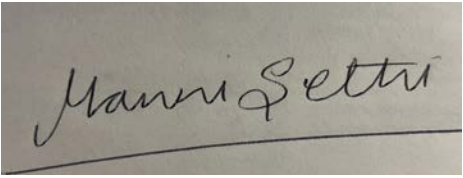


Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First Community Health Choices	Submission Date: 1/1/2024
Policy Number: ccp.1199	Effective Date: 1/2016 Revision Date: November 1, 2024
Policy Name: Peroral endoscopic myotomy	
Type of Submission – Check all that apply: New Policy Revised Policy* <input checked="" type="checkbox"/> Annual Review – No Revisions Statewide PDL	
*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below: See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 



Peroral endoscopic myotomy

Clinical Policy ID: CCP.1199

Recent review date: 11/2023

Next review date: 3/2025

Policy contains: Achalasia; dysphagia; esophageal diverticula; gastroparesis; laparoscopic Heller myotomy; peroral endoscopic myotomy; pneumatic dilation.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Peroral endoscopic myotomy is clinically proven and, therefore, may be medically necessary for treatment of esophageal achalasia when all of the following criteria are met (Kohn, 2021; Vaezi, 2020):

- Age 18 years or older.
- Either:
 - Treatment-naïve.
 - Recurrent or persistent achalasia following pneumatic dilation or laparoscopic Heller myotomy.
- Diagnosis of esophageal achalasia type I, II, or III based on high resolution manometry.
- Eckardt symptom score greater than 3.
- Findings consistent with achalasia on contrast esophagram and esophagogastroduodenoscopy.
- Procedure is performed in centers with expertise trained in the procedure and with onsite thoracic surgical backup capability.

Peroral endoscopic myotomy is investigational/not clinically proven and, therefore, not medically necessary for treatment of:

- Refractory gastroparesis (Aghaie Meybodi, 2019; Camilleri, 2013; Mohan, 2020).
- Esophageal diverticula (Mandavdhare, 2021).
- Esophageal achalasia in pediatric populations (Dirks, 2021; Kohn, 2021; Zhong, 2021b).

Limitations

Contraindications to peroral endoscopic myotomy include (Kohn, 2021; Vaezi, 2020):

- Known coagulopathy.
- Presence of liver cirrhosis.
- Diagnosis of secondary achalasia or other organic causes of dysphagia, including but not limited to:
 - Esophageal varices.
 - Eosinophilic esophagitis.
 - Barrett's esophagus.
 - Esophageal stricture.
 - Malignant or premalignant esophageal lesions.
 - An extremely dilated esophageal body (> 6 cm).
- Pregnancy at the time of treatment.
- Severe pulmonary disease.
- Prior therapy that may compromise the integrity of the esophageal mucosa or lead to submucosal fibrosis, including recent esophageal surgery, radiation, endoscopic mucosal resection, or radiofrequency ablation.
 - Note: Previous therapies for achalasia, such as pneumatic dilation, botulinum toxin injection, or laparoscopic Heller myotomy, are not contraindications to peroral endoscopic myotomy.

Alternative covered services

- Open or laparoscopic esophagomyotomy with or without fundoplication.
- Endoscopically guided pneumatic dilation.
- Botulinum toxin injection.
- Oral pharmacologics (e.g., calcium channel blockers, long-acting nitrates, anticholinergics, β -adrenergic agonists, and theophylline).

Background

Achalasia is an esophageal motility disorder of the esophageal smooth muscle layer and the lower esophageal sphincter. Incomplete lower esophageal sphincter relaxation, increased lower esophageal sphincter pressure, and aperistalsis of the distal one-third of the esophageal body characterize the disorder (Friedel, 2013). Achalasia is rare in the pediatric population and even less so in children younger than five years of age (Franklin, 2014). The majority of cases are idiopathic, but the disorder can be associated with malignancy (especially involving the gastro-esophageal junction) and as a part of the spectrum of Chagas disease. In rare cases, achalasia is transmitted genetically (Franklin, 2014; Friedel, 2013).

The Eckardt scoring system is most frequently used for the evaluation of symptoms, stages, and efficacy of achalasia treatment (Laurino-Neto, 2018). It attributes zero to three points to each of the four symptoms of the disease (dysphagia, regurgitation, chest pain, and weight loss). Point totals range from 0 to 12, with a higher score indicating more severe symptoms. Scores of 0-1 correspond to clinical stage 0, 2-3 to stage I, 4-6 to stage II, and greater than 6 to stage III.

