, to determine the long-term effect of GES on obesity.

Bortolotti (2002) noted that there are currently 3 principal methods of GES: (i) gastric electrical pacing, (ii) high-frequency GES, and (iii) sequential neural electrical stimulation. The first method aims to reset a regular slow-wave rhythm, but is unable to re-establish efficient contractions and a normal gastric emptying. High-frequency GES, although inadequate to restore a normal gastric emptying, nevertheless strikingly improves the dyspeptic symptoms, such as nausea and vomiting, giving patients a better quality of life and a more satisfactory nutritional status. The last method, neural electrical gastric stimulation, consists of a microprocessor-controlled sequential activation of a series of annular electrodes which encircle the distal 2/3 of the stomach and induce propagated contractions, resulting in a forceful emptying of the gastric content. The latter method is the most promising, but it has so far only been tested in animals and would need to be tested in patients with gastroparesis before it can be used as a solution for this disease. All the aforementioned clinical studies, however, were not controlled, and nearly all were published in abstract form.

Gastric Pacing/Gastric Electrical Stimulation (GES), continued

The evidence from few randomized controlled trials and a number of case series in the published peer-reviewed medical literature indicates that gastric electrical stimulation (GES) (e.g., Enterra Therapy) may be a safe and effective option for those patients with intractable nausea and vomiting secondary to gastroparesis who have failed all other treatments. The use of GES or gastric pacing remains unproven for the treatment of other conditions such as obesity. Optimal patient selection criteria, electrode position, lead number, and stimulation patterns have not yet been determined. Additional well-designed studies are needed to demonstrate the safety and effectiveness of GES for these indications.

Billing/Coding Information

CPT CODES

43647	Laparoscopy, surgical; implantation or replacement of gastric neurostimulator electrodes, antrum
43648	Laparoscopy, surgical; revision or removal of gastric neurostimulator electrodes, antrum
43881	Implantation or replacement of gastric neurostimulator electrodes, antrum, open
43882	Revision or removal of gastric neurostimulator electrodes, antrum, open
64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
95980	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient measurements) gastric neurostimulator pulse generator/transmitter; intraoperative, with programming
95981	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient measurements) gastric neurostimulator pulse generator/transmitter; subsequent, without reprogramming
95982	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient measurements) gastric neurostimulator pulse generator/transmitter; subsequent, with reprogramming

HCPCS CODES

C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)
C1897	Lead, neurostimulator test kit (implantable)
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension

Gastric Pacing/Gastric Electrical Stimulation (GES), continued

L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

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Gastric Pacing/Gastric Electrical Stimulation (GES), continued

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Revision History

Gastric Pacing/Gastric Electrical Stimulation (GES), continued

Revision Date	Summary of Changes
7/10/23	For Commercial Plan Policy, removed previous criteria #1 as a requirement: "Gastroparesis has been present > 1 year since initial radiographical diagnosis."

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MEDICAL POLICY

GASTRIC PERORAL ENDOSCOPIC MYOTOMY (G-POEM)/PYLOROPLASTY FOR GASTROPARESIS

Policy # 681

Implementation Date:7/1/24
Review Dates:
Revision Dates:2/20/25

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Gastroparesis is a syndrome of delayed gastric emptying in the absence of a mechanical obstruction, which usually presents with symptoms of nausea, vomiting, early satiety, bloating, or upper abdominal pain. Most cases of gastroparesis are idiopathic, diabetic, or postsurgical.

Initial management of gastroparesis consists of dietary modification, optimization of glycemic control and hydration, and pharmacologic therapy with prokinetic and antiemetic medications. Patients who are refractory to medical therapy may require surgical interventions in the forms of tube gastrostomy, subtotal gastrectomy, or pyloroplasty.

Gastric peroral endoscopic myotoomy (G-POEM) and laparoscopic pyloroplasty have been successful in small studies in treating gastroparesis. G-POEM has the theoretical potential to induce dumping syndrome. G-POEM should be reserved for patients with refractory gastroparesis. There is evidence from a pilot sham-controlled study that G-POEM is efficacious in gastroparesis, that G-POEM may be superior to gastric electrical stimulation in the long-term, and that it can be applied as adjunctive therapy in patients who remain symptomatic after gastric electrical stimulation.

The G-POEM procedure myotomizes the pylorus, rather than the lower esophageal sphincter. For G-POEM, a submucosal tunnel is typically created 5 cm proximal to the pylorus along the greater curvature or anterior gastric wall. A short (2 cm) antral myotomy is then performed in addition to pyloromyotomy via the submucosal tunnel.

Pyloroplasty is a procedure that widens the opening between the antrum and duodenum to facilitate passage of gastric contents.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

A. Select Health covers gastric peroral endoscopic myotomy (G-POEM) or pyloroplasty for members who meet all the following criteria (1−3):

1. Has severe gastroparesis with poor response to medical therapy; and

2. Has had a positive response with botulim toxin; and

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3. Patient will not proceed with gastric electrical stimulation.

B. Pyloroplasty is allowed after appropriate conservative therapy for treatment of refractory or recurrent gastric ulcers.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT CODES

43499 Unlisted procedure, esophagus

43800 Pyloroplasty

Key References

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3. Khasha, M. A. Peroral endoscopic myotomy (POEM). UpToDate. Last Review: Aug. 11, 2023.

Revision History

Revision Date	Summary of Changes
2/20/25	For Commercial Plan Policy, modified requirements in criteria #B as follows: "Pyloroplasty is allowed after appropriate conservative therapy for treatment of refractory or recurrent gastric ulcers."

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MEDICAL POLICY

IB-STIM

Policy # 637
Implementation Date:10/14/19
Review Dates: 10/15/20, 11/18/21, 9/15/22, 10/13/23, 11/1/24
Revision Dates:

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Irritable bowel syndrome (IBS) is the most prevalent of the functional gastrointestinal disorders (FGIDs). Current estimates are that IBS affects up to 10% to12% of adults in North America. Although it can affect all individuals regardless of age, creed, or gender, IBS is more common among women and is most diagnosed in younger individuals (aged < 50). IBS is characterized by recurrent abdominal pain and altered bowel habits; bloating and distention frequently coexist.

The diagnosis of IBS is made by taking a careful history, eliciting key symptoms, performing a physical examination, and limited diagnostic testing. IBS is categorized into 4 main subtypes based on the predominant bowel habit: IBS with constipation (IBC-C); IBS with diarrhea (IBS-D); IBS with mixed symptomology (IBSM); and unclassified IBS.

The IB-Stim is a percutaneous electrical nerve field stimulator (PENFS) system intended to be used in patients 11 to 18 years of age with functional abdominal pain associated with irritable bowel syndrome (IBS). The IB-Stim is intended to be used for 120 hours per week up to 3 consecutive weeks, through application to branches of Cranial Nerves V, VII, IX, and X, and the occipital nerves identified by transillumination, as an aid in the reduction of pain when combined with other therapies for IBS.

IB-Stim stimulator is a battery-operated micro-stimulation appliance weighing 5 grams designed as a disposable product for a single use. IB-Stim stimulator is placed behind the patient's ear and connected to stimulation needles on the auricle. IB-Stim stimulator offers regular therapy over several days. The appliance transmits low-frequency electric pulses. No safety data exists in patients 11 to 18 years of age with IBS treated longer than 4 weeks.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does not cover the IB-Stim device as it is considered experimental/investigational; there is insufficient evidence to assess the safety and/or impact of this device on health outcomes or management of patients.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT CODES

64999	Unlisted procedure, nervous system (when specified as implantation of electrodes or a pulse generator whether for trial or permanent placement of a peripheral subcutaneous field stimulation)

Key References

1. Hayes, Inc. Evidence Analysis Research Brief. (2019). IB-Stim (Innovative Health Solutions) for Treatment of Pain Associated with Irritable Bowel Syndrome.

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MEDICAL POLICY

INJECTABLE BULKING AGENTS IN THE TREATMENT OF FECAL INCONTINENCE

Policy # 531

Implementation Date: 7/3/13

Review Dates: 8/28/14, 8/20/15, 8/25/16, 8/17/17, 8/1/18, 10/20/19, 10/15/20, 11/18/21, 9/15/22, 10/3/23, 10/6/24

Revision Dates: 6/10/15, 11/13/23

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Fecal incontinence (FI) is the inability to control bowel movements, causing stool to leak unexpectedly from the rectum. Also called bowel incontinence, fecal incontinence ranges from an occasional leakage of stool while passing gas, to a complete loss of bowel control in someone who is older than four years old.

Common causes of FI include constipation, diarrhea, and muscle or nerve damage. FI may be due to a weakened anal sphincter associated with aging or damage to the nerves and muscles of the rectum and anus from giving birth. A variety of treatments are available for FI, depending on the severity of symptoms. Treatments may include dietary changes, medications, special exercises that help better control the bowels, or surgery.

Another method sometimes used in the injection of "bulking agents" is to increase the barrier effect of the anal sphincter. This is performed when there is some intact anal muscle function, and the degree of the incontinence is limited. These inert agents include collagen, silicone particles, and carbon beads. Solesta (under license from and manufactured by Q-Med AB for Salix Pharmaceuticals, Inc.) is a new injectable bulking agent using gel consisting of dextranomer microspheres in stabilized hyaluronic acid-based gel of non-animal origin (NASHA) gel as the bulking agent. It is hypothesized Solesta expands the submucosal layer of the proximal anal canal, thereby augmenting bowel control. The procedure to inject the bulking agent itself is simple. Following evacuation enema, and using an anoscope, the surgeon injects 4 x 1 milliliters (mL) of Solesta into the deep submucosal layer in the proximal part of the high-pressure zone of the anal canal about 5 mm above the dentate line. The procedure can be repeated 4 weeks after the first treatment, if necessary. Administration of Solesta is an outpatient procedure which may be performed with or without local anesthesia.

Per ASCRS 2023 Clinical Practice Guidelines for fecal incontinence: "Given the limited improvement over placebo, diminishing long-term results, and cost, injectable bulking agents are not considered first-line treatment for FI."

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does not cover injectable bulking agents in the treatment of fecal incontinence as the long-term clinical utility of this therapy is not defined; nor is this therapy recommended according to current societal guidelines. This meets the plan's definition of experimental/investigational.

Injectable Bulking Agents In The Treatment Of Fecal Incontinence, continued

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The extensive literature review of bulking agents for the treatment of fecal incontinence (FI) identified seven systematic reviews and eleven peer-reviewed journal articles which met inclusion criteria for this report. All the articles were published between 2007 and 2013 and included over 575 patients diagnosed with fecal incontinence. Follow-up periods between six and sixty-one months (average = 23.2 months) were noted in the studies.

The recent Hayes Brief systematic review published in November of 2012 was specific in assessing Solesta. It is important to note this review was after the time of the FDA approval. It gave the technology a D2 rating and concluded: "The overall quality of the evidence is low given the paucity of controlled studies and small study sizes. Larger, independent, randomized, sham-controlled studies are needed to further evaluate the efficacy, durability, and safety of this treatment, and to compare it with standard therapies and other alternatives. There is also a need to examine variables that predict which patients will derive the most clinical benefit from this therapy to better define patient selection criteria." The same conclusions were drawn from the other five systematic reviews included in this report, including the AHRQ Horizon scanning publication, published in June of 2012. The conclusions from the 2010 Cochrane review may best summarize the issues related to bulking agents used for fecal incontinence, in that the methodological weaknesses and the limited number of trials concerning bulking agents for FI offer no definitive evidence of safety and efficacy. All systematic reviews noted that more studies were needed in order to draw definitive conclusions.

Where most of the systematic reviews gave unfavorable synopses of the clinical utility, safety, efficacy, and durability of the treatment, the majority (5 of 8) of the primary literature were generally favorable for the same endpoints. Most of the papers showed durability out to two years or longer (Maeda et al. showed durability for 61 months), statistically significant improvements in quality of life, and a decrease in incontinence episodes.

