	Stop PPI Therapy				**Pressure**
Lipka et al (2015)[24]					
Patients (studies), n	118 (3)	88 (2)		153 (4)	110 (3)
MD (95% CI)	RR=0.87 (0.75 to 1.00)	-5.24 (-12.95 to 2.46)		1.56% (-2.56% to 5.69%)	0.32 mm Hg (-2.66 to 2.02 mm Hg)
p	0.06	0.18		0.46	0.79
I^2 (p)	0%	96% (<0.001)		99% (<0.001)	96% (<0.001)
Range of N	24-51	22-64		22-64	
	Heartburn Score				**Johnson-DeMeester Score**
Perry et al (2012)[28]					
Patients (studies), n	525 (9)	433 (9)	299 (6)	364 (11)	267 (7)
Mean follow-up, mo	24.1	19.8	9.5	11.9	13.1
Baseline (SE)	3.55 (3.9)	26.11 (27.2)	36.45 (51.6)	10.29% (17.8%)	44.37 (93)
Posttreatment (SE)	1.19 (3.4)	9.25 (23.7)	46.12 (61.9)	6.51% (12.5%)	28.54 (33.4)
p	0.001	0.001	0.001	0.003	0.007

CI: confidence interval; GERD-HRQL: Gastroesophageal Reflux Disease Health-related Quality of Life; LES: lower esophageal sphincter; MD: mean difference; PCS: Physical Component Summary; RCT: randomized controlled trial; RR; relative risk; SE: standard error; SF-36: 36-Item Short-Form Health Survey.

Randomized Controlled Trials

Although not included in the meta-analyses tabulated in Table 14, Kalapala et al (2017) published interim results from a small RCT of 20 patients randomized to PPI plus Stretta or PPI alone, with 3 months of follow-up.[30] While short-term outcomes such as GERD symptoms and cessation of PPIs appeared improved for the Stretta group, the study sample was small and power calculations were not conducted.

Controlled Trials Comparing TERF With Laparoscopic Fundoplication

Liang et al (2015) reported on a prospective comparison of laparoscopic Toupet fundoplication with the Stretta procedure (see Table 17).[31] Of 165 patients treated, 125 (76%) completed the 3-year follow-up (65 fundoplications, 60 Stretta) and were included in the analysis. Although the 2 groups were comparable in symptoms at baseline, 9 patients in the Stretta group had revised treatment and were not included in the final symptom scores. A similar percentage of remaining patients in the 2 groups achieved complete PPI independence and had similar improvements in belching, hiccup, cough, and asthma. The Stretta procedure was less effective than laparoscopic fundoplication in reducing symptoms of heartburn, regurgitation, and chest pain (see Table 18). Significantly more patients in the Stretta group underwent reoperation, while more patients in

the fundoplication group complained of bloating, but this difference was not statistically significant. This study lacked randomization and, along with not reporting the TERF failures, had a high loss to follow-up. Also, while symptom scores were comparable at baseline, the study might have been subject to selection bias related to treatment choice, which affected baseline differences for other variables.

Table 17. Characteristics of Studies Comparing TERF With Laparoscopic Fundoplication

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	FU, y
Liang et al (2015)[31]	Comparative cohort	China	2011	165	TERF	Laparoscopic fundoplication	3

FU: follow-up; TERF: transesophageal radiofrequency.

Table 18. Results Comparing TERF With Laparoscopic Fundoplication

Study	PPI Independence	Improvement in Heartburn Score	Improvement in Regurgitation Score	Improvement in Chest Pain Score	Reoperation	Bloating
Liang et al (2015)[31]						
TERF	68.3%	2.53	2.41	2.96	11.8%	0%
LF	72.3%	4.05	4.03	5.50	0%	6.2%
p	0.627	0.01	0.004	0.005	0.006	0.120

LF: laparoscopic fundoplication; PPI: proton pump inhibitor; TERF: transesophageal radiofrequency.

Prospective Cohort Studies

Long-term follow-up from case series and cohort studies can inform the durability of TERF. For example, 5- and 10-year follow-ups after TERF were reported in 2014 (see Table 19).[32,33] Elimination of PPI use was similar for both studies at around 42% (see Table 20). Liang et al (2014) reported that symptoms of heartburn, regurgitation, chest pain, cough, and asthma were all decreased compared with baseline. Noar et al reported symptom improvement in 72% of patients and elimination of dysplasia in 85% of patients, but the interpretation of these findings is limited due to the 34% loss to follow-up in this study.