The diagnostic standard is esophageal manometry on which achalasia displays the following characteristics; incomplete relaxation of the lower esophageal sphincter in response to swallowing, high resting lower esophageal sphincter pressure, and absent esophageal peristalsis. Chicago Classification criteria based on high-resolution manometry define achalasia syndromes according to different patterns of esophageal contractility that accompany impaired esophagogastric junction (Kahrilas, 2015):

- Type I indicates 100% failed peristalsis.
- Type II, 100% failed peristalsis and panesophageal pressurization in at least 20% of swallows.
- Type III, no normal peristalsis and premature/spastic contractions in at least 20% of swallows.

Other tests include barium contrast radiography and endoscopic assessment of the gastroesophageal junction and gastric cardia, as recommended, to rule out pseudoachalasia and mechanical obstruction.

Achalasia is an incurable chronic condition that requires lifelong follow up. Treatment goals are to relieve symptoms, improve esophageal emptying, and prevent further esophageal dilation. Current treatment options aim to decrease the resting pressure in the lower esophageal sphincter (Vaezi, 2020).

Established treatments for achalasia are open or laparoscopic esophagomyotomy (also known as Heller myotomy), with or without an antireflux procedure, and pneumatic dilation. However, their effectiveness decreases over time, and each is associated with procedural risks. Esophagectomy is reserved for patients with end-stage achalasia, characterized by megaesophagus or sigmoid esophagus, and significant esophageal dilation and tortuosity. Botulinum toxin injection into the lower esophageal sphincter is restricted, generally, to patients for whom pneumatic dilation and esophagomyotomy are not considered appropriate because of inherent patient-related risks. Oral pharmacologic interventions (e.g., calcium channel blockers and long-acting nitrates) are among the least effective. No intervention significantly affects esophageal peristalsis, and despite initial success of these interventions, lower esophageal sphincter hypertonicity returns over time, requiring repeat interventions (Vaezi, 2020).

Peroral endoscopic myotomy is a hybrid technique derived from natural orifice transluminal endoscopic surgery and advances in endoscopic submucosal dissection to perform a myotomy (Friedel, 2013). Developed in Japan, it involves an esophageal mucosal incision, followed by creation of a submucosal tunnel crossing the esophagogastric junction and myotomy before closure of the mucosal incision. Peroral endoscopic myotomy represents a novel, minimally invasive, and potentially effective endoscopic treatment for achalasia.

Several therapeutic interventions directed to the pylorus for treatment for refractory gastroparesis have been developed over the last decade but have achieved limited success (Khouri, 2018). These options include intrapyloric injections of botulinum toxin, transpyloric stenting, and surgical pyloroplasty. An application of peroral endoscopic myotomy to the pyloric valve called gastric peroral endoscopic myotomy or gastric peroral endoscopic pyloromyotomy has emerged as a potential treatment for refractory gastroparesis.

Esophageal diverticula are herniations of the esophagus typically resulting from an increased intraesophageal pressure or periesophageal chronic inflammation (Yam, 2021). There is emerging interest in the use of the peroral endoscopic myotomy procedure to treat esophageal diverticula, particularly Zenker's diverticula.

Findings

We identified two systematic reviews (Barbieri, 2015; Wei, 2015) and three evidence-based guidelines for this policy (American Society for Gastrointestinal Endoscopy 2014; Stefanidis, 2012; Vaezi, 2013). The evidence consists of single-arm studies and four individual, indirect comparisons of peroral endoscopic myotomy to laparoscopic Heller myotomy. No randomized controlled trials had been published when this policy was initially written. There is considerable overlap of investigators and, presumably, patient groups, which reflects clinical

experience with peroral endoscopic myotomy limited to relatively few centers around the world. Some studies included patients with other types of esophageal motility disorders, as well as variable prior treatment exposure.

The evidence was insufficient to support the use of peroral endoscopic myotomy as a treatment for achalasia. Guidelines from the American College of Gastroenterologists (Vaezi, 2013), the Society of American Gastrointestinal and Endoscopic Surgeons (Stefanidis, 2012), and the American Society for Gastrointestinal Endoscopy (2014) highlight the need for randomized controlled trials comparing the long-term efficacy peroral endoscopic myotomy to established alternatives for treatment of achalasia before widespread adoption.