The data between the systematic reviews and the primary literature is conflicting. The reviews noted methodological flaws existent in the studies, few papers in general, lack of established protocols, and patient selection criteria. However, peer-reviewed primary literature noted an improvement in patient quality of life, a decrease in incontinence episodes, a low morbidity profile, and durability out to even five years.

In conclusion, perianal bulking agents do show a certain degree of safety and efficacy for the treatment of FI. However, methodological weaknesses and few prospective, randomized, controlled trials limit the ability to draw definitive conclusions concerning the clinical utility of this technology. Given these deficits and the low quality of evidence, a GRADE 2c rating would be appropriate for the data concerning bulking agents for the treatment of FI.

In 2011, the FDA approved a nonanimal stabilized hyaluronic acid dextranomer gel (NASHA Dx) for submucosal injection in patients with passive FI. The largest series evaluating this approach at the time was a randomized, double-blinded, placebo-controlled, multicenter trial of 206 patients from Europe and

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the United States. In this study, at 6-month follow-up, 52% of patients in the NASHA Dx group reported 50% or more reduction in FI episodes, compared to 31% of patients in the placebo arm (p = 0.008). A subsequent 36-month follow-up indicated that 57% of study patients still had 0% or more improvement in FI episodes compared to baseline, but median Wexner scores in this group of patients only decreased from 14 at baseline to 11 at 36 months (p < 0.001), indicating fairly significant persistent FI.

Additionally, most patients whose function improved in this trial had 2 separate injections of the bulking agent. In a retrospective study with long-term follow-up of 19 patients treated with an injectable for FI, ultrasound evaluation indicated that less than 14% of the injected substance was still present after 5 years, and the Wexner scores of these patients had returned to pretreatment baseline. Given the limited improvement over placebo, diminishing long-term results, and cost, injectable bulking agents are not considered first-line treatment for FI.

Billing/Coding Information

Not covered for the indications listed above

CPT CODES

46999	Unlisted procedure, anus

HCPCS CODES

J3490	Unclassified drugs **(**Solesta NDC: 89114-850-03)
C9399	Unclassified Drugs or Biologicals
L8605	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal, 1 ml, includes shipping and necessary supplies

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Revision History

Revision Date	Summary of Changes
11/13/23	For Commercial Plan Policy, revised policy to no longer provide coverage of this therapy: "Select Health does not cover injectable bulking agents in the treatment of fecal incontinence as the long-term clinical utility of this therapy is not defined; nor is this therapy recommended according to current societal guidelines. This meets the plan's definition of experimental/investigational."

Select Health

Injectable Bulking Agents In The Treatment Of Fecal Incontinence, continued

Select Health

Select Health

MEDICAL POLICY

IN-VIVO DETECTION OF MUCOSAL LESIONS WITH ENDOSCOPY

Policy # 574

Implementation Date: 10/15/15

Review Dates: 10/20/16, 10/19/17, 10/14/18, 10/20/19, 10/15/20, 12/4/21, 9/15/22, 10/19/23, 11/1/24

Revision Dates:

Description

Colonoscopy is the gold standard for detecting and removing polyps from the colon. Removal of polyps found at the time of routine screening colonoscopy has been shown to reduce the subsequent development of colorectal cancer. Several enhancements to standard colonoscopic evaluation have been developed in an attempt to improve polyp detection.

The Optical Biopsy System is one such system. It is designed to be used as an additional tool during colonoscopy to assist the physician in determining whether certain colon polyps are potentially cancerous and should be removed. The Optical Biopsy System consists of a laser, an optical fiber, analytical software, and a user-interface console. The laser light is directed at a suspicious polyp. The polyp absorbs the light and redirects it through the fiber to a computer. The software determines whether the polyp has the potential to become malignant. The Optical Biopsy System is not intended to be used as a standalone device, or as a diagnostic test to be done instead of colonoscopy. As with the standard colonoscopy, after the endoscopic examination is complete, the biopsy samples are sent to the pathology department for evaluation.

Another enhancement uses narrow band imaging (NBI). During colonoscopy, the endoscope normally emits a white light. NBI converts the white light to a narrower wavelength, which results in a bluish light. The blue light increases the contrast of the surface structures of the colon. Combining the narrow band image with video processing equipment further enhances the anatomical structures of the colon. The EVIS EXERA 160A System (Olympus Medical Systems Corp) is one example of an NBI system.

Confocal laser (fluorescent) endomicroscopy is also being investigated as a tool to enhance the in vivo analysis of the GI tract. The confocal laser endomicroscope combines a confocal laser microscope mounted in the distal tip of a conventional video endoscope. This enables the practitioner to view the GI tract without making a surgical incision (endoscopy), and to magnify the area being examined using a microscope. A fluoroscopic agent is also used to enhance tissue visibility. Practitioners have the option of storing images either digitally or on video, so that, if necessary, they may be viewed later.

Chromoendoscopy involves the topical application of stains or pigments to improve tissue localization, characterization, or diagnosis during endoscopy. Several agents have been described that can broadly be categorized as absorptive (vital) stains, contrast stains, and reactive stains. Absorptive stains (e.g., Lugol's solution and methylene blue) diffuse or are preferentially absorbed across specific epithelial cell membranes. Contrast stains (e.g., indigo carmine) highlight surface topography and mucosal irregularities by permeating mucosal crevices. Reactive stains (e.g., Congo red and phenol red) undergo chemical reactions with specific cellular constituents, resulting in a color change. The stains used for chromoendoscopy are transient.

In-Vivo Detection of Mucosal Lesions with Endoscopy, continued

Chromoendoscopy and narrow band imaging may enable endoscopists to accurately determine if lesions are neoplastic, and if there is a need to remove them and send material to pathology. At this point, these technologies do not have an impact on surveillance intervals (Lieberman, 2012).

NCCN guidelines on colorectal cancer screening indicate that because targeted biopsies have been found to improve detection of dysplasia, NBI may be an appropriate screening tool for individuals with a history of ulcerative colitis (NCCN, 2013).

It has been proposed that NBI may assist in the distinction between normal and abnormal GI mucosa. While these image-enhancing technologies may increase visibility of the GI mucosa and may therefore enable the physician to identify additional suspicious lesions, additional studies on this technology are needed to demonstrate that this technology improves clinical outcomes over standard practices.

Billing/Coding Information

CPT CODES

43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy
43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy
43499	Unlisted procedure, esophagus [when specified as in vivo analysis of gastrointestinal lesions (e.g., fiberoptic analysis, narrow band imaging or multi-band imaging)]
45399	Unlisted procedure, colon [when specified as in vivo analysis of gastrointestinal lesions (e.g., fiberoptic analysis, narrow band imaging, multi-band imaging, chromoendoscopy, or confocal laser endomicroscopy)]
45999	Unlisted procedure, rectum [when specified as in vivo analysis of gastrointestinal lesions (e.g., fiberoptic analysis, narrow band imaging, multi-band imaging chromoendoscopy, or confocal laser endomicroscopy)]
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session

HCPCS CODES

No specific codes identified

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In-Vivo Detection of Mucosal Lesions with Endoscopy, continued

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Select Health

In-Vivo Detection of Mucosal Lesions with Endoscopy, continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover in-vivo techniques in the assessment of mucosal changes in endoscopic procedures. The impact of these technologies has not been proven to alter health outcomes. This meets the plan's definition of experimental/investigational.

Excluded technologies, include, but are not limited to:

1. Fluorescence Spectroscopy
2. Fluorescence Endoscopy
3. Optical Coherence Tomography
4. Fiberoptic Analysis
5. Multiband Imaging
6. Narrow Band Imaging
7. Chromoendoscopy

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

For Average Risk Patients

Kahi and colleagues (2010) randomized 660 patients who had been referred for screening colonoscopy at 4 medical centers to undergo either high-definition with indigo carmine dye (n=321) or high-definition white light (standard) colonoscopy (n=339). Both methods were comparable in identifying advanced neoplasms. One invasive cancer was detected in each group, neither of which was a flat adenoma. Chromocolonoscopy identified smaller (less than 5 mm) adenomas per participant (0.8 vs. 0.7) and more flat adenomas (0.6 vs. 0.4) than did white light colonoscopy, but the absolute difference was small. The authors concluded that based on the small magnitude and uncertain clinical significance of the differences, the routine usage of high-definition chromocolonoscopy for colorectal cancer screening in average-risk individuals is not supported.

In another study, Pohl and colleagues (2011) conducted a prospective, randomized, two center study to determine whether pancolonic chromoendoscopy (PCC) using enhanced mucosal contrast (indigo carmine dye) results in higher rates of adenoma detection than standard colonoscopy. The study included a mixed population, including presenting for primary colorectal cancer screening (51%) and individuals presenting for diagnostic colonoscopy (49%). The use of chromoendoscopy resulted in an increased overall detection rate for adenomas (0.95 vs. 0.66 per subject), flat adenomas (0.56 vs. 0.28 per subject) and serrated lesions (1.19 vs. 0.49 per subject) ($p < 0.001$). However, there was no significant difference in the detection of adenomas 10 mm or larger between the groups. While this study included a mixed

Select Health

population of subjects undergoing screening and diagnostic colonoscopy, the authors do not report results separately for the screening and the diagnostic colonoscopy groups.

In a Hayes review performed in 2013, they concluded: "The results of these studies are equivocal regarding the efficacy of chromoendoscopy for patients receiving colonoscopy for routine indications. Findings were conflicting regarding whether chromoendoscopy improved detection of neoplasia, although results suggested that chromoendoscopy facilitated differentiation of neoplastic and non-neoplastic lesions when the Kudo pit classification criteria were employed. However, none of the studies evaluated whether utilization of the chromoendoscopy had any impact on management or clinical outcomes in patients undergoing routine colonoscopy.

Symptomatic Individuals and Individuals at Increased Risk for Colorectal Cancer

In a 2010 Cochrane review, Brown and colleagues (2010) set out to determine whether the use of chromoscopy enhances the detection of neoplasia and polyps during endoscopic examination of the colon and rectum. Five randomized controlled trials (1,059 subjects) from 2002–2008 were included in the review of studies comparing chromoendoscopy and conventional colonoscopy. Study subjects included individuals with gastrointestinal symptoms and an increased risk for colorectal cancer; individuals with inflammatory bowel disease or polyposis syndromes were not included. The primary outcome measures for each intervention included the number of polyps detected per subject, the number of neoplastic polyps detected per subject, the number of subjects with at least one polyp, and the number of subjects with at least one neoplastic polyp. Secondary outcomes included the number of diminutive neoplastic polyps per subject, the number of subjects with at least one diminutive neoplastic polyp, the number of subjects with three or more neoplastic polyps, the extubation time, and the site of the lesion in the colon.

Although there were some methodological drawbacks and differences in study design, the authors found that combining the results showed a significant difference in favor of chromoscopy for all detection outcomes. Chromoscopy yielded more subjects with at least 1 neoplasm (odds ratio [OR], 1.67; confidence interval [CI], 1.29−2.15) and significantly more subjects with 3 or more neoplastic lesions (OR, 2.55; CI, 1.49−4.36). The authors concluded that there appears to be strong evidence that chromoscopy enhances the detection of neoplasia in the colon and rectum.

In a prospective study by Li and colleagues (2010), researchers investigated whether the morphology of the depression area at the surface of colorectal neoplasia with depression can be used for predicting its invasive depth and histology. Of the 296 lesions examined, 66 (22.3%) contained an area of central depression, including 43 in nonpolypoid (flat and depressed) lesions (66%) and 23 in polypoid (10%). The overall accuracy of depressive morphology in distinguishing between low-grade dysplasia and high-grade dysplasia/invasive cancer was 86.4%. The researchers concluded that chromocolonoscopy to determine morphology depression could be used as a complementary method to assess the degree of atypia and invasive depth in colorectal neoplasia. The authors acknowledged that the clinical value of depression morphology is limited by the fact that most colorectal lesions do not contain a depression area.

Concerning the 2013 Hayes review performed on chromoendoscopy used during screening or surveillance colonoscopy in patients with hereditary nonpolyposis colorectal cancer syndrome, the organization concluded there was a paucity of evidence for this indication and does not recommend it for coverage.

