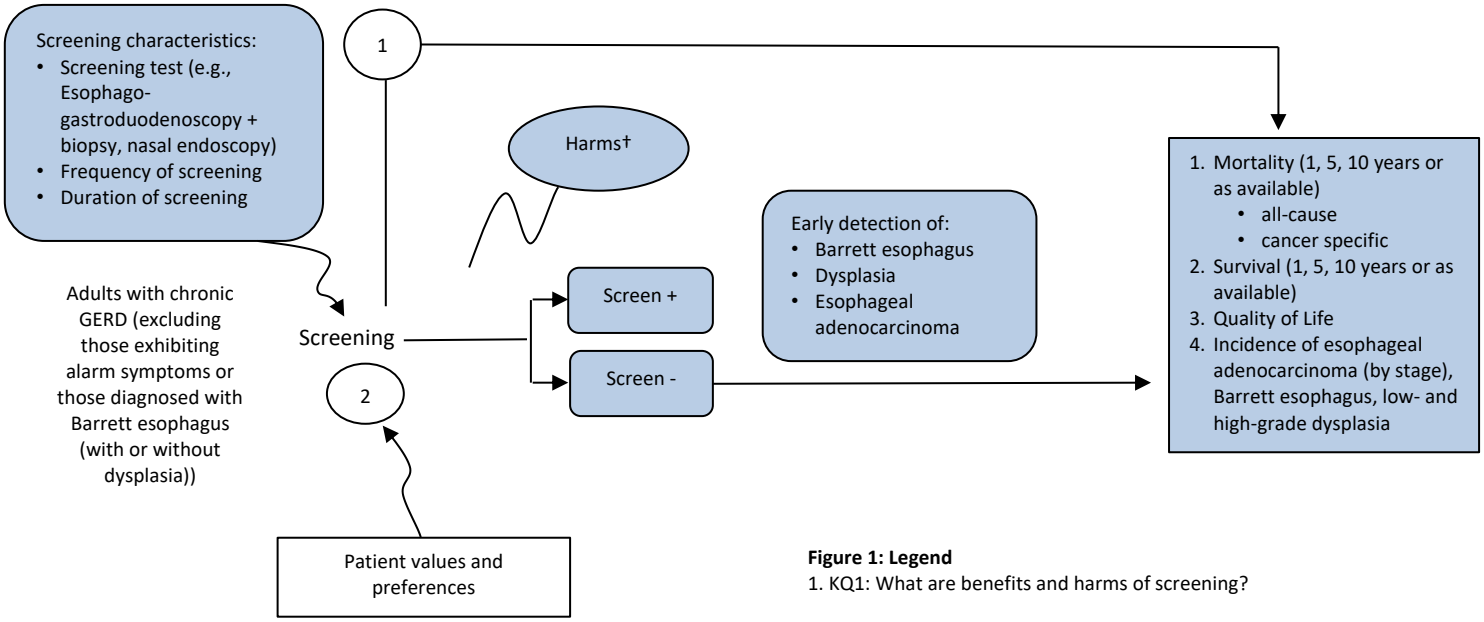
Appendix 1 (as supplied by the authors): Appendices for the Esophageal Adenocarcinoma Screening Guideline

Appendix 1A

Analytic Framework



†Harms of screening

1. Life threatening, severe, or medically significant consequences (such as requiring hospitalization or prolongation of hospitalization; disabling (limiting self-care or activities of daily living)
2. Psychological effects (i.e., anxiety and depression)
3. Major or minor medical procedures
4. Overdiagnosis

Figure 1: Legend

1. KQ1: What are benefits and harms of screening?

2. KQ2: How do adults weigh benefits and harms of screening (patient preferences)?

3. KQ3: What are the benefits and harms of treatment for Barrett esophagus, dysplasia and stage 1 esophageal adenocarcinoma?

Appendix to: Groulx S, Limburg H, Doull M, et al. Guideline on screening for esophageal adenocarcinoma in patients with chronic gastroesophageal reflux disease. *CMAJ* 2020. doi: 10.1503/cmaj.190814

Appendix 1B – Evidence to Decision Framework

Question

Should we screen patients with chronic gastroesophageal reflux disease for esophageal adenocarcinoma (EAC) and precancerous conditions (dysplasia and Barrett esophagus (BE))?