In 2016, we identified one new systematic review and meta-analysis comparing laparoscopic Heller myotomy and peroral endoscopic myotomy (Marano, 2016) and one narrative review of laparoscopic esophagomyotomy procedures for achalasia in children (Pandian, 2016). The new evidence suggests comparable short-term outcomes in adults with either treatment-naïve or treatment-experienced achalasia. The evidence for laparoscopic esophagomyotomy procedures in children is scant. No policy changes are warranted at this time.

In 2017, we added no new findings, and no policy changes are warranted at this time.

In 2018, we added one professional guideline based on expert consensus (Kahrilas, 2017). While peroral endoscopic myotomy appears to be a safe, effective, and minimally invasive option for achalasia in the short term, long-term effectiveness data and optimal patient selection criteria are still lacking (Kahrilas, 2017). No policy changes are warranted at this time. The policy ID was changed from CP# 08.03.04 to CCP.1199.

In 2019, we added two systematic reviews and meta-analyses of gastric peroral endoscopic myotomy for treatment of refractory gastroparesis that suggest gastric peroral endoscopic myotomy is safe, feasible, and effective in the short-term, but offers no clear advantage over surgical pyloroplasty (Aghaie Meybodi, 2019; Mohan, 2020). In the Aghaie Meybodi (2019) systematic review (seven before-after studies, $n = 196$ participants), the clinical success rate of gastric peroral endoscopic myotomy, defined as statistically significant improvement in the mean Gastroparesis Cardinal Symptom Index from pre- to post-procedure was 82% (95% confidence interval: 74% to 87%). The average mean values of gastric emptying, reported as the percentage of gastric retention four hours after a solid meal, were significantly decreased two to three months after the procedure (-22.3 , 95% confidence interval: -32.9 to -11.6 , $P < .05$).

Results of an indirect comparison (Mohan, 2020) of gastric peroral endoscopic myotomy (11 studies, $n = 332$ participants) and surgical pyloroplasty (seven studies, $n = 375$ participants) suggest comparable rates of clinical success based on the subjective Gastroparesis Cardinal Symptom Index score ($P = .81$) and 4-hour gastric emptying study results ($P = .91$) and comparable overall adverse event rates. Both procedures had a comparable overall mean hospital length of stay. Based on meta-regression analysis, idiopathic gastroparesis, prior treatment with botulinum toxin and gastric stimulator appears to have positive predictive effects on the 4-hour gastric emptying study results after gastric peroral endoscopic myotomy.

The American College of Gastroenterology mentions gastric peroral endoscopic myotomy as an emerging surgical option for gastroparesis, but made no specific recommendations (Camilleri, 2013). Rigorous trials are needed to define the optimal candidate and long-term outcomes associated with the procedure.

For treatment of esophageal achalasia, we added three systematic reviews, including a network meta-analysis, of adults (Aiolfi, 2020; Evensen, 2019; Li, 2019), one systematic review of pediatric patients (Lee, 2019), and one new guideline (Zaninotto, 2018). All analyses confirm previous policy findings of the short-term safety and efficacy of peroral endoscopic myotomy and the need for long-term comparative effectiveness data from rigorously designed trials.

The International Society for Diseases of the Esophagus issued conditional recommendations for peroral endoscopic myotomy as a less invasive treatment option for achalasia based on comparable short- and medium-term outcomes to those of Heller myotomy (GRADE: very low-quality evidence) and pneumatic dilation (GRADE:

low-quality evidence) for control of symptoms regardless of previous treatment such as botulinum toxin injections (GRADE: very low-quality evidence) (Zaninotto, 2018). The Society recommends peroral endoscopic myotomy as a first-line treatment option for adults with sigmoid esophagus (compared to esophagectomy) and as a second-line treatment for persistent or recurrent symptoms after laparoscopic myotomy or graded pneumatic dilation (GRADE: low-quality evidence). For pediatric patients with idiopathic achalasia, especially for those ages 5 years or older, laparoscopic or endoscopic myotomy (compared to pneumatic dilation) is the preferred treatment (GRADE: very low-quality evidence).

In 2020, we changed the coverage for peroral endoscopic myotomy from investigational to medically necessary for treatment-naïve patients. We added two trials confirming peroral endoscopic myotomy was at least as effective as pneumatic dilation (Ponds, 2019; Netherlands Trial Register number NTR3593) and laparoscopic Heller myotomy (Werner, 2019; ClinicalTrials.gov number, NCT01601678), but also had a higher incidence of reflux esophagitis and proton pump inhibitor use.