Identification and Surveillance of Dysplasia in Individuals with Inflammatory Bowel Disease (IBD)

Kiesslich and colleagues (2003) conducted a randomized controlled trial to test whether chromoendoscopy might facilitate the early detection of intraepithelial neoplasias and colitis-associated colon carcinomas. A total of 165 individuals with longstanding UC were randomized in a 1:1 ratio to undergo conventional colonoscopy or colonoscopy with chromoendoscopy using 0.1% methylene blue. Five mucosal biopsy specimens were taken every 10 cm between the rectum and cecum. Circumscript lesions in the colon were evaluated according to a modified pit pattern classification. Significantly more intraepithelial neoplasms were identified in the chromoendoscopy group compared to the conventional colonoscopy group (32 vs. 10, p=0.003). The authors concluded chromoendoscopy permits more accurate diagnosis of the extent and severity of the inflammatory activity in UC compared with conventional colonoscopy, but acknowledge additional controlled studies are needed.

In-Vivo Detection of Mucosal Lesions with Endoscopy, continued

Rutter and colleagues (2004) carried out a comparative study which sought to determine if routine pancolonic indigo carmine dye spraying would improve the macroscopic detection of dysplasia and reduce the dependence on non-targeted biopsies. The targeted biopsy protocol with pancolonic chromoendoscopy required fewer biopsies than taking multiple non-targeted biopsies (157 biopsies as opposed to 2,904 biopsies). In addition, the targeted biopsy protocol identified dysplasia in significantly more individuals than the non-targeted protocol (7/100 subjects vs. 0/100 subjects, p=0.02).

In another study, researchers (Kiesslich, 2007) conducted a randomized controlled trial to assess the value of chromoendoscopy (0.1% methylene blue) combined with endomicroscopy for the *in vivo* diagnosis of intraepithelial neoplasia in individuals with UC. The authors reported that by using chromoscopy with endomicroscopy, 4.75-fold more neoplasias could be detected (p=0.005) than with conventional colonoscopy, although 50% fewer biopsy specimens (p=0.008) were required. The presence of neoplastic changes could be predicted by endomicroscopy with high accuracy (sensitivity, 94.7%; specificity, 98.3%; accuracy, 97.8%).

Marion and colleagues (2008) prospectively compared dye-spray technique using methylene blue to standard colonoscopic surveillance in detecting dysplasia in individuals over 18 years of age with either extensive ulcerative colitis (at least left-sided) or Crohn's colitis involving at least one-third of the colon. The authors concluded that colonoscopic surveillance of chronic colitis subjects using methylene blue dye-spray targeted biopsies results in improved dysplasia yield compared to conventional random and targeted biopsy methods. The authors acknowledged that there is still controversy surrounding the natural history of dysplasia in colitis and state that a long-term follow-up of the participants in the study is planned.

Hlavaty and colleagues (2011) carried out a cohort study comparing white light (standard) endoscopy and chromoendoscopy performance in the detection of intraepithelial neoplasia (IEN) in subjects with either ulcerative colitis or Crohn's colitis. There were no IENs found on random biopsies versus 6 low-grade or high-grade IENs in 4 participants (2 detected by white light endoscopy, 4 additional by chromoendoscopy) from targeted biopsies, p=0.02. A total of 100 suspicious lesions were identified and analyzed by chromoendoscopy and histology. Thirty-two of 100 lesions (2 of 30 flat vs. 30 of 70 pedunculated lesions) could not be examined by confocal laser endoscopy. The sensitivity of chromoendoscopy/confocal laser endomicroscopy for low-grade or high-grade IEN was 100/100%, the specificity 96.8/98.4%, positive predictive value was 62.5/66.7% and negative predictive value was 100/100%. The authors concluded that chromoendoscopy increases the diagnostic yield of white light endoscopy and that targeted biopsies are superior to random biopsies in the screening of IEN in individuals with IBD. The authors also concluded that confocal laser endoscopy did not provide additional clinical benefits. Limitations of the study include its small sample size, and the bias created by allowing participants to choose either conventional or chromoendoscopy. Another potential bias for the study results is that the endoscopes used for white light endoscopy and chromoendoscopy/confocal laser endoscopy were not the same.

Wu and colleagues (2012) conducted a meta-analysis to investigate the diagnostic accuracy of chromoendoscopy for dysplasia in individuals with ulcerative colitis. The inclusion criteria consisted of: (1) chromoendoscopy employed as the comparative group; (2) sufficient data for analysis; and (3) histological diagnosis used as the gold standard. Studies excluded from the meta-analysis were those in which the individuals did not have histological confirmation, studies with fewer than 10 participants, those which did not contain sufficient data and reviews and meta-analyses. A total of six randomized controlled trials met the inclusion criteria. Of the 6 studies, a total of 1528 subjects were included, of whom 1505 had ulcerative colitis and 23 had Crohn's disease. Indigo carmine dye spray was used in three studies and methylene blue in the other three. The results of the meta-analysis demonstrated a pooled sensitivity of 83.3%, specificity of 91.3%, and diagnostic odds ratio of 17.54. Although the researchers concluded that chromoendoscopy has medium to high sensitivity and high diagnostic accuracy for dysplastic lesions in ulcerative colitis, they also acknowledged that the studies included in the meta-analysis had several limitations. These limitations included the fact that the baseline characteristics of the participants varied in each of the included studies and no consideration was given to the experience of the endoscopist or the characteristics of the medical facility. The authors recommended that additional studies be conducted to further assess the cost-effectiveness, tolerance and application of this technique in the clinical setting.

Neumann and colleagues (2011) reviewed the endoscopic and histological characteristics of the dysplasia-associated lesion or mass (DALM) and non-colitis mucosa (adenoma-like mass [ALM]) in the context of therapeutic procedures and proposed seven basic rules for the detection of neoplasia. While

the authors concluded that emerging endoscopic imaging techniques (chromoendoscopy, magnification endoscopy, and confocal laser endomicroscopy) offer the potential for real time in vivo diagnosis of intraepithelial neoplasia, they did not include these technologies in their recommendations for the detection of dysplasia.

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Status Evaluation Report on chromoendoscopy provides the following summary:

> Chromoendoscopy: is inexpensive, safe, and relatively easy to perform, although the method is not standardized for several stains and the staining patterns are subject to observer interpretation. There is a need to build consensus on the staining techniques and terminology of the mucosal patterns for most applications, in addition to proving efficacy and reproducibility in high-quality, randomized, controlled trials before chromoendoscopy can be incorporated into routine clinical practice. The cost-effectiveness of tissue staining for various GI conditions has not been established, and its stance relative to commercially available competing, and less cumbersome ''chromoendoscopy without dye'' techniques, such as narrow-band imaging, remains to be seen (ASGE, 2007).

The American Gastroenterological Association (AGA) position statement on the diagnosis and management of colorectal neoplasia in patients with IBD (Farraye, 2010) recommends surveillance colonoscopy with extensive biopsies of all anatomic sections in patients with IBD. Chromoendoscopy or another image enhancing method was recommended for physicians with experience using the technique. This guideline also states that the sensitivity for detecting dysplasia by chromoendoscopy is higher than for white light endoscopy and therefore is an acceptable technique for experienced endoscopists. The guideline acknowledges that training issues and the time required for surveillance examinations need to be examined carefully. However, it also noted that the natural history of chromoendoscopically detected dysplasia is currently unknown.

The National Comprehensive Cancer Network (NCCN) guidelines on colorectal cancer screening state that "biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy, narrow-band imaging, autofluorescence, or confocal endomicroscopy. Targeted biopsies have been found to improve detection of dysplasia and should be considered for surveillance colonoscopies in patients with ulcerative colitis" (NCCN, 2013).

Although there is emerging evidence that chromoendoscopy may yield higher polyp detection rates, it is not known if the additional polyps detected are clinically significant and if this higher detection rate results in a meaningful clinical outcome benefit.

In a Hayes review performed in 2013: “Overall, the results of these studies suggest that chromoendoscopy during colonoscopy improved diagnostic yield of dysplasia in patients with IBD. However, these studies do not address whether the enhanced detection of dysplasia has an impact on long-term patient management and outcome. Ullman (2007) has suggested that the use of chromoendoscopy in this patient population may simply result in stage migration, whereby many patients were advanced from a “no dysplasia evident” stage to a “low grade dysplasia” stage. He further noted that such stage migration may improve survival within each stage, without altering the overall patient outcome.

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (also known as confocal fluorescent endomicroscopy) is an endoscopic technique that makes it possible to carry out confocal microscopic examination of the mucosal layer during endoscopic procedures. According to the American Society of Gastrointestinal Endoscopy:

> Confocal laser endomicroscopy … is based on tissue illumination with a low-power laser with subsequent detection of the fluorescence light reflected from the tissue through a pinhole. The term confocal refers to the alignment of both illumination and collection systems in the same focal plane. The laser light is focused at a selected depth in the tissue of interest and reflected light is then refocused onto the detection system by the same lens. Only returning light refocused through the pinhole is detected. The light reflected and scattered at other geometric angles from the illuminated object or refocused out of plane with the pinhole is excluded from detection. This dramatically increases the spatial resolution of confocal endomicroscopy, thus providing an 'optical biopsy' - histological examination of the superficial layer of the GI tract.

In-Vivo Detection of Mucosal Lesions with Endoscopy, continued

> Confocal imaging can be based on tissue reflectance or tissue fluorescence. The confocal devices based on tissue reflectance do not require any contrast agents, but available prototypes have had numerous technical problems and relatively low resolution, which significantly compromise in-vivo imaging and clinical utility. In contrast, confocal endomicroscopy based on tissue fluorescence uses local and/or intravenous contrast agents and generates high-quality images comparable with traditional histological examination (ASGE, 2009).

At least two confocal laser endomicroscopy systems have received U.S. Food and Drug Administration (FDA) clearance. According to the FDA pre-market summary letter (K042740):

> The Pentax Confocal Laser System is a required accessory for legally marketed video endoscopes equipped with a confocal laser imaging module. The system is intended to allow confocal laser imaging of the internal microstructure of tissues in the anatomical track assessed by the endoscope.

The FDA premarket notification letter (K061666) for the F-600 System (Cellvizio® Confocal Miniprobe™) indicates this device is a "confocal laser system that is intended to allow confocal laser imaging of the internal microstructure of tissues in the anatomical tract, that is, GI or respiratory, accessed by the endoscope."

The American Society of Gastroenterology states that additional studies are needed to determine how confocal fluorescent endomicroscopy will affect the practice of screening, surveillance, and early diagnosis of benign, premalignant, and malignant lesions of the GI tract (ASGE, 2009).

The NCCN guidelines on colorectal cancer screening indicate confocal endomicroscopy may be an appropriate screening tool for individuals with a history of ulcerative colitis (NCCN, 2013).

Confocal laser endomicroscopy is reported to provide enhanced visualization of the vascular networks of gastroesophageal mucosa and could potentially help to distinguish malignant from normal mucosa. However, the peer-reviewed literature on this technology consists of predominantly small, non-randomized, uncontrolled trials. At the present time there is inadequate data to demonstrate that this technology clearly improves clinical outcomes as compared with standard endoscopy and biopsy.

Fiberoptic Analysis

One device for fiberoptic analysis of colorectal polyps has received FDA pre-market approval (that is, the Optical Biopsy System™, SpectraScience, in Minneapolis, MN). According to the FDA Summary of Safety and Effectiveness Data, this device should be used as an aide to lower gastrointestinal endoscopy as follows:

> For the evaluation of polyps less than 1 cm in diameter that the physician has not already elected to remove. The device is only to be used in deciding whether such polyps should be removed (which includes submission for histological examination).

The FDA approval for this device was based in part on the results of a prospective study of 101 individuals undergoing colonoscopy that evaluated the sensitivity and specificity of the fiberoptic system compared to physician assessment alone. While fiberoptic analysis may identify additional adenomatous polyps that the physician considered to be hyperplastic based on visual assessment, it is difficult to determine the clinical significance of these findings. It is not clear how the physician decided to select additional polyps for fiberoptic analysis, or whether the same results could be obtained by simply randomly taking a biopsy of a subset of polyps that were considered hyperplastic on visual assessment.