POPULATION:	Adults (≥18 years old) with chronic gastroesophageal reflux disease (GERD) excluding those with alarm symptoms or those diagnosed with Barrett esophagus (with or without dysplasia).
INTERVENTION:	Screening for EAC, BE and/or dysplasia
COMPARISON:	No screening
MAIN OUTCOMES:	Benefit: Reductions in mortality, incidence of EAC, BE, dysplasia, and stage of EAC. Increased survival. Harms: Life threatening, severe, or medically significant consequences of screening (i.e. hospitalization, disability), reduced quality of life, psychological effects, major and minor medical procedures following screening, and overdiagnosis.
SETTING:	Primary care in Canada
PERSPECTIVE:	Population

Background

EAC is one of the more deadly forms of cancer with a poor survival rate among symptomatic cases. The most important risk factors for EAC are associated precancerous conditions (BE, dysplasia), older age (≥50 years), male sex and gastroesophageal reflux disease (GERD), (1-6). Additional risk factors include family history of EAC, white ethnicity, high BMI (particularly abdominal obesity), smoking and (1-4,6,7). Chronic acid reflux increases the risk of EAC approximately 5 to 7 fold, and the majority of BE cases (60%) also report a prior diagnosis of GERD (7-9). However, most patients with GERD do not develop EAC and it remains difficult to predict those that will progress (10). Chronic GERD was initially described in our protocol as symptoms of GERD for ≥12 months (with no specific frequency) and/or PPI (or other pharmacotherapy) use for GERD for ≥12 months. However, Using the pre-defined definition of chronic GERD would have resulted in no included studies. The definition was later expanded to include what study authors considered chronic GERD, and indirectness to the main study question was addressed in the GRADE assessments. Estimates from a Markov model demonstrate that among patients age 60 with weekly GERD symptoms approximately 0.035% of males and 0.004% of females would develop EAC (11). Screening presents a possible mechanism for identifying precancerous conditions (i.e. BE and/or dysplasia) among GERD patients who may be at a higher risk

	of EAC. Currently, most cases of EAC are diagnosed following symptoms such as dysphagia, recurrent vomiting, anorexia, weight loss or gastrointestinal bleeding; at which point the cancer may have already progressed (6). Screening may help diagnose EAC at an earlier stage which allows for a better prognosis (12). Patients diagnosed with BE or high grade dysplasia could also be treated or monitored to prevent the progression to EAC (13). The Task Force sought to investigate whether screening patients with GERD for EAC, BE or dysplasia would help reduce the incidence and mortality of EAC and improve patient important outcomes.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○No ○Probably no **X Probably yes** ○Yes ○Varies ○Don't know	It is estimated that 5.7 new cases per 100,000 population of esophageal cancer will be diagnosed in 2017 with a 5-year survival rate of only 14% (14). The most common type of esophageal cancer is EAC for which GERD is one of the most important risk factors (15). The incidence of EAC has doubled in the past 20 years (14). Currently, most cases of EAC are diagnosed following alarm symptoms such as dysphagia, odynophagia, recurrent vomiting, anorexia, weight loss or gastrointestinal bleeding; at which point the cancer may have already progressed (6). It is hypothesized that screening may help diagnose EAC at an earlier stage which allows for a better prognosis (12). An estimated 3.4 to 6.8 million Canadians experience chronic GERD (weekly moderate to severe symptoms or greater than weekly mild symptoms) (16,17). Currently, most GERD patients are not routinely screened for EAC. However, if BE is diagnosed they may be followed by endoscopy surveillance to ensure it does not progress to EAC (18,19). There are no current national screening guidelines but there are two previous Canadian guidelines focused on treatment and management (Alberta, 2009 and Canadian Association of Gastroenterology, 2004) (18,19).	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○Trivial ○Small ○Moderate	**<u>BENEFITS – SCREENING, DIRECT EVIDENCE</u>**	

	○Large ○Varies **X Don't know**	**EGD compared to no prior EGD for screening for EAC and precancerous conditions (BE and dysplasia)** **Setting**: Hospital-based **Intervention**: EGD **Comparison**: no prior EGD