Table 19. Cohort Study and Case Series Characteristics

Study	Country/Institution	Participants	Follow-Up, y	Loss to Follow-Up
Liang et al (2014)[32]	China	152 who failed PPI therapy	5	9%
Noar et al (2014)[33]	University of Pittsburgh	149 who failed PPI therapy	10	34% (7% deceased)

PPI: proton pump inhibitor.

Table 20. Cohort Study and Case Series Results at Follow-Up

Study	Elimination of PPI Use	Symptom Improvement	Elimination of Dysplasia	Bloating
Liang et al (2014)[32]	42.8%	p<0.001 vs pretreatment		8.7%
Noar et al (2014)[33]	41%	72%	85%	

PPI: proton pump inhibitor.

Section Summary: Transesophageal Radiofrequency (Stretta Procedure)
Four RCTs (N range, 22-64 patients), three of which were sham-controlled, reported some improvements in symptoms following treatment with TERF. However, measures of esophageal acid exposure were typically not improved. Also, meta-analyses of these same studies found no significant improvements in outcomes. The findings of improvements in symptoms but not esophageal acid exposure have led to questions whether TERF is acting by reducing sensation in the esophagus. Although single-arm studies have shown maintenance of symptom relief at 5 to 10 years, interpretation depends on the efficacy of the procedure in the short term. A nonrandomized comparative study has suggested that symptom relief with TERF is lower than with fundoplication and there is a greater incidence of reoperations. Larger RCTs with longer follow-up are needed to define the risks and benefits of this procedure better.

Esophageal Bulking Agents

Clinical Context and Test Purpose
The purpose of esophageal bulking agents is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with GERD.

The question addressed in this evidence review is: Does the use of esophageal bulking agents improve the net health outcomes in individuals with?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with GERD.

Interventions
The therapy being considered is esophageal bulking agents.

Comparators
The following therapies and practices are currently being used to treat GERD: PPI therapy and laparoscopic fundoplication.

Outcomes
The general outcomes of interest are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity.

Timing
Though not completely standardized, follow-up for GERD symptoms would typically occur in the months to years after starting treatment.

Setting
Patients with GERD are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Durasphere
The available evidence for Durasphere consists of a single case series. One open-label pilot study by Ganz et al (2009) assessed 10 GERD patients injected Durasphere (Carbon Medical Technologies), a bulking agent approved for treatment of urinary and fecal incontinence, at the gastroesophageal junction.[34] At 12 months, 7 (70%) patients discontinued all antacid medication completely. No erosion, ulceration, or sloughing of material was noted at any injection site.

Gatekeeper Reflux Repair System
The available evidence for Gatekeeper Reflux Repair System consists of a single RCT reported by Fockens et al (2010).[35] In this industry-funded sham-controlled single-blind, multicenter study randomized 118 patients into Gatekeeper (n=75) or sham (n=43) treatment. An additional 25 patients were treated as lead-ins during the initial training of investigators and included only in the safety analysis. The patients were implanted initially with 4 Gatekeeper prostheses. At 3 months, 44% of implanted patients received retreatment with up to 4 additional prostheses due to unsatisfactory symptom control. The primary safety endpoint was a reduction in serious device- and procedure-related adverse events, compared with a surgical procedure composite complication rate of 15%. Four serious adverse events were reported (2 perforations, 1 pulmonary infiltrate related to a perforation, 1 severe chest pain). The primary efficacy end point was a reduction in heartburn symptoms using the GERD-HRQL questionnaire. Planned interim analysis after 143 patients were enrolled found that heartburn symptoms and esophageal acid exposure had improved significantly in both the Gatekeeper and sham groups at 6 months, but there was no significant difference between groups. The trial was terminated early due to a lack of efficacy.

Polymethylmethacrylate Beads
The available evidence for polymethylmethacrylate beads consists of a single case series. A case series by Feretis et al (2001) evaluated on transesophageal submucosal implantation of polymethylmethacrylate beads in 10 patients with GERD who were either refractory to or dependent on PPIs.[36] While a significant decrease in symptom scores was noted at posttreatment follow-up (time not specified), the small number of patients and lack of long-term follow-up precluded

scientific analysis. No additional studies have been identified evaluating this treatment option.