Multi-Band Imaging

Multi-band imaging (MBI) is a real time, on demand digital image processing technique that enhances the appearance of mucosal surface structures by using selected wavelengths of light to create reconstituted virtual images. MBI can also be used in combination with electronic or optical magnification for better visualization of the mucosa. Similar to narrow band imaging (NBI), MBI is being investigated as an imaging technique to enhance visualization of the vascular network and surface texture of the mucosa in an effort to improve tissue characterization, differentiation, and diagnosis. MBI is being investigated as a tool to enhance the diagnosis of several conditions, including but not limited to high grade dysplasia and esophageal cancer and for differentiation of subtypes of gastric metaplasia and colorectal lesions.

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Status Evaluation Report on NBI and multiband imaging (ASGE, 2008) includes MBI as one of the emerging technologies that may

improve the diagnosis and characterization of mucosal lesions of the GI tract, in particular as an adjunctive technique to magnification endoscopy. The report notes that some of the limitations of MBI include, but are not limited to, the fact that while a classification of multi-band mucosal patterns has been described for various conditions (e.g., Barrett's esophagus and colon polyps), it has not yet been standardized or validated sufficiently to establish guidelines for routine practice. Also, the optimal MBI preset(s) for tissue diagnosis or differentiation have not been determined and may be dependent upon the location or type of lesion being examined. The authors state that there is a need for randomized, controlled, multicenter trials assessing these new imaging modalities (NBI and MBI) against conventional white light endoscopy and other techniques (e.g., chromoendoscopy) for various GI conditions. As in the case of NBI, the authors concluded that MBI may improve the diagnosis and characterization of mucosal lesions of the GI tract, especially when used as an adjunctive technique to magnification endoscopy. However, more research addressing the standardization of image characterization, further image-to-pathology correlation and validation, and the impact of MBI on individual outcomes are necessary before endorsing its use can be considered routine practice of GI endoscopy.

Narrow Band Imaging

Narrow band imaging is another illumination technology which was developed primarily to enhance visualization of the mucosal microvasculature and to improve identification of vascular alterations indicative of pathologic conditions (ASGE, 2008). NBI is being investigated as a tool to enhance the identification of lesions associated with several conditions, including but not limited to gastroesophageal reflux disease (GERD), Barrett's esophagus, chronic ulcerative colitis, and GI cancer. NBI received FDA clearance through the 510(K) pre-market process, which included NBI with the existing EVIS EXERA 160A System (Olympus Medical Systems Corp) endoscopic equipment and indicates the technology is appropriate for endoscopic diagnosis, treatment and video observation.

Chiu and colleagues (2007) carried out a comparative study evaluating the diagnostic efficacy of NBI in differentiating neoplastic from non-neoplastic colorectal lesions. In this prospective study, 180 colorectal lesions from 133 subjects were observed with conventional colonoscopy, low-magnification and high-magnification NBI and chromoendoscopy. A histologic analysis was later carried out on the lesions. Endoscopic images were stored electronically and randomly allocated to two readers for evaluation. The sensitivity, specificity and diagnostic accuracy of each endoscopic modality were assessed by reference to histopathology. The researchers reported that NBI and chromoendoscopy scored better under high magnification than under low magnification in comparison with conventional colonoscopy. The diagnostic accuracy of NBI with low or high magnification was significantly higher than that of conventional colonoscopy (low magnification: $p=0.04$ for reader 1 and $p=0.004$ for reader 2; high magnification: $p<0.001$ for both readers) and was comparable to that of chromoendoscopy. The authors concluded that both low-magnification and high-magnification NBI can distinguish neoplastic from non-neoplastic colorectal lesions; the diagnostic accuracy of NBI was better than that of conventional colonoscopy and equivalent to that of chromoendoscopy. The authors also acknowledged that the role of NBI in screening colonoscopy needs further evaluation.

Ignjatovic and colleagues (2009) carried out a prospective study to evaluate the accuracy of polyp characterization using optical diagnosis compared with histopathology, the current gold standard. Four endoscopists at a single facility evaluated consecutive individuals with positive fecal occult blood test results or previous adenomas. Of the 363 polyps that were less than 10 mm (identified in 130 individuals), 278 had both histopathologic and endoscopic diagnoses. The histopathological examination revealed 198 of these polyps to be adenomas and 80 non-neoplastic lesions (of which 62 were hyperplastic). Endoscopic diagnosis using NBI had a sensitivity of 94%, a specificity of 89%, and an overall accuracy of 93%. This diagnostic method allowed for assignment of a surveillance interval immediately after colonoscopy in 82 of the 130 individuals who had polyps less than 10 mm. Assignment accuracy was 95% according to the U.S. Multisociety Guidelines and 98% according to United Kingdom (U.K.) guidelines. The researchers acknowledged that this study had several limitations including the following: (1) colonoscopists had different levels of experience; (2) study took place in an academic training area; and (3) equipment used (Lucera, Olympus, Japan) was only available in the U.K. and Japan.

Another study (Tischendorf, 2010) evaluated the diagnostic accuracy of NBI endoscopy with and without high magnification to differentiate neoplastic from non-neoplastic colorectal polyps. A total of 200 colorectal polyps from 131 individuals were evaluated. Half (100) of these lesions were classified using NBI endoscopy with high optical magnification and the remaining 100 lesions were classified using high-

In-Vivo Detection of Mucosal Lesions with Endoscopy, continued

definition endoscopy without high magnification. An assessment of the clarity of the vessel network and a histologic examination were completed on all lesions. The sensitivity and specificity of NBI endoscopy with high magnification to differentiate neoplastic versus non-neoplastic lesions was 92.1% and 89.2% respectively. Comparable in performance, high-definition NBI endoscopy without high magnification resulted in a sensitivity of 87.9% and specificity of 90.5%. However, visualization of the capillary network was better with NBI endoscopy with optical magnification compared with high-definition NBI endoscopy without high magnification. When compared with NBI endoscopy, white-light endoscopy, with or without magnification, resulted in inferior discrimination between neoplastic and non-neoplastic polyps. The researchers conceded that one of the limitations of this study was the relatively low number of polyps that were included and stated that "definitive conclusions cannot be drawn and larger studies are warranted to determine whether or not smaller but statistically significant differences between NBI-based endoscopy with and without high magnification exist."

Ezoe and colleagues (2011) carried out a multicenter, prospective, randomized trial that compared the real-time diagnostic yield of conventional white-light imaging (C-WLI) for small, depressed gastric mucosal cancers with that of magnifying narrow-band imaging (M-NBI) in individuals with undiagnosed depressed lesions less than or equal to 10 mm in diameter identified by endoscopy. The diagnostic accuracy, sensitivity, and specificity for C-WLI and M-NBI were 65%, 40%, and 68% and 90%, 60%, and 94%, respectively. Combining M-NBI with C-WLI increased accuracy to 97%, sensitivity to 95%, and specificity to 97%. The researchers concluded that C-WLI in combination with M-NBI is better than using either modality alone. The study suggests that M-NBI may enhance the ability to diagnose subtle characteristics of mucosal cancers better than C-WLI in a select, high-risk population. Use of both modalities was statistically superior to C-WLI alone but not to M-NBI alone.

Nagorni and colleagues (2012) conducted a meta-analysis which compared standard or high definition white light colonoscopy with NBI colonoscopy for detection of colorectal polyps. Eight randomized controlled trials (3,673 participants) were included in the analyses. The authors found there was no convincing evidence that NBI is significantly better than high-definition white light colonoscopy for the identification of subjects with colorectal polyps or colorectal adenomas. However, the authors did conclude that NBI might be better than standard definition white light colonoscopy and equal to high definition white light colonoscopy for identification of subjects with colorectal polyps, or colorectal adenomas.

Researchers (Ignjatovic, 2012) conducted a multicenter study comparing NBI with high-definition white light endoscopy. The randomized, controlled trial included 112 participants with chronic ulcerative colitis who underwent colonoscopic surveillance with either procedure. Fifty-six subjects were allocated to the NBI group and the other half were included in the white light endoscopy group. Targeted biopsies of suspicious areas and quadratic random biopsies every 10 cm were obtained from both groups. The primary outcome measure was the proportion of participants with at least one area of dysplasia detected. In a prespecified mid-point analysis, the criteria for trial discontinuation were met and the trial was stopped and analyzed at this point. The researchers found no difference in the primary outcome between the 2 groups with 5 subjects in each group having at least 1 dysplastic lesion. The yield of dysplasia from random nontargeted biopsies was 1/2707 (0.04%). Random background biopsies were ineffective in detecting dysplasia.

In another study, researchers conducted a meta-analysis to determine whether use of NBI enhances the detection of adenomas. A total of six studies were included in the analyses. When the data was analyzed, the authors found there was no statistically significant difference in the overall adenoma detection rate with the use of NBI or white light colonoscopy and there was no statistically significant difference in polyp detection rate using NBI or white light colonoscopy. The researchers concluded NBI did not increase adenoma or polyp detection rates (Dinesen, 2012).

Sakamoto and colleagues (2012) compared interpretation times between NBI and magnifying chromoendoscopy (MCE) techniques in distinguishing between neoplastic and non-neoplastic small colorectal lesions. A total of 693 consecutive participants who underwent colonoscopy at a single medical facility in Japan were enrolled. When the first lesion was detected by conventional white-light observation, the participant was randomly assigned to undergo a sequence of NBI and MCE observations (group A: NBI-MCE, group B: MCE-NBI). The time to diagnosis with each modality (NBI, from changing to NBI until diagnosis; MCE, from the start of indigo carmine solution spraying until diagnosis) was recorded by an independent observer. The sensitivity, specificity, and diagnostic accuracy of the first modality used in

In-Vivo Detection of Mucosal Lesions with Endoscopy, continued

each group (NBI or MCE) were assessed by referring to the histopathological data. Seventy-one participants (137 lesions) were randomized to group A, and 80 participants (163 lesions) to group B. The median interpretation times were 12 seconds (interquartile range [IQR]: 7-19 seconds) in group A, and 17 seconds (IQR: 12−24 s) in group B, the difference being significant (p<0.001). The authors reported no significant differences were observed between NBI and MCE in terms of sensitivity, specificity, and diagnostic accuracy and concluded NBI reduces the interpretation times for distinguishing between neoplastic and non-neoplastic small lesions during colonoscopies, without loss of diagnostic accuracy.

Kobayashi and colleagues (2012) conducted a meta-analysis comparing the diagnostic test performance of chromoendoscopy and NBI for colonic neoplasms. Twenty-seven of the 1342 articles screened met the inclusion criteria. Pooled sensitivity for chromoendoscopy and NBI was 0.94 (95% CI, 0.92−0.95) and 0.94 (0.91−0.97), and specificity was 0.82 (0.77−0.88) and 0.86 (0.83−0.89), respectively. There were no differences in sensitivity (p=0.99) or specificity (p=0.54) between the 2 methods. In the secondary analysis, pooled sensitivity for chromoendoscopy and NBI was 0.93 (95% CI, 0.90−0.97) and 0.96 (0.93−0.99) and specificity was 0.80 (0.73−0.87) and 0.85 (0.78−0.92) respectively. Overall, the pooled false-negative rate was 0.057 (95% CI, 0.040−0.73) for chromoendoscopy and 0.057 (95% CI, 0.028−0.085) for NBI. The authors concluded that chromoendoscopy and NBI had similar diagnostic test characteristics in the assessment of colonic neoplasms; however, the false-negative rate for both methods of 5.7% is an unacceptably high rate, and therefore, neither method is ready for general use.

Dutta and colleagues (2013) explored whether NBI is superior to conventional white light gastroscopy (WLG) in detecting potentially premalignant gastric lesions. In a randomized prospective crossover, 200 individuals above 45 years of age with dyspepsia and no alarming symptoms (weight loss, vomiting, hematemesis, melena, dysphagia), underwent gastric mucosal examination. The authors concluded that NBI was superior to WLG for detection of atrophic gastritis and intestinal metaplasia.