Outcomes	**Anticipated absolute effects***(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no prior EGD	**Risk with EGD**				
Survival (20)	Study authors report that there was no difference in long-term survival between those who had received a prior EGD and those who had not (HR 0.82 [95%CI 0.52-1.29]). Adjusting for age, comorbidities, and year of diagnosis yielded similar results (HR 0.93 [95% CI, 0.58-1.50]).			(1 observational study)	⨁◯◯◯ VERY LOW[a,b,c]	
EAC stage 1 at diagnosis (20)	123 per 1,000	**279 per 1,000** (128 to 609)	**RR 2.27** (1.04 to 4.95)	155 (1 observational study)	⨁◯◯◯ VERY LOW[a,b,c]	
EAC stage unknown at diagnosis (21)	One out of 153 patients, not under surveillance for BE, had received an EGD in the previous five years. An additional 15 had received an EGD more than five years ago, with no additional details on timing. For the purposes of this review, these patients were grouped with those with no prior EGD. This one patient was diagnosed with "unknown stage" of EAC.			153 (1 observational study)	⨁◯◯◯ VERY LOW [c,d,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **EGD**: Esophagogastroduodenoscopy **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. The study consisted of a group of veterans, and there was a significant difference between groups on comorbidities.
b. GER identified by ICDs codes 530.10-530.12, 530.81, or 787.1
c. Too few participants

d. This study consists of patients diagnosed with EAC at the VA Medical Centre. The authors do not provide a comparison for the participants of interest for this review, as their larger population included 29 patients undergoing surveillance for BE. These participants were excluded from our results. This left one patient not under surveillance for BE who received an EGD in the previous five years.

e. GERD was not defined and only two-thirds of the participants included in this review had GERD diagnosis.

No evidence was found on screening for the following benefits: mortality rates (other than survival (all cause)); quality of life; incidence of BE and dysplasia.

Although risk factors such as age (≥50 years), male sex, family history, white race/ethnicity, abdominal obesity and smoking may increase the risk for esophageal adenocarcinoma, relevant trials and cohort studies did not include sufficient data within each category to support modifying our screening recommendation based on these factors, alone or in combination.

BENEFITS – SCREENING MODALITIES, INDIRECT EVIDENCE

Indirect evidence from studies comparing screening modalities (22-26) reported on incidence of EAC, dysplasia, suspected BE and confirmed BE, with only one (26) finding a significant effect. More suspected high grade Barrett esophagus cases were identified via esophagogastroduodenoscopy (EGD) versus video capsule esophagoscopy (VCE) however it is unclear if these were confirmed histologically (27). Two other RCTs (28,29) focused on biopsy methods and did not find any statistically significant difference in rates of confirmed BE (27).

EGD compared to transnasal esophagoscopy (TNE) for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Hospital- and office-based (depending on modality)

Intervention: EGD

Comparison: TNE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with TNE	Risk with EGD				
Incidence of suspected BE (23)	51 per 1,000	**106 per 1,000** (66 to 171)	**RR 2.09** (1.30 to 3.36)	981 (1 observational study)	⨁◯◯◯ VERY LOW [d,j,k]	Includes those with Grade 2 and 3, as those with Grade 1 would not have been considered as BE in Chang 2011 and Sami 2015.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Although risk factors such as age (≥50 years), male sex, family history, white race/ethnicity, abdominal obesity and smoking may increase the risk for esophageal adenocarcinoma, relevant trials and cohort studies did not include sufficient data within each category to support modifying our screening recommendation based on these factors, alone or in combination.

BENEFITS – TREATMENT, LINKED EVIDENCE

An overview of systematic reviews examined the effectiveness of pharmacological, surgical, chemical ablative, thermal ablative techniques and combined techniques in reducing progression to EAC or high grade dysplasia (from BE or low grade dysplasia), reduction in length of BE, eradication and mortality (30).

Many findings did not reach clinical or statistical significance or were not estimable due to zero events in either the control or intervention groups (e.g. mortality) (30). Results indicate that photodynamic therapy, radiofrequency ablation and endoscopic mucosal resection of Barrett esophagus (with or without proton pump inhibitors) provide a statistically significant increase in eradication or clearance of dysplasia (very low to moderate-certainty evidence) (30). Possible reduction in progression to EAC was also observed with photodynamic therapy (very low-certainty evidence) (30). There was insufficient evidence to show an effect on mortality.

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○Large
○Moderate
○Small
○Trivial

○Varies
x Don't know

HARMS – SCREENING

No evidence was found comparing screening to no screening for the following harms: Life threatening, severe, or medically significant consequences (such as requiring hospitalization or prolongation of hospitalization; disabling (limiting self-care or activities of daily living); psychological effects (i.e., anxiety and depression); major or minor medical procedures; overdiagnosis.