Section Summary: Esophageal Bulking Agents
The evidence on injection of bulking agents includes an RCT terminated early due to lack of efficacy and case series. High-quality data from large RCTs are needed to compare bulking procedures with both sham controls and with the currently accepted treatments for GERD (ie, drug therapy, laparoscopic fundoplication). Well-designed trials should use standardized outcome measures to examine both subjective (eg, GERD-HRQL scores) and objective (eg, esophageal acid exposure) effects on health outcomes.

Summary of Evidence
For individuals who have GERD and a hiatal hernia of 2 cm or less that is not controlled by PPIs who receive TIF (eg, EsophyX), the evidence includes 2 RCTs comparing TIF with PPI therapy, nonrandomized studies comparing TIF with fundoplication, and case series with longer term follow-up. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The highest quality RCT (RESPECT) was sham-controlled that compared TIF with PPI therapy while the other RCT (TEMPO) compared TIF with maximum PPI therapy. Both trials found a significant benefit of TIF on the primary outcome measure in about 65% of patients. The sham-controlled trial reported improvement in 45% of the sham-controlled group and no benefit on secondary subjective outcome measures. The nonblinded RCT found significant improvements in subjective measures but no difference in objective outcome measures compared with PPI therapy. Together, these trial results would suggest a strong placebo effect of the surgery and a modest benefit of TIF in patients whose symptoms were not controlled by PPIs. For these patients, the most appropriate comparator would be laparoscopic fundoplication. Studies comparing TIF with fundoplication have limitations that include earlier TIF procedures and unbalanced groups at baseline and are inadequate to determine relative efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD and a hiatal hernia of 2 cm or less that is controlled by PPIs who receive TIF (eg, EsophyX), the evidence includes 2 RCTs and observational studies with longer term follow-up. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. A sham-controlled trial found that the time to resume PPI therapy was longer following TIF and the remission rate was higher, indicating that TIF is more effective than no therapy. The nonblinded RCT found a benefit of TIF compared with continued PPI therapy for subjective measures, but not for the objective measures of pH normalization and esophagitis. These results raise questions about a possible placebo effect for the procedure. Also, observational studies have indicated a loss of treatment effectiveness over time. Adverse events associated with the procedure (eg, perforation) may be severe. At present, the available evidence does not support the use of this intervention in patients whose

symptoms are adequately controlled by medical therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD who receive endoscopic radiofrequency energy (eg, Stretta), the evidence includes 4 small RCTs, a nonrandomized comparative study, and observational studies with longer term follow-up. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The RCTs reported some improvements in symptoms and quality of life following treatment with radiofrequency energy compared with sham controls. However, objective measures of GERD and a meta-analysis of these studies found no significant improvements in outcomes, raising questions about the mechanism of the symptom relief. Symptom relief is reported to be lower than after fundoplication, and reoperations greater. Larger RCTs with longer follow-up, preferably compared with fundoplication, are needed to define the risks and benefits of this procedure better. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have GERD who receive esophageal bulking agents, the evidence includes an RCT and case series. Relevant outcomes are symptoms, change in disease status, quality of life, medication use, and treatment-related morbidity. The RCT for a single product was terminated early due to lack of efficacy, while other products have only case series to support use. High-quality data from large RCTs are needed to compare bulking procedures with both sham controls and with the currently accepted treatments for GERD (ie, drug therapy, laparoscopic fundoplication). Well-designed trials should use standardized outcome measures to examine whether subjective improvement (eg, discontinuation of medication therapy, GERD-HRQL scores) is supported by objective improvement (eg, esophageal acid exposure). The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input

In response to requests for clinical input on transesophageal radiofrequency (Stretta) as a treatment of gastroesophageal reflux disease (GERD), input was received from 1 physician specialty society (2 reviewers) and 3 academic medical centers while this policy was under review in 2015. Input was mixed on the treatment of GERD with transesophageal radiofrequency to create submucosal

thermal lesions of the gastroesophageal junction (ie, Stretta). Potential conflicts of interest were noted by 2 reviewers.

2011 Input

In response to requests for clinical input on transoral incisionless fundoplication (TIF) using EsophyX, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review in 2011. Reviewers agreed that TIF differed sufficiently different from laparoscopic Nissen fundoplication to warrant evaluation as a separate procedure. Reviewers considered TIF (ie, EsophyX) to be investigational for the treatment of GERD.