The American Cancer Society (ACS) and the U.S. Multi-Society Task Force on Colorectal Cancer jointly published a guideline regarding colonoscopy surveillance after polypectomy which indicates that there is currently insufficient evidence that the evolving technology of NBI should be part of routine post polypectomy surveillance at this time (Winawer, 2006).

The American Society for Gastrointestinal Endoscopy ASGE Technology Status Evaluation Report on NBI and multiband imaging. (ASGE, 2008) includes NBI as one of the emerging technologies that may improve the diagnosis and characterization of mucosal lesions of the GI tract, in particular as an adjunctive technique to magnification endoscopy. However, additional studies addressing the standardization of image characterization, further image-to-pathology correlation and validation, and the impact of this technology on individual outcomes are necessary before endorsing the use of NBI in the routine practice of GI endoscopy.

The American Gastroenterological Association (AGA) Institute technology assessment on image-enhanced endoscopy (AGA, 2008) includes NBI in the category of "imaged-enhanced endoscopy (IEE)" which "encompasses various means of enhancing contrast during endoscopy using dye, optical, and/or electronic methods." The technology assessment states that "equipment-based IEE is increasingly reported to aid in the detailed visualization of the microvessels and surface structures of neoplastic, metaplastic, and hyperplastic tissues." However, "IEE is not routinely used in the management of diseases of the small intestine."

According to the American College of Gastroenterology (ACG) Guidelines for Colorectal Cancer Screening 2008 (Rex 2009):

> Narrow band imaging does not enhance mucosal inspection by endoscopists with high adenoma detection rates but may be a useful teaching tool for enhancement of flat lesion detection by endoscopists with low adenoma detection rate. The ACG recommends that clinical gastroenterologists follow actively the technical developments pertaining to mucosal inspection enhancement techniques and incorporate such techniques into practice, as they are proven to be both effective and practical. However, endoscopists should understand that no enhancement technique replaces the need for a meticulous inspection.

The US Multi-Society Task Force on Colorectal Cancer released updated consensus guidelines for colonoscopy surveillance after screening and polypectomy. According to the consensus group:

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MEDICAL POLICY

LINX SYSTEM FOR THE MANAGEMENT OF GERD

Policy # 520
Implementation Date:1/28/13
Review Dates: 2/20/14, 3/19/15, 2/11/16, 2/16/17, 2/15/18, 2/10/19, 2/20/20, 2/18/21, 12/20/21, 2/20/24, 6/7/25
Revision Dates:6/20/24

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Gastroesophageal reflux disease (GERD) refers to a condition in which the lower esophageal sphincter opens spontaneously for varying periods of time or does not close properly, and stomach contents rise up into the esophagus. Other names for this condition include acid reflux or acid regurgitation disease, because digestive acids rise with the food. Most of these people can manage the discomfort of heartburn with lifestyle changes and over-the-counter medications. Persistent reflux occurring more than twice a week can eventually lead to more serious health problems. Those with persistent GERD may need more routine medications at higher doses than available over-the-counter medications or surgery to reduce symptoms.

Most commonly, GERD is easily treated with medications to suppress acid production. These medications can be over-the-counter medications such as antacids (e.g., Tums), histamine-2 receptor antagonists (e.g., Zantac), or proton pump inhibitors (e.g., Nexium). When acid suppression is inadequate to alleviate symptoms or patients tire of using medication daily, surgery is contemplated to correct the problem. The most common surgeries involve wrapping the stomach around the esophagus to create a reinforced lower esophageal sphincter; this type of surgery is called a fundoplication.

The implantable LINX Reflux Management System (Torax Medical Inc., Shoreview, MN) is a string of magnetic beads that is affixed around the distal esophagus at the gastroesophageal junction to prevent GERD. Each of the beads in this bracelet carries a weak magnetic force holding the beads opposed, similar to the constricted LES. The force typical of the esophageal body pressure generated with a swallow is enough to disrupt the magnetic force holding these beads together, thereby opening the ring of magnets and allowing a swallowed bolus to pass, similar to the relaxation of the LES. Immediately following this bolus passage, the beads re-oppose, and the distal esophagus is again closed. This device is placed laparoscopically in a manner similar to how a laparoscopic fundoplication is performed.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers implantation of the LINX device for members who meet <u>all</u> the following criteria:

1. 18−74 years of age; and
2. BMI ≤ 35; and

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LINX System For The Management of Gerd, continued

3. Documented typical symptoms of GERD for longer than 6 months (e.g., regurgitation or heartburn which is defined as a burning epigastic or substernal pain which responds to acid neutralization or suppression); and
4. Refractory to ideal medical management (i.e., requires twice daily proton pump inhibitor (PPI), potassium-competitive acid blocker (PCAB), or other anti-reflux drug therapy, diet and lifestyle change discussed); and
5. Hiatal hernia ≤ 3cm as determined by endoscopy; and
6. Total Distal Ambulatory Esophageal pH, must meet the following:
   i) pH < 4 for ≥ 4.5% of the time with discontinuation of any GERD medications for at least 7 days prior to testing; and
7. Distal esophageal motility (average of sensors 3 and 4) is ≥ 35 mmHg peristaltic amplitude on wet swallows or ≥ 70% (propulsive) peristaltic sequences; and
8. Symptomatic improvement on PPI therapy demonstrated by a GERD-Health-Related Quality of Life (GERD-HRQL) score of ≤ 10 on PPIs and ≥ 15 off PPIs, or a ≥ 6-point improvement when comparing their on PPI score and off GERD-HRQL score; and
9. Fundoplication cannot be performed due to anatomy; and

10. None of the following:
    a. History of gastroesophageal surgery, anti-reflux procedures, including endoscopic anti-reflux procedures
    b. Suspected or confirmed esophageal or gastric cancer
    c. Esophagitis - Grade C or D (LA Classification)
    d. Symptoms of dysphagia more than once per week within the last 3 months.
    e. Diagnosed with Scleroderma
    f. Diagnosed with an esophageal motility disorder such as but not limited to Achalasia, Nutcracker Esophagus, or Diffuse Esophageal Spasm or Hypertensive LES
    g. History of or known esophageal stricture or gross esophageal anatomic abnormalities (Schatzki's ring, obstructive lesions, etc.)
    h. Esophageal or gastric varices
    j. Pregnant or breastfeeding
    k. Life expectancy less than 3 years
    l. Diagnosed psychiatric disorder (e.g., bipolar, schizophrenia, etc.); not including depression being treated with appropriate medication(s), which would require statement of clearance from the treating Behavioral Health team
    m. Suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials
    n. Current electrical implant or metallic abdominal implant

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

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Summary of Medical Information

Limited published evidence is available to assess the efficacy and safety of the LINX Reflux Management System. Only one systematic review and three peer-reviewed papers were met inclusion criteria for the technology assessment completed on December 11, 2012. All published data on the LINX system is from between 2008 and 2012. Additionally, a Hayes "Search and Summary" was published on the LINX system in September of 2012.

In the Hayes Search and Summary, it was specifically noted there is currently insufficient evidence to conduct a comprehensive health technology assessment on the safety and efficacy of LINX. Yet, differing from the conclusion reached by Hayes, Smith et al., two years prior when LINX was only available through an FDA trial, noted that outcomes were significantly improved compared to baseline after surgery at three months and one-year follow-ups. Limitations to this study were a lack of randomization, longer term outcomes beyond 1 year or comparative outcomes to standard therapies.

Though the number primary studies are limited they do suggest the LINX system to be efficacious and potentially durable in treating GERD. Bonavina et al. found in a trial published in 2010 that 44 patients who underwent LINX surgery reduced their PPI use by 85% and 90% after one and two years respectively. Unfortunately, no information is given in the paper which shows what the baseline PPI use was at the beginning of the study. All that is mentioned is that use decreased after the surgery. Similarly, no patients enrolled in the trial were taking H2RAs which leaves the question unanswered as to how well the LINX system works in that cohort. Analogous results and study limitations were found in a previous study by the same author published two years prior. Similarly, in a 2012 study by Lipham et al., 80% of participants had a complete cessation of PPIs at three years follow-up. In every studied outcome (device migration, erosion, PPI use post-implantation, pH normalization and esophageal acid exposure), the group found statistically significant improvement after three years. As in the two studies by Boniva et al. no conclusions can be drawn regarding the benefit of the LINX device in patients currently taking H2RAs or calcium carbonate. These studies also suggest a good safety profile for this device. None of the devices identified issues with early device migration or other surgical complications beyond those one might expect with a laparoscopic procedure. These studies experience the same limitations noted in the Hayes Search and summary in that there is a lack of outcome studies out to five years and a lack of comparative studies to standard antireflux procedures and anti-reflux medication use.

The technology assessment concluded current evidence, though limited, demonstrates that the LINX system is efficacious and safe in decreasing symptoms of GERD up to three years after surgery. However, no evidence exists demonstrating the benefit of the LINX system in patients taking H2RA medications or calcium carbonate tabs. The lack of data out to five years, the complete lack of randomized, prospective trials and head-to-head trials against Nissen fundoplication do not allow for firm conclusions on this technology.

Billing/Coding Information

CPT CODES

43284	Laparoscopy, surgical, esophageal sphincter augmentation procedure, placement of sphincter augmentation device (ie, magnetic band), including cruroplasty when performed
43285	Removal of esophageal sphincter augmentation device
43289	Unlisted laparoscopy procedure, esophagus

HCPCS CODES

No specific codes identified

Key References

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2. Bonavina, L, Saino, GI, Bona, D, et al. (2008). Magnetic augmentation of the lower esophageal sphincter: results of a feasibility clinical trial. J Gastrointest Surg. 12. 12:2133-40.
3. Castell, DO. (1975). Diet and the lower esophageal sphincter. Am J Clin Nutr. 28. 11:1296-8.
4. Feldman, M. (2010). Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Saunders Elsevier. Last Update: Available: http://www.mdconsult.com/books/page.do? eid=4-u1.0-B978-1-4160-6189-2.00043-3--s0020&isbn=978-1-4160-6189-2&uniqId=383159680-5#4-u1.0-B978-1-4160-6189-2.00043-3--s0020. Date Accessed: November 19, 2012.

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MEDICAL POLICY

PANCRAGEN MOLECULAR DIAGNOSTIC TEST FOR EVALUATION OF PANCREATIC CYSTS

Policy # 603
Implementation Date:11/29/16
Review Dates: 12/21/17, 12/4/18, 12/16/19, 12/17/20, 12/6/21, 1/17/23, 12/11/23, 12/8/24
Revision Dates: 1/24/17, 12/23/24

Description

Pancreatic cysts may be detected in over 2% of patients who undergo abdominal imaging for unrelated reasons, and this frequency increases with age.

Most pancreatic cystic neoplasms (PCNs) are detected incidentally when abdominal imaging is performed for other indications. PCNs account for more than 50% of pancreatic cysts, even in patients with a history of pancreatitis. The first step in evaluating a cyst is to obtain magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP). Cross-sectional imaging is obtained to determine if there are features present that can identify the specific cyst type and to determine if there are any findings that increase the risk of malignancy (large cyst > 3 cm, a solid component within the cyst, main pancreatic duct dilation). Endoscopic ultrasound with fine-needle aspiration (EUS-FNA) provides high-quality imaging of the pancreas and the opportunity to sample pancreatic lesions, which increases diagnostic accuracy. The addition of intraductal EUS may also increase diagnostic accuracy but is not part of the routine evaluation of pancreatic cysts.

Once a cyst has been aspirated, it undergoes analysis of any fluid obtained. This includes cytology, CEA level, and amylase, along with genetic testing for KRAS, GNAS, and sometimes other markers. In some instances, these markers are indeterminate and a decision to either monitor the cyst with periodic imaging based on established guidelines, or surgical intervention, must be undertaken with less certainty as to the true necessity of this invasive intervention.