HARMS – SCREENING MODALITIES, INDIRECT EVIDENCE

EGD compared to transnasalesophagoscopy (TNE) for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Hospital- and office-based (depending on modality)

Intervention: EGD

Comparison: TNE

Outcomes	**Anticipated absolute effects***(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with TNE	**Risk with EGD**				
Life threatening, severe, or medically significant consequences (31)	Serious adverse events were assessed 1 and 30 days after the procedure. No serious adverse events were reported in any of the study arms. Hospital-based TNE and mobile-based TNE were combined for this outcome under TNE.			209 (1 RCT) [a]	⨁◯◯◯ VERY LOW[b,c,d]	

		Psychological effects (anxiety before the procedure) (32)	Authors report those who experienced no anxiety, and mild, moderate and severe anxiety before the procedure. There was no difference between screening modalities (p=0.084)	(1 RCT) [e]	⨁◯◯◯ VERY LOW[d,g,m]
		Psychological effects (anxiety during insertion) (32)	Authors report those who experienced no anxiety and mild, moderate and severe anxiety during insertion of the tube. There was a statistically significant difference between modalities (p=0.0001), with those randomized to (unsedated) TNE experiencing more anxiety during insertion.	(1 RCT) [e]	⨁◯◯◯ VERY LOW[d,g,m]
		Psychological effects (anxiety during procedure) (31,33,34)	Chang 2011 appears to only have given the questionnaire to the TNE group and reports the results using median score and the range, Sami 2015 reports the results using mean (Standard Deviation) on a scale of 0-10, and Jobe 2006 reports the results using the number of participants who selected the level of anxiety as "none", "mild", "moderate", and "severe". Both Sami and Jobe report a statistically significant differences between modalities with those randomized to TNE experiencing more anxiety during the procedure, p<0.001 and p=0.0001, respectively.	(3 RCTs) [e]	⨁◯◯◯ VERY LOW[c,d,g,i,m]
		*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio			

		GRADE Working Group grades of evidence **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect **Explanations** a. Defined in Sami 2015 as safety (adverse events including pain, abdominal discomfort, bleeding, perforation, or need for hospitalization) b. Many domains were judged as high risk of bias (e.g., allocation concealment, blinding of participants, personnel and outcome assessors) c. Defined as "heartburn or acid regurgitation >1 week, <1 week, or none" using a GERQ questionnaire d. Too few participants. e. One study is a randomized crossover design (Jobe 2006) f. Many domains were judged as unclear (e.g., sequence generation, allocation concealment, blinding of participants and personnel, etc); as such the overall ROB was considered moderate risk. g. GERD defined as "heartburn, regurgitation or dysphagia" h. Many domains were judged as high risk of bias (e.g., blinding of participants, personnel and outcome assessors, etc). i. Symptoms obtained through questionnaires and were not clearly defined j. GERD was not defined in the cohort. k. GERD was not defined and the assessment of the outcome could be influenced by the personnel's knowledge and possible bias to the screening modality. l. No description of allocation concealment in Sami 2015, and some selective outcome reporting. m. Participants were aware of what screening modality they were being given and this could influence the level of anxiety.	

Transnasal esophagoscopy (TNE) compared to esophageal video capsule esophagoscopy (VCE) for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Outpatient clinic and Clinical Research Centre (depending on study)
Intervention: TNE
Comparison: VCE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with VCE	Risk with TNE				
Psychological effects (anxiety, nervousness, or worry before the procedure) (35)	167 per 1,000	**380 per 1,000** (222 to 647)	**RR 2.28** (1.33 to 3.88)	177 (1 RCT)	⊕◯◯◯ VERY LOW [b,d,g]	
Psychological effects (anxiety during the procedure) (33)	156 per 1,000	333 per 1,000 (190 to 586)	RR 2.14 (1.22 to 3.77)	177 (1 RCT)	⊕◯◯◯ VERY LOW [b,c,d,g]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **TNE**: Transnasal esophagoscopy; **VCE**: video capsule esophagoscopy

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Personnel and outcome assessors were aware of screening modality and could be influenced by this knowledge.
b. Chak 2014 defined GERD based on symptoms of GERD (from questionnaire) or use of acid suppression medicine (within 7 days of screening).

c. Chang 2011 defined GERD based on symptoms obtained through validated questionnaires.
d. Too few participants.
e. Chak 2014 was considered low risk but contributed a greater amount of data to the outcome. Chang 2011 was considered high risk, but only contributed 20 participants to each comparison.
f. Many ROB domains were unclear due to lack of reporting for this study.
g. Participants were aware of screening modality and could be influenced by this knowledge. Personnel could also influence the level of anxiety by knowledge of the screening modality.