Long-term outcome data beyond two years for any of the established achalasia treatments are limited, but retreatment is needed in 23% to 35% of patients five to seven years after pneumatic dilation, and in 18% to 27% of patients at a median of 5.3 years after Heller myotomy (Khashab, 2020). Retreatment data after long-term follow-up following peroral endoscopic myotomy are not yet available, but one case series reported symptomatic success in 83% of 23 patients followed for at least five years (Teitelbaum, 2018).

With these factors in mind, the American Society for Gastrointestinal Endoscopy made the following recommendations regarding peroral endoscopic myotomy (Khashab, 2020):

- Laparoscopic Heller myotomy, pneumatic dilation, and peroral endoscopic myotomy are effective therapeutic modalities for patients with achalasia. Decision between these treatment options should depend on achalasia type, local expertise, and patient preference (strong recommendation; high-quality evidence).
- Peroral endoscopic myotomy is the preferred treatment for type III achalasia (weak recommendation; very low-quality evidence).
- In patients with failed initial myotomy (peroral endoscopic myotomy or laparoscopic Heller myotomy), pneumatic dilation or redo myotomy using either the same or an alternative myotomy technique may be offered (weak recommendation; very low-quality evidence).
- Patients undergoing peroral endoscopic myotomy should be counseled regarding the increased risk of post procedure reflux compared with pneumatic dilation and laparoscopic Heller myotomy, and the need for post procedure objective testing for esophageal acid exposure, long-term acid suppressive therapy, and surveillance upper endoscopy (weak recommendation; low-quality evidence).
- Peroral endoscopic myotomy and laparoscopic Heller myotomy are comparable treatment options for management of patients with achalasia types I and II, and the treatment option should be based on shared decision-making between the patient and provider (weak recommendation; low-quality evidence).

Two systematic reviews and meta-analyses attempted to identify patient-specific demographics, clinical predictors, or modifications to the endoscopic technique that would improve patient outcomes, including reducing the incidence of reflux esophagitis, and help guide treatment choices, but the evidence was inconclusive or insufficient to produce evidence-based recommendations (Oude Nijhuis, 2020; Mota, 2021).

Low-quality evidence from two systematic reviews and meta-analyses suggests peroral endoscopic myotomy is feasible, safe, and effective when used as a salvage procedure after laparoscopic Heller myotomy (Huang, 2021; Tan, 2021). Evidence from prospective, controlled studies with long-term follow-up are needed to confirm these

findings. There is no consensus to inform the optimal salvage treatment in patients who have failed initial treatment or have recurred after prolonged follow-up (Khashab, 2020).

In 2021, we added new evidence examining peroral endoscopic myotomy as a salvage procedure for esophageal achalasia in adults (Huang, 2021; Kohn, 2021; Tan, 2021; Vaezi, 2020, Zhong, 2021a) and in pediatric populations (Dirks, 2021; Kohn, 2021; Zhong, 2021b), and for esophageal diverticula (Kamal, 2021; Mandavdhare, 2021). We updated the American College of Gastroenterology guideline (replaced Vaezi [2013] with the 2020 update). The new evidence is sufficient to support the medical necessity of peroral endoscopic myotomy as a salvage procedure in adults with esophageal achalasia.

In cases of symptom recurrence after a primary intervention, repeat endoscopic myotomy is often technically challenging, is associated with a high risk of adverse events, and may result in longer hospital stays. The American College of Gastroenterology (Vaezi, 2020) expanded the indications for adults to include peroral endoscopic myotomy as a salvage procedure following pneumatic dilation or laparoscopic Heller myotomy in the settings of treatment failure or recurrent disease. The Society of American Gastrointestinal and Endoscopic Surgeons (Kohn, 2021) does not specify the use of peroral endoscopic myotomy as an initial or salvage treatment in its recommendations.

In a meta-analysis (Tan, 2021, $n = 2,197$ patients with mixed achalasia subtypes) of 15 medium- to high-quality nonrandomized studies, peroral endoscopic myotomy achieved high pooled technical (98.0%) and clinical (90.8%) success rates and significantly reduced the Eckardt score (mean difference 5.77, $P < .001$) and lower esophageal sphincter pressure (mean difference 18.3 mm Hg, $P < .001$) in patients who underwent prior surgical or endoscopic treatment. In a subgroup analysis of seven studies, the clinical outcomes for technical success, clinical success, and adverse events expressed as relative risk were similar between previously treated and treatment-naïve patients.

The results of two other systematic reviews and meta-analyses (Huang, 2021, nine studies, $n = 272$ patients; Zhong, 2021, eight studies, $n = 1,797$ patients) confirm these findings. Both guidelines and the new meta-analyses recommend randomized clinical trials and follow-up beyond two years to confirm these findings.