PancraGEN (Interpace Diagnostics LLC, Parsippany, NJ), formerly Pathfinder TG (RedPath Diagnostics) is a laboratory test that integrates cytological, fluid chemistry (CEA, amylase), imaging, and DNA analysis into 4 diagnostic categories that works to help stratify the risk of malignancy, particularly in cysts with indeterminate features. On a DNA level, PancraGEN measures the quantity, quality, and level of DNA damage (specifically, the presence and clonality of loss of heterozygosity mutations (LOH) next to tumor suppressor genes and oncogene point mutations) that is causally responsible for pancreatic cancer. PancraGEN measures 15 genetic markers which are distributed across 10 chromosomal regions including KRAS and GNAS.

Cyst fluid chemistry (i.e., CEA, amylase), imaging, levels of atypia, and cellularity are abstracted from the patients' records provided by the managing physician. Parameters of these initial tests are used along with the results of DNA analysis to compute a malignancy risk estimate to help guide surgery.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover the PancraGEN molecular diagnostic test for routine evaluation of pancreatic cysts as it is considered experimental/investigational.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information
Two systematic reviews and 14 primary studies were identified that met inclusion criteria for this review. Data on > 1,500 samples have been reported in the literature since 2006. Most of the literature on PancraGEN or Pathfinder (as this test was previously known) was related to the clinical validity of the test, namely, the test's ability to accurately profile tissue samples versus cytology, cyst fluid, or other standard means of cyst assessment. All the studies that noted sensitivity and specificity showed that the test has higher of the latter than the former, with specificities ranging from 75% to 100%. Of the 14 primary studies, only 1 paper (Das et al.) discussed the health economics of the test, and identified the noteworthy number needed to treat as 56. Similarly, only 2 papers (Kowalski and Loren et al.) discussed the potential clinical utility of the study showing that use of the test may improve patient surveillance.

In general, the literature shows some measure of clinical validity but fails to prove the clinical utility of the test (e.g., altering treatment plans, improving morbidity and mortality, improving progression-free survival, etc.). Given that the test has an average specificity of 88%, the lack of clinical utility data, limited follow-up periods in the literature, and evidence of improved outcomes resulting from use of PancraGEN, the current body of evidence is not sufficient to draw meaningful conclusions regarding the clinical usefulness of the test.

According to the American College of Gastroenterology (ACG) clinical guideline: Diagnosis and Management of Pancreatic Cysts (Elta, 2018) Recent studies have shown that integrating molecular testing with cyst clinical features increases the sensitivity and specificity for identifying IPMNs or MCNs. Unfortunately, they are costly and have not helped determine cancer risk. Their use may be considered in cases in which the diagnosis is unclear, and the results are likely to change management (Conditional recommendation, very low quality of evidence).

In 2018 Arner and colleagues studied the addition of DNA molecular analysis in a retrospective review of 46 patients, they concluded that molecular analysis alters the clinical management of pancreatic cystic lesions most often when CEA levels are intermediate (45–800 ng/mL) or when no CEA concentration is available. Use of DNA molecular analysis can be considered in this cohort, and they concluded that further study of molecular markers in pancreatic cystic lesions is recommended.

In 2019, Farrell and colleagues reported results of a cohort study of 478 participants to determine the incremental predictive value of molecular analysis of pancreatic cyst fluid to assess for malignancy risk over the long term. A total of 209 participants had surgical pathology-derived outcomes and 269 had clinical follow-up of > 2 years. Cysts were classified based on (HRS) High risk stigmata (jaundice, main pancreatic duct >1 cm, solid pancreatic masses) and worrisome features (WFs) classified as (mural nodule, mucin or papillary projection; main pancreatic duct, .5-.9 cm; cyst size >3 cm; pancreatitis, abrupt changes in main pancreatic duct with distal atrophy and lymphadenopathy). Forty-two participants had high risk stigmata (HRS), 272 lacked both HRS and worrisome features (WFs), and 164 lacked HRS but had WFs. DNA abnormalities did not statistically change the long-term malignancy risk in participants with

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HRS nor in those individuals who were lacking both HRS and WFs. Although the presence of ≥ 2 DNA abnormalities in the cohort with worrisome (WF) significantly increased the malignancy risk (relative risk, 5.2; p=0.002) and the absence of all DNA abnormalities significantly decreased risk (relative risk, 0.4; p=0.040), this testing did not provide prospective evidence of impact on clinical outcomes.

In summary, the body of peer-reviewed literature concerning PancraGEN is insufficient to establish the analytic validity, clinical validity, and clinical utility of this test. There is insufficient literature and evidence to demonstrate that the topographic genotyping used in PancraGEN is an effective method to aid in the management of individuals with pancreatic cysts or solid pancreaticobiliary lesions when other testing methods are inconclusive or unsuccessful. There is also a lack of peer-reviewed evidence demonstrating that the use of topographic genotyping in the management of individuals with pancreatic cysts results in improved clinical outcomes.

Billing/Coding Information

CPT CODES

81479	Unlisted molecular pathology procedure
84999	Unlisted chemistry procedure

HCPCS CODES

No specific codes identified

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Revision History

Revision Date	Summary of Changes
12/23/24	For Commercial Plan Policy, modified exclusion as follows: “Select Health does NOT cover the PancraGEN molecular diagnostic test for ***routine evaluation*** of pancreatic cysts as it is considered experimental/investigational.”

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MEDICAL POLICY

PILLCAM ESO (ESOPHAGUS)

Policy # 278
Implementation Date:8/15/05
Review Dates: 8/17/06, 8/23/07, 8/13/09, 8/19/10, 9/15/11, 11/29/12, 10/24/13, 10/23/14, 10/15/15, 10/20/16, 10/19/17, 10/14/18, 10/20/19, 10/15/20, 12/7/21, 9/15/22, 10/13/23, 11/1/24
Revision Dates: 1/17/06, 8/18/08, 1/13/21

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Gastroesophageal reflux disease (GERD) is a common chronic disorder characterized by recurrent heartburn, regurgitation, and/or difficulty swallowing. It can lead to esophagitis, Barrett's esophagus, esophageal erosion or ulceration, and esophageal stricture. Esophagitis is an inflammatory condition caused by chronic irritation of the condition that can progress to esophageal adenocarcinoma. Each year, approximately 700,000 Americans with GERD are diagnosed with Barrett's esophagus, and a small number of these progresses to esophageal cancer.

The standard manner to assess for the presence of Barrett's epithelium is flexible fiber optic upper GI endoscopy with multiquadrant biopsies spaced 1−2 cm apart. A new technology, The Given Diagnostic System with the PillCam ESO Capsule has been developed and is being promoted as a replacement for routine surveillance of Barrett's epithelial changes in patients at risk for GERD and for surveillance in patients with esophageal varices due to chronic liver disease.

The PillCam ESO capsule is a disposable miniature battery-powered endoscopic camera designed to be swallowed and acquire esophageal images as it progresses down the esophagus. The capsule, which is about the size of a multivitamin, is equipped with miniature cameras on both ends and an internal transmitter. Three sensor arrays are strategically placed on the patient's chest and receive digital transmissions from the camera capsule as it progresses down the esophagus. The sensors are connected to a data recorder, which is worn on a belt around the waist. The patient swallows the capsule lying down and is then raised in a series of inclinations over a total of 5 minutes. The PillCam ESO travels through the esophagus by normal peristaltic waves, flashing 14 times per second, each time capturing images of the inner lining of the esophagus. The battery life of the PillCam ESO is about 20 minutes. The procedure usually lasts approximately 5 minutes. It does not require any topical or systemic anesthesia. The PillCam capsule moves through the digestive tract by peristalsis and is excreted naturally within 24−48 hours.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover PillCam ESO. Current published literature fails to demonstrate adequate statistical validity of this technology compared to standard endoscopic studies. This meets the plan's definition of experimental/investigational.

Pillcam® ESO (Esophagus), continued

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

In January 2008, a Hayes Medical Technology Directory was published on PillCam ESO. The report identified published studies evaluating the efficacy and safety of capsule endoscopy for the diagnosis of esophageal disease. The report stated that PillCam ESO is well-tolerated and safe but that the need for follow-up EGD in some patients is a limitation of the procedure. The report further noted while certain contraindications are known for the procedure (e.g., bowel abnormalities that may obstruct passage of the device), patient selection criteria for the procedure continue to evolve. Hayes concluded that the evidence for the device is limited and assigned a 'C' rating for indications where confirmatory biopsy is unlikely and a 'D' rating for individuals with specific contraindications that may hinder passage of the capsule.

Seven additional studies meeting search criteria have been published since the January 2008 Hayes Report. These studies evaluated use of PillCam ESO for a variety of indications and evidence for the procedure varied. In one manufacturer sponsored study, de Franchis et al. tested 288 patients with esophageal varices (195 diagnostic, 93 surveillance) using PillCam ESO with EGD as the gold standard test. Overall agreement between the 2 tests was 85.8% (kappa = 0.73). PillCam ESO had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 84%, 88%, 92%, and 77%, respectively. Test parameters were similarly high in differentiating between varices requiring treatment and varices requiring surveillance with sensitivity, specificity, PPV, and NPV at 78%, 96%, 87%, and 92%, respectively. The authors still concluded, however, that EGD should be used for screening for large varices. They suggested that PillCam may improve adherence to screening programs, while noting that no data are available to support this supposition.

Another manufacturer sponsored study by Gralnek et al. included 28 patients with esophageal pathology including GERD, esophagitis, Barrett's esophagus, esophageal varices, and other esophageal lesions. Both EGD and capsule endoscopy were performed on the same day and read in random order by the study investigator who was blinded to the EGD results. PillCam ESO produced definitive results in 30/43 lesions (69.8 %) and EGD in 29/43 (67.4%). Overall agreement between the 2 procedures was 86% (kappa = 0.68). Sensitivity, specificity, PPV, and NPV were as follows: Barrett's 100%, 74%, 64%, and 100%, respectively; esophagitis: 80%, 87%, 57%, and 95%, respectively. Though the authors conclude that PillCam ESO provides high-quality visualization of the esophagus, they call for further prospective studies with larger sample sizes.

In 98 patients with symptoms of esophageal disease, 2/3 of whom already had an abnormal EGD. Delvaux et al. reported PPV 80.0 % and NPV of 61.1% for capsule endoscopy. Overall agreement between EGD and capsule endoscopy per patient (kappa = 0.42) and per findings (kappa = 0.40) was moderate. Inter-rater agreement was similarly moderate for findings (kappa = 0.39) and quality assessment (kappa = 0.24). Galmiche et al. enrolled 89 (77 completed the study) patients with chronic reflux symptoms. The overall sensitivity, specificity, PPV, and NPV of PillCam to detect Barrett's Esophagus were 71%, 99%, 83%, and 98%. For hiatal hernia, sensitivity, specificity, PPV, and NPV of PillCam were 36%, 91%, 71%, and 71% Overall agreement between EGD and PillCam ESO for esophagitis and ESEM were 0.74 and 0.72, respectively.

Pillcam® ESO (Esophagus), continued

In Pena et al., 22 cirrhotic patients scheduled for outpatient EGD at a single medical center for screening or surveillance of esophageal varices underwent EGD and ECG. The ECE was able to accurately identify 82% of varices graded II or higher by EGD (9/11). The ECE overestimated the size of the varices in 6 subjects when compared to EGD, whereas PIllCam ESO underestimated the size in a single subject. All patients tolerated both studies well. There was no statistical difference in the overall satisfaction scores between the PillCam ESO and EGD and all subjects stated they would perform each study again if instructed by their physician.

In Qureshi et al., 20 adults with biopsy-proven Barrett's esophagus, PillCam ESO confirmed this diagnosis in 44.4% of study participants. The authors also reported poor interobserver agreement and concluded that PillCam ESO could not be recommended for screening of short segment Barrett's. Sharma et al. reported test characteristics form sensitivity, specificity, positive PPV, and NPV of ECE for BE in GERD patients were 67%, 87%, 60%, and 90%, respectively. The sensitivity, specificity, PPV, and NPV of ECE for BE patients undergoing surveillance were 79%, 78%, 94%, and 44%, respectively. The sensitivity, specificity, PPV, and NPV for erosive esophagitis were 50%, 90%, 56%, and 88%, and for hiatal hernia were 54%, 67%, 83%, and 33%, respectively. The authors concluded these diagnostic rates were not yet accurate enough to recommend PillCam ESO for routine clinical practice.