Practice Guidelines and Position Statements

American Society for Gastrointestinal Endoscopy

The American Society for Gastrointestinal Endoscopy (2015) published guidelines on endoscopic procedures for GERD.[37] In its review of the EsophyX and Stretta procedures, the Society noted some positive findings but discrepancies between subjective and objective outcome measures or a lack of objective outcome measures in reported trials, concluding that these techniques represent "potentially new therapeutic indications for GI endoscopy", but that prospective trials using objective measures of GERD as the primary end point could be useful in defining the clinical role of these procedures.

American College of Gastroenterology

Updated guidelines from the American College of Gastroenterology (2013) indicated the use of current endoscopic therapy or transoral incisionless fundoplication (TIF) could not be recommended as an alternative to medical or traditional surgical therapy (conditional recommendation, moderate level of evidence).[1] The guidelines also cited limited data on small numbers of subjects and short duration of follow-up.

Society of American Gastrointestinal and Endoscopic Surgeons

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES; 2017) updated its evidence-based guidelines on endoluminal treatments for GERD.[38] SAGES gave a strong recommendation based on moderate quality evidence that TIF using EsophyX can be performed with an acceptable safety risk in selected patients. SAGES concluded that EsophyX results in better control of GERD symptoms than proton pump inhibitor (PPI) treatment in the short term (6 months), and leads to similar improvements in objective GERD measures compared with PPIs. TIF appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. SAGES found no comparative, controlled trials between TIF and surgical fundoplication, but preliminary evidence suggested that surgical fundoplication can be used safely after TIF failure.

SAGES gave a strong recommendation based on moderate quality evidence that Stretta is safe for adults and significantly improves health-related quality of life

score, heartburn scores, the incidence of esophagitis, and esophageal acid exposure in patients with GERD. Stretta was found more effective than PPI, but less so than fundoplication.

American Society of General Surgeons

The American Society of General Surgeons (ASGS; 2011) issued a position statement on transoral fundoplication stating that "ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence."[39]

American Gastroenterological Association

The American Gastroenterological Association (2016) issued a technology coverage statement on minimally invasive surgical options for GERD.[40] Based on a literature review of 4 randomized controlled trials, a multicenter registry, and case series with longer term follow-up, the Association stated:

> "…evidence is sufficient to demonstrate sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization and improvement in esophageal pH with transoral fundoplication. The selection criteria for transoral fundoplication includes GERD patients with BMI [body mass index] ≤ 35, hiatal hernia ≤ 2 cm, esophagitis LA [Los Angeles classification] grade A or B, Barrett's esophagus ≤ 2 cm, and absence of achalasia and esophageal ulcer. This option should be considered in patients not responding to PPI therapy (symptoms of regurgitation) who have documented objective evidence of GERD (pathologic acid exposure on pH testing (both off and on medication)) or esophagitis."

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE; 2013) updated its guidance on endoscopic radiofrequency treatment for GERD, concluding: "The evidence on the safety of endoscopic radiofrequency ablation for gastro-esophageal reflux disease is adequate in the short and medium term, but there is uncertainty about longer-term outcomes. With regard to efficacy, there is evidence of symptomatic relief, but objective evidence on reduction of reflux is inconclusive…."[41] NICE noted "concern on the part of some specialists about the possibility that symptoms may improve as a result of denervation caused by the procedure; if that were the case then failure to recognize and treat reflux might lead to complications in the long term."

NICE (2011) issued guidance on endoluminal gastroplication for GERD, concluding that "The evidence on endoluminal gastroplication for gastroesophageal reflux disease raises no major safety concerns. Evidence from a number of RCTs [randomized controlled trials] shows a degree of efficacy in terms of reduced medication requirement in the short term, but changes in other efficacy outcomes

are inconsistent, and there is no good evidence of sustained improvement in esophageal pH measurements…."[42]

NICE (2004) issued guidance on bulking agents for GERD found that "Current evidence on the safety and efficacy of endoscopic injection of bulking agents for gastro-esophageal reflux disease does not appear adequate for this procedure to be used without special arrangements…."[43] NICE (2016) removed guidance on endoscopic bulking agents/hydrogel implants from guidelines on treatment for "dyspepsia and gastro-esophageal reflux" because the product had been withdrawn by the manufacturer.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 21.