For pediatric patients with achalasia, the Society of American Gastrointestinal and Endoscopic Surgeons issued weak recommendations extrapolated from adult experience, acknowledging the uncertainty in the available evidence particularly where children are concerned (Kohn, 2021):

- Peroral endoscopic myotomy or laparoscopic Heller myotomy for pediatric patients with type I and II achalasia based on surgeon and patient's shared decision-making (conditional recommendation, very low certainty evidence).
- Peroral endoscopic myotomy preferred to laparoscopic Heller myotomy for pediatric patients with type III achalasia (expert opinion).

The evidence for pediatric populations comprises two systematic reviews (Dirks, 2021, two studies, $n = 39$; Zhong, 2021b, 11 studies, $n = 389$) of small observational studies that have inherent biases and heterogeneous populations with respect to previous interventions, procedural modifications, follow-up periods, and disease severity. While the results suggest peroral endoscopic myotomy is feasible, safe, and efficacious in decreasing Eckardt symptom scores with some durability, the limited evidence is insufficient to support its routine use in children with achalasia.

A systematic review and meta-analysis (Mandavdhare, 2021) of 19 studies ($n = 341$ patients) compared the efficacy and safety of peroral endoscopic myotomy to flexible endoscopic septum division for esophageal diverticula. The clinical success, technical success, and adverse event rates for peroral endoscopic myotomy were 87%, 95.19%, and 10.22%, respectively. Compared to flexible endoscopic septum division, peroral endoscopic myotomy was associated with higher clinical success (relative risk 1.13, 95% confidence interval

1.05 to 1.22, n = eight studies) and comparable technical success (relative risk 0.99, 95 confidence interval 0.95 to 1.02, n = eight studies). The procedure time, length of hospital stay, and recurrence rate were comparable between procedures.

In 2022, we added systematic reviews/meta-analyses of peroral endoscopic myotomy, including:

- Seven studies (n = 469) of geriatric patients determined the treatment was safe and effective, based on technical success (98.1%), clinical success (92.5%), lower Eckardt score (6.09 points), lower esophageal sphincter pressure (13.53 mm Hg), adverse events (9.0%), and clinical reflux (17.4%) (Zhong, 2022).
- Ten studies (n = 482) of patients with refractory gastroparesis showed “modest” success after one year (clinical success = 61%), adverse events = 8% (Kamal, 2022).
- Eleven studies (n = 2,342) tracked patients for a median of 48 months documented a clinical success rate of 87.3% and a symptomatic reflux rate of 22.0% (Vespa, 2023).
- Twenty-four studies (n = 1,987) concluded peroral endoscopic myotomy with an anterior or posterior approach and laparoscopic Heller’s myotomy can be initially recommended (Shiu, 2022).

In 2023, we added the following systematic reviews/meta-analyses:

- In four studies (n = 385) for patients with refractory gastroparesis, peroral endoscopic myotomy (versus surgical procedures pyloromyotomy and pyloroplasty) had lower procedural time ($P < .001$) and lower length of stay ($P < .001$). Reduction in symptoms score did not differ between groups (Aziz, 2023).
- In 21 studies (n = 2,698) that reviewed long-term outcomes of peroral endoscopic myotomy for achalasia, clinical success rates after two, three, four, and five years were 91.3%, 90.4%, 89.8%, and 82.2%. The pooled incidence of symptomatic reflux and reflux esophagitis were 23.9% and 16.7% (Zhang, 2023).
- In 17 studies (n = 3,591), peroral endoscopic myotomy outcomes for esophageal motility disorders were followed for a mean of 48.9 months. Mid-term and long-term clinical success rates were 87% and 84%. Gastroesophageal reflux occurred (long-term) in 23% of patients; the erosive esophagitis rate was 27%, and 41% of patients had increased esophageal acid exposure (Nabi, 2023).

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On September 7, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “peroral endoscopic myotomy” and “esophageal achalasia” (MeSH). We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

- 10/2015: initial review date and clinical policy effective date: 1/2016
- 10/2016: Policy references updated.
- 10/2017: Policy references updated.
- 10/2018: Policy references updated. Policy ID changed.
- 11/2019: Policy references updated. Gastric peroral endoscopic myotomy added.
- 11/2020: Policy references updated. Coverage changed to medically necessary.
- 11/2021: Policy references updated. Coverage modified.
- 11/2022: Policy references updated.

11/2023: Policy references updated.