In summary, the evidence supporting PillCam ESO is limited, particularly for conditions like Barrett's esophagus where biopsy is required for diagnosis. Studies examining the cost-effectiveness of the procedure are needed. Though use of PillCam ESO may encourage greater compliance with routine screening as it is more easily tolerated than EGD, data supporting this conclusion are limited. The single study that measured treatment preferences found that patients were willing to undergo either procedure again if it were recommended by their doctor. Additional research is needed before PillCam ESO can be recommended as an alternative to EGD.

Billing/Coding Information

CPT CODES

Not Covered: Investigational/Experimental/Unproven for this indication

91111	Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), esophagus with physician interpretation and report
91229	Unlisted diagnostic gastroenterology procedure

HCPCS CODES

No specific codes identified

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Pillcam® ESO (Esophagus), continued

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Disclaimer

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MEDICAL POLICY

PROGNOSTIC SEROGENETIC TESTING FOR CROHN'S DISEASE (PROMETHEUS PROGNOSTIC)

Policy # 484
Implementation Date:5/9/11
Review Dates: 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 9/18/18, 4/17/19, 4/6/20, 4/15/21, 3/18/22, 4/20/23, 4/18/24, 4/9/25
Revision Dates: 4/6/21

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Inflammatory bowel disease consists of Crohn's disease (CD), Ulcerative Colitis (UC), and indeterminate colitis. They are distinguished by the presence of idiopathic and chronic inflammation of the digestive tract. The natural history of CD is characterized by a spectrum of clinical and pathologic patterns that is extremely variable and unpredictable. CD can involve any part of the gastrointestinal tract from the oropharynx to the perianal area.

The diagnosis of CD is usually established with endoscopic findings or imaging studies in a patient with a compatible clinical history. Physical examination may be normal or show nonspecific signs (pallor, weight loss) suggestive of CD. More specific findings include perianal skin tags, sinus tracts, and abdominal tenderness.

The typical course in patients with CD involving the small and/or large intestine is one of intermittent exacerbation of symptoms followed by periods of remission. Approximately 10%–20% of patients experience a prolonged remission after initial presentation. Another study found that 53%–70% of patients developed stricturing or penetrating disease at 10 years follow-up. Predictors of a relatively severe course include less than 40 years of age at the time of presentation, the presence of perianal disease, and initial requirement for glucocorticoids. Because CD is neither medically nor surgically curable, patients require life-long therapeutic approaches to maintain symptomatic control, improve quality of life, avoid hospitalizations and surgery, and minimize complications.

Multiple auto-antibodies have been detected in patients with inflammatory bowel disease. Antibody tests have shown promise in distinguishing CD from UC and in predicting the disease course of inflammatory bowel disease in some reports. Elevated levels of C-reactive protein (CRP) have been observed in patients with inflammatory bowel disease and are generally higher in CD than in UC. CRP determination may have a role in distinguishing between these diseases, as well as in differentiating patients with IBD from those with symptoms caused by other disorders. Levels of CRP are reported to correlate with CD activity. Some studies have suggested that increased CRP levels predict the risk of relapse in patients with CD, but discordant results have also been published. It has been suggested that CRP may help in prediction of the outcome and risk of surgery, and in identification of patients who are likely to benefit most from specific treatments.

The Prometheus Crohn's Prognostic test (Prometheus Inc., San Diego, CA) combines 6 serologic markers and 3 genetic mutation markers to provide physicians with a personalized serogenetic profile for their patients. This test is purported to help physicians quantify patients' risk of developing disease complications and is designed to provide information to assist physicians in determining optimal treatment strategies for their Crohn's patients.

Prognostic Serogenetic Testing for Crohn's Disease (Prometheus® Monitr™), continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover the Prometheus Prognostic test for prognostic serogenetic testing for Crohn's disease to determine risk of disease progression. Limited data exists to demonstrate clinical utility; this meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

There is clear evidence from retrospective studies suggesting that the NOD2 mutations are associated with a variety of severe CD phenotypes. NOD2 polymorphisms increase the risk of erroneous activation of NF-kB which in turn may impact the transcription of tumor necrosis factor alpha, which may increase the risk of CD onset. The presence of two NOD2 mutations has an association with an increased risk of complicated disease; however, single mutations have weak associations. Since the Prometheus test algorithm is proprietary, it is difficult to say how much the addition of these mutations adds to the predictive ability of 7 serology markers, especially since the primary purpose of the serology markers is to distinguish Crohn's disease from UC rather than predict the occurrence of complicated CD.

For biomarkers, including genetic polymorphisms/mutations, to be useful for guiding decisions about management and/or treatment of Crohn's disease, their test performance characteristics must be clearly defined in the context of clinical settings where they will be used. For CD, there are many other predictors (e.g., clinical signs/symptoms, imaging, other lab-based tests) that are currently used by clinicians to estimate risk for severe disease. Consequently, the challenge for the Prometheus Crohn's Prognostic test (algorithm) is how good it is at providing information that helps clinicians reassess risk of severe disease above and beyond information the clinician already has access to. The typical course of CD also demonstrates that upwards of 80% will need surgery in their lifetime. It is not known what contribution, if any, the Prometheus test provides to clinicians caring for these or other CD patients with a disease profile defined by numerous other biomarkers.

No prospective randomized, controlled trials were identified where the Prometheus test or similar tests were used to guide management/treatment strategies. The recently published study upon which the Crohn's Prognostic test is based, was retrospective and acknowledged the limitations of such a study and the need for additional investigations, which would be both prospective and longitudinal.

Additionally, the CD patients predicted to have complicated disease must have a proven response to an effective therapy that results in a substantial change in the natural history of the patients. While it is true that multiple studies, including systematic reviews, have demonstrated that medical treatments for CD can be effective at various levels, substantial questions remain about not only their cost-effectiveness but also their ability to substantially impact the long-term course of disease.

A meta-analysis by Alder et al., describes the unpredictable nature of Crohn's and emphasizes the need for a predictive tool that is both sensitive and specific. The study underscores the need for cost-effective therapy resulting in a change in the natural history of these patients. The analysis demonstrated a relative

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risk (RR) of 1.58 for surgery if any NOD2 mutation was present. This represents a 58% increase in surgical risk. However, complicated disease was increased by only 17% with any NOD2 mutation. The finding that the presence of 2 NOD2 mutations had 98% sensitivity for complicated disease highlights the need for prospective studies to demonstrate that earlier aggressive intervention will improve health outcomes.

Furthermore, studies exploring response rates of anti-TNF alpha drugs in patients with versus without a NOD2 mutation have been limited due to small sample sizes.

Billing/Coding Information

Not covered: Experimental/investigational/Unproven for this indication

CPT CODES

83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
86141	C-reactive protein; high sensitivity (hsCRP)

HCPCS CODES

No specific codes identified

Key References

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Prognostic Serogenetic Testing for Crohn's Disease (Prometheus® Monitr™), continued

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MEDICAL POLICY

TRANSCUTANEOUS ELECTRICAL STIMULATION DEVICES FOR NAUSEA AND VOMITING

Policy # 199
Implementation Date: 9/30/03
Review Dates: 8/26/04, 8/25/05, 8/17/06, 8/23/07, 8/21/08, 8/13/09, 12/16/10/, 10/13/11, 7/18/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 8/3/18, 10/20/19, 10/15/20, 12/7/21, 9/15/22, 10/13/23
Revision Dates:

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Nausea and vomiting are common complications of many conditions, including pregnancy, post-operative nausea and vomiting (PONV), and chemotherapy induced nausea and vomiting (CINV). Although current pharmacologic antiemetic therapy can provide satisfactory solutions for most of these situations, some patients may fail to gain relief or prefer nonpharmacoltherapeutic means to resolve their problem. Subsequently, researchers have investigated non-pharmacologic antiemetic approaches such as transcutaneous electrical nerve stimulation (TENS). While TENS has traditionally been used to treat pain, researchers have suspected that TENS may also decrease nausea and vomiting. A TENS device consists of an electronic stimulus generator that transmits pulses of electric current to electrodes on the skin. While the mechanism of action of TENS is unknown, it has been postulated that the electrical pulses on the skin may cause central release of endorphins, and the resulting pain relief may decrease the sensation of nausea and curtail the subsequent vomiting. An alternative theory is that TENS has a direct effect on the muscles of the stomach, causing normal stomach contractions to replace the abnormal contractions associated with nausea.

Neuromodulation devices emit pulses to nerves that run along the inner wrist. Intermittent pulses along these nerves are thought to stimulate the body's central nervous system to positively modulate the body's reaction to nausea. Prior to 2009, a neuromodulating device under the trade name ReliefBand was selectively distributed in the clinical market for post-operative nausea. The rights to this device were acquired by Alvaren Pharmaceuticals who has subsequently obtained FDA approval for the renamed PrimaBella device is available as a single patient use unit with replaceable batteries and conductive gel. Both devices are Class II neuromodulation devices. The ReliefBand is no longer available and the PrimaBella is only FDA approved for nausea and vomiting associated with pregnancy indicated for use in nausea and vomiting of pregnancy.

The PrimaBella device works by gently stimulating the median nerve in the wrist to modulate nerve impulses and restore normal signals between the brain and stomach, thus, reducing nausea and vomiting. More specifically, PrimaBella delivers intermittent electrical pulses that stimulate the body's central nervous system to positively modulate the body's reaction to nausea and vomiting.

PrimaBella neuromodulation technology is unique from other neuromodulation devices in that it uses programmed, frequency-specific, electrical pulses that in theory may cause nerves to trigger signals rather than block the nerve signals. This process applies electronic pulses in a four-second cycle and prevents the body from accommodating and ignoring the pulses. The PrimaBella refers to these uniquely designed pulses and the process as "nerve stimulation therapy."

The amplitude, frequency, pulse width, and waveform characteristics employed by the PrimaBella device make it unique and give it specific properties. The amplitude (strength) of the PrimaBella pulse is 40 mA.

Transcutaneous Electrical Stimulation Devices For Nausea and Vomiting, continued

COMMERCIAL PLAN POLICY/CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover transcutaneous electrical stimulation or neuromodulation devices for nausea and vomiting. Current data does not support the use of this device as a proven technology.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Summary of Medical Information

Three systematic reviews have evaluated PrimaBella or its predecessor, ReliefBand, for treatment of nausea and vomiting. A 2005 Hayes Directory included the device in a review of acupuncture/ acupressure for treatment of nausea and vomiting, with specific focus on treatments that treated the number 6 meridian point of the pericardium channel of Hand-Jueyin (P6). In this review it was concluded that: "The evidence regarding alleviation of morning sickness by P6 stimulation is limited, less rigorous than for PONV, and equivocal. P6 stimulation and sham stimulation by wristband were found to be equally effective in reducing symptoms and gastric distress in motion sickness. Additional, well-designed, randomized controlled trials are required to evaluate acupuncture relative to other antiemetic therapies, to establish optimal treatment protocols, and to clarify which patients are most likely to benefit from therapy." In that review, only 1 study was identified that utilized either ReliefBand or PrimaBella. The review noted several randomized, placebo-controlled trials which suggested that P6 stimulation via acupressure can be effective for post-operative nausea and vomiting, particularly for women and for morning sickness with pregnancy leading to a 'B' rating for both indications. Evidence for other indications is more limited and Hayes gave 'C' ratings for the treatment for postoperative nausea and vomiting in men and children, chemotherapy-associated nausea and vomiting, and for acute myocardial infarction-associated nausea and vomiting.

A second Hayes review from 2006 reviewed transcutaneous electrical nerve stimulation (TENS) for the treatment of nausea and vomiting; eight studies involved the ReliefBand. The study concluded that: "Although there is some evidence that TENS may provide nausea and vomiting relief for some patients with postoperative nausea and vomiting, results are conflicting, and the studies have methodological flaws that hamper evaluation of the efficacy of TENS. Studies evaluating the utility of TENS for control of chemotherapy-associated nausea and vomiting also provided conflicting results and were limited and methodologically flawed. Only 1 study evaluating TENS for control of pregnancy-associated nausea and vomiting met review criteria."