Table 21. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01118585[a]	Prospective Outcome Evaluation of Transoral Incisionless Fundoplication (TIF) for the Treatment of Gastroesophageal Reflux Disease (GERD): The TIF Registry Study	500	Dec 2017 (ongoing)
NCT01682265	Stretta in Reflux Uncontrolled by Intake of Inhibitors of Protons Pump (IPP)-The SIRUP Trial-Multicentric, Randomized, Double Blind, Prospective Study	60	May 2019
NCT02366169[a]	A Worldwide Post-Market Surveillance Registry to Assess the Medigus Ultrasonic Surgical Endostapler (MUSE™) System for the Treatment of GERD	200	Dec 2019
Unpublished			
NCT02211105	Laparoscopic Nissen Fundoplication (LNF) Surgery Versus Transoral Incisionless Fundoplication (TIF): Anti- Reflux Treatment Registry	46	Apr 2017 (terminated)
NCT01110811[a]	A Randomized Controlled Trial Comparing Transoral Incisionless Fundoplication (TIF) Using EsophyX With Sham Procedure for the Treatment of PPI Dependent GERD: the TIF vs. Sham Study	60	Mar 2017 (unknown)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Billing Coding/Physician Documentation Information

43200 Esophagoscopy, flexible, transoral; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)

43201 Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance

43210 Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed (new code 1/1/16)

43212 Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and dilation and guide wire passage, when performed)

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

43266 Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and post-dilation and guide wire passage, when performed.)

43499 Unlisted procedure, esophagus

C9724 Endoscopic full-thickness plication of the stomach using endoscopic plication system (EPS); includes endoscopy (Deleted code 1/1/2016)

ICD-10 Codes

K21.0, K21.9 Gastro-esophageal reflux disease code list

Effective in 2016, there is a specific CPT code for transoral incisionless fundoplication:

43210 Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed

Prior to 2016, there was no specific CPT code for transoral incisionless fundoplication. If it was performed endoscopically, it would have been reported with CPT code 43499, unlisted procedure, esophagus. If it is performed as part of a laparoscopic hybrid surgery, it should be reported with CPT code 43659, unlisted laparoscopy procedure, stomach.

There is a CPT code specific to the radiofrequency procedure:

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.

Endoscopic submucosal injection of a bulking agent would most likely be coded using 43201 – Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance – or code 43236 – Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance.

Endoscopic implantation of a prosthesis would most likely be coded using code 43212 – Esophagoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and postdilation and guide wire passage, when performed), code 43266 – Esophagogastroduodenoscopy, flexible, transoral; with placement of endoscopic stent (includes pre- and postdilation and guide wire passage, when performed), – or code 43499 – unlisted procedure, esophagus.

Additional Policy Key Words

- EndoCinch, Treatment for Gastroesophageal Reflux Disease
- Endoscopic Gastroplasty or Gastroplication
- Enteryx
- Gastroesophageal Reflux Disease (GERD), Transesophageal Therapies
- Gastroplasty or Gastroplication, Endoscopic
- GERD, Transesophageal Therapies
- Radiofrequency Ablation, Gastroesophageal Junction
- Stretta Procedure
- Transesophageal Therapies of GERD

Policy Implementation/Update Information

2/1/01 New policy. Added to Surgery section, considered investigational.

2/1/02 Policy statement revised to include endoscopic submucosal implantation of polymethylmethacrylate beads into the lower esophageal as

investigational.
2/1/03 No policy statement changes.
2/1/04 Policy statement revised to include endoscopic submucosal implantation of a biocompatible polymer (i.e., Enteryx™) as investigational.
2/1/05 No policy statement changes.
2/1/06 No policy statement changes.
2/1/07 No policy statement changes.
2/1/08 No policy statement changes.
2/1/09 No policy statement changes.
2/1/10 No policy statement changes.
2/1/11 No policy statement changes.
2/1/12 Policy statements on biocompatible polymer and PMMA beads combined as bulking agents; remains investigational
2/1/13 No policy statement changes.
2/1/14 No policy statement changes. Added new codes revised and deleted for 2014.
2/1/15 No policy statement changes.
3/1/15 Added Investigational statement regarding Transoral incisionless fundoplication. NDO Plicator, Endocinch, and Enteryx removed from policy. Removed biocompatible liquid polymer from Investigational statement. Updated coding.
2/1/16 Added CPT code. No policy statement changes.
2/1/17 No policy statement changes.
2/1/18 No policy statement changes.
2/1/19 No policy statement changes