Separate from the systematic reviews, seven studies met criteria for inclusion in this report. All of these used the ReliefBand rather than the PrimaBella device in its present form. These included several randomized studies in which ReliefBand was compared against alternative therapies for nausea and vomiting.

Several studies have been done specific to pregnancy-related nausea. Habib et al. randomly assigned 94 patients undergoing Cesarean delivery to either ReliefBand at the P6 point (active group) or an active ReliefBand applied to the dorsum of the wrist (sham control group). There was no statistically significant

difference between the active and sham control groups in the incidence of intraoperative/postoperative nausea (30% vs. 43%/23% vs. 41%), vomiting (13% vs. 9%/26 vs. 37%), need for rescue antiemetics (23% vs. 18%/34% vs. 39%), or complete response (55% vs. 57%/51% vs. 34%). There was also no difference between the 2 groups in nausea scores, number of vomiting episodes, or patient satisfaction with postoperative nausea and vomiting management.

Rosen et al. examined the effectiveness of ReliefBand to treat nausea and vomiting in early pregnancy. They randomized 230 women to receive a device for nerve stimulation therapy or an otherwise identical but non-stimulating placebo device. The primary outcome variable, the time-averaged change in Rhodes Index total experience, was significantly better in the study group than in the control group. Weight gain over the three-week trial period was significantly greater in study patients when compared with the control group for the entire population studied. Of women with an active device, 77% gained weight during the study period, compared with 54% of controls. There was no significant difference in the use of additional medication during the trial period. Of women in the study group, 72% did not use additional medications during the study period, compared with 75% in the control group. There were no significant differences in the number of women who used additional prescription medication between the study and control groups.

Though none of these studies used the PrimaBella device, both the ReliefBand and PrimaBella devices are essentially the same so it is reasonable to assume that both would produce similar results.

In summary, multiple systematic reviews and empirical studies demonstrate equivocacy in the evidence as to whether PrimaBella/ReliefBand provides relief for pregnancy-related nausea and vomiting. No studies demonstrate significant improved efficacy or safety compared to ondansetron.

Billing/Coding Information

CPT CODES

No specific codes identified

HCPCS CODES

E0765 FDA approved nerve stimulator, with replaceable batteries for treatment of nausea and vomiting

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Transcutaneous Electrical Stimulation Devices For Nausea and Vomiting, continued

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MEDICAL POLICY

TRANSENDOSCOPIC ANTI-REFLUX PROCEDURES

Policy # 198
Implementation Date: 10/03
Review Dates: 11/18/04, 12/15/05, 2/15/07, 2/21/08, 5/17/08, 6/11/09, 6/17/10, 8/16/11, 8/16/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 6/23/18, 6/25/19, 6/10/20, 6/17/21, 5/19/22, 6/8/23, 6/13/24, 6/17/25
Revision Dates: 10/14/08, 8/16/10

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Description

Gastroesophageal reflux disease (GERD), also known as reflux esophagitis, is probably the most prevalent clinical condition that arises from the gastrointestinal (GI) tract. Reflux occurs when the gradient between the LES pressure and the intragastric pressure is compromised because of a transient or sustained reduction in the former, or an elevation in the latter. Most patients with GERD have decreased LES pressures. However, some patients have normal LES pressures, but their sphincters relax inappropriately, thus, resulting in refluxes.

The standard approach to GERD is to suppress acid production with the use of proton pump inhibitor (PPI) medications and lifestyle modifications. About 1−2% of cases need surgery and most are medically responsive. These procedures are designed to raise the pressure within the LES by wrapping a portion, or all, of the fundus portion of the stomach around the esophagus. With the advent of laparoscopic anti-reflux surgery, the 2 most common procedures are the Nissen fundoplication and the Toupet partial fundoplication.

Endoscopic or endoluminal approaches are being developed to similarly impede reflux and may be categorized into injection bulking, placating, and radiofrequency techniques. One technique available for endoscopic treatment of GERD is the injection of bulking agents under endoscopic guidance into the esophageal wall at the level of the esophagogastric junction. Intended to impede reflux the bulking effect results from a combination of the retained material and consequent tissue response. Several injectable bulking agents have been considered including collagen, polytetrafluoroethylene paste, polymethylmethacrylate (PMMA), and ethylene vinyl alcohol with tantalum (**Enteryx** Polymer, Enteric Medical Technologies, Palo Alto, Calif. and Boston Scientific International). These materials are injected in a low-viscosity state through standard or large-bore injection needles. Fluoroscopic guidance may be used to monitor delivery and retention of radio-opaque components. Enteryx is a biocompatible polymer with a radiopaque marker that is in liquid form until injected, at which time it polymerizes into a solid state. Application is achieved by fluoroscopic-guided injection of 4–8 cc into the muscle and deep submucosal region of the lower esophageal sphincter. The Enteryx procedure is performed under intravenous sedation in the outpatient setting. The FDA removed this product from the market in 2008.

Another technique involves the use of radiofrequency energy to scar or shrink the GE junction. This procedure is called the **Stretta** procedure. This procedure involves the application of precisely controlled RF energy delivered to create lesions in the muscle of the LES and gastric cardia. The resorption of these lesions over the following weeks creates a tighter LES and a less compliant cardia. The tighter valve is thought to provide significantly increased resistance to gastric reflux.

The **Bard Endocinch** entails insertion of a thin, flexible endoscopic tube into the patient's esophagus. The end of the scope holds a tiny device, much like a miniature sewing machine, which place stitches in 2 different locations near the LES. The suturing material is then tied to effectively tighten the valve and

prevent reflux. The procedure requires no incisions and usually no general anesthesia. It is performed on an outpatient basis, and patients usually can return to work the next day.

Similar to Endocinch, the **EsophyX** device is used for a transoral incisionless fundoplication (TIF). Under general anesthesia, the EsophyX device is introduced into the body transorally and advanced into the esophagus under visualization of a video camera inserted down the central shaft of the device. The EsophyX device is then used to form and fasten several tissue folds or plications, to create an antireflux valve at the gastroesophageal junction. The procedure is called a natural orifice surgery (NOS) procedure because the EsophyX device is introduced into the body through the mouth, rather than through an abdominal incision.

Another technique that entered into the market in 2008 is called the **SRS Esophageal Endoscope**. The SRS system (Medigus, Inc., Israel) is a method and apparatus for performing endoluminal partial anterior fundoplication that duplicates one of the existing standard procedures for treatment of GERD, but at the same time does not require anesthesia or violation of the abdominal cavity. The system consists of a specialized flexible endoscope. The system resembles a standard gastroscope and includes a video processor, light source, and suction-irrigation apparatus. The specialized parts of the system include a stapler and ultrasound sight for alignment. When the procedure is performed, a disposable cartridge of staples is inserted into the rigid section of the scope (measuring about 6 cm). The average time of a complete procedure is 35 minutes.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover the Enteryx procedure. It is considered investigational due to a distinct lack of evidence comparing this therapy to standard surgical therapies and limitation to short-term uncontrolled studies (6–12 months) for a condition that is life-long in nature.

Select Health does NOT cover the Stretta procedure. It is considered investigational due to lack of evidence showing comparable efficacy with standard surgical treatments for chronic, medically unresponsive GERD.

Select Health does NOT cover the Bard Endocinch procedure. It is considered investigational due to lack of evidence showing comparable efficacy with standard surgical treatments for chronic, medically unresponsive GERD.

Select Health does NOT cover the EsophyX device. It is considered investigational due to the lack of evidence related to the long-term durability of this procedure; and the lack of direct comparison to the Nissen procedure, which is considered the standard of care.

Select Health does NOT cover the SRS esophageal endoscope. It is considered investigational due to lack of FDA approval and evidence showing comparable efficacy with standard surgical treatments for chronic, medically unresponsive GERD.

SELECT HEALTH MEDICARE (CMS)

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SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Select Health

Transendoscopic Anti-Reflux Procedures, continued

Summary of Medical Information

Lack of randomized, placebo/sham-controlled trials of adequate size and duration leave conclusions about the efficacy of the Enteryx procedure open to question due to selection bias, placebo effect, random error, and durability, respectively. Only when these issues are adequately addressed can determination of effectiveness in routine practice settings be addressed; where it is likely that outcomes will be less successful than trial settings.

Galimiche and Bruley in 2003 stated: "The fact that acid exposure does not return to normal, despite apparently excellent clinical results, is difficult to explain and suggests an important placebo effect in these uncontrolled studies."

The American Gastroenterological Association Consensus Development Panel made the following notes for the Effect of Endoscopic Therapy for GERD on the Need for Medical Therapy:

- Current endoscopic / intraluminal therapeutic procedures are approved for safety, not efficacy
- There is currently no adequate randomized clinical trial evidence to support endoscopic/intraluminal therapies
- The public and physicians should be educated about the risk and limitations of endoscopic/intraluminal procedures

Additionally, the BCBS TEC review from October 2002 evaluated each of the new transendoscopic anti-reflux procedures. They concluded that current literature fails to pass the TEC criteria for each technology and that none of the technologies have been able to demonstrate an improvement in the health outcomes of patients in non-investigational settings. On the other hand, The American Gastroenterological Association Consensus Development Panel for the Effect of Surgical Fundoplication on the Need for Medical Therapy and the Risk of Esophageal Adenocarcinoma also noted:

- The best data indicate that only 40% of patients have complete, long-term HB relief after surgery
- Overall, 1%–30% of patients resume medical therapy years after anti-reflux surgery
- Guidelines for the use of surgery and reports of morbidity and mortality outcomes are based on studies that do not meet accepted standards for clinical evidence
- Side effects (e.g., late dysphagia, lowered QoL) of anti-reflux surgery are more serious and widespread than currently believed

No studies have been published on the use of the SRS system for the treatment of GERD. Therefore, the utility of this procedure could not be evaluated. The Enteryx system was recalled by the FDA in October 2005.

In July 2010, a technology assessment was performed on the EsophyX device. Three systematic reviews were identified which discussed endoscopic anti-reflux procedures. Only 1 of the 3 systematic reviews yielded any evaluation of endoscopic plication. None of the reviews specifically mentioned the EsophyX device. In the Hayes Directory Report published in 2007, which discussed endoscopic placation, a "D" rating was given based upon "concerns regarding durability of the technique (high degree of suture loss), and paucity of evidence from randomized placebo-controlled trials involving patients with these conditions." The Hayes directory report also noted the only comparative studies found in the primary literature were those comparing surgery with a baseline of PPI use. Subsequently, Hayes offered the following: "To determine the efficacy of endoscopic procedures for GERD, randomized controlled trials that include a placebo treatment or another medical or surgical therapy are needed … No randomized controlled trials compared endoscopic therapies with a surgical therapy or antireflux medication."

Specific to the Esophyx procedure, a search of the primary literature yielded only 6 papers concerning EsophyX and endoluminal fundoplication. Of these 6, 3 are by G.B. Cadiere, a member of the Surgeon Advisory Board for EndoGastric Solutions, the manufacturer of EsophyX. Between all six papers, only 185 patients were studied (119 by Cadiere) over 6–24 months. No long-term data are available concerning this procedure. Demyttenaere et al. and Repici et al. both note that 12%–20% of patients went on to have Nissen fundoplication within one year of the initial surgery. Approximately 50% of patients were still using PPIs within a year of the TIF procedure.

Though endoluminal fundoplication and the EsophyX procedure demonstrate at least a moderate improvement in reflux symptoms with a decreased usage of PPI or H2RA therapy, there is not sufficient

improvement illustrated in long-term, randomized controlled trials to support any claims to its superiority over conventional treatments.

Billing/Coding Information

Not covered: Investigational/Experimental/Unproven for this indication

CPT CODES

43201	Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed

HCPCS CODES

A4270	Disposable endoscope sheath, each

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