TNE compared to Transoral EGD for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Hospital-based
Intervention: TNE
Comparison: Transoral EGD

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Transoral EGD	**Risk with TNE**				
Life threatening, severe, or medically significant consequences (22)	0 per 1,000	Not estimable due to zero count in comparison group	Not estimable	59 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Zaman, 1999 reported n=0/34 serious, or medically significant consequences with transoral EGD and 1/25 with TNE
Anxiety prior to screening Scale from: 0 to 10 (22)		The mean anxiety prior to screening in the intervention group was 0.6 lower (2.13 lower to 0.93 higher)	-	59 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,f]	
Anxiety during insertion Scale from: 0 to 10 (22)		The mean anxiety during insertion in the intervention group was 0.3 lower (1.83 lower to 1.23 higher)	-	59 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,f]	

Anxiety during the procedure Scale from: 0 to 10 (22)		The mean anxiety during the procedure in the intervention group was 0 (1.68 lower to 1.68 higher)	-	59 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,f]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **EGD**: Esophagogastroduodenoscopy; **RR:** Risk ratio; **TNE**: Transnasal esophagoscopy

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

HARMS – TREATMENT, LINKED EVIDENCE

An overview of systematic reviews examined the effectiveness of pharmacological, surgical, chemical ablative, thermal ablative techniques and combined techniques in reducing progression to EAC or high grade dysplasia (from BE or low grade dysplasia), reduction in length of BE, eradication and mortality (30). Harms such as stricture formation, bleeding and perforation were also examined.

Many findings did not reach clinical or statistical significance or were not estimable due to zero events in either the control or intervention groups.

Very low to low-certainty evidence indicates no statistically significant difference in bleeding or perforation between treatment modalities (30). Compared to radiofrequency ablation, endoscopic mucosal resection showed a statistically significant increase in stenosis and strictures (very low-certainty evidence) (30). Stricture formation was also statistically increased with photodynamic therapy plus proton pump inhibitors when compared to

		proton pump inhibitors alone (very low-certainty evidence) (30). There was no data on quality of life, psychological effects, additional medical procedures or overdiagnosis (30).	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** **X Very low** ○ Low ○ Moderate ○ High ○ No included studies	**Screening:** Very Low – the overall certainty of evidence for the critical outcomes is very low; We are very uncertain about the absolute effects of screening on the critical outcomes. **Screening (indirect evidence):** Very Low – the overall certainty of evidence for the critical outcomes is very low; We are very uncertain about the absolute effects of screening on the critical outcomes. **Treatment (indirect linked evidence):** Not estimable (review of reviews). However, the certainty of evidence for all the critical outcomes was very low to moderate. We are very uncertain about the absolute effects of treatment on the critical outcomes.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** **X Important uncertainty or variability** ○ Possibly important	A systematic review of patient values and preferences examined willingness to participate in different screening trials comparing screening modalities (36). Overall, acceptability of screening procedures was low but evidence was insufficient to assess how participants weigh the benefits and harms of screening (36). As an indirect measure of acceptability, factors that contribute to willingness to be screened were examined. In one study, among 1,210 invited participants, 52% did not respond to the letter, 32% declined screening (no reason provided), 1% were ineligible, and 0.2% cited difficulty attending (35). Two other studies also had high refusal rates (45 of 105; 43% and 19 of 62; 31% respectively) due to anxiety, lack of interest, fear of gagging, unwillingness to be study subjects, or reluctance to undergo transnasal procedures (22,37). KT process, Phase I: Overall, many participants indicated that they would be hesitant to engage in invasive screening due to the potential risks involved (38). Thus, many individuals	

	uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	may perceive a guideline to be more socially acceptable it if encourages clinicians to engage in shared decision making with patients. KT process, Phase II: Results from surveys and focus groups on patient values and preferences reported a moderate desire to be screened (median rating =6 out of 9 (where 1=not at all, and 9=very much)) (39). For many respondents, personal experience, individual or familial risk factors, and their fear of missing an early diagnosis outweighed the invasiveness and risks of screening. For some, the lack of evidence and perceived risk would have led to the opposite decision (39). Based on the inconsistent and very limited evidence from the systematic review and results from the focus groups, there is likely important variability in patient values and preferences regarding their decision to undergo screening for esophageal adenocarcinoma.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** **X Favors the comparison** ○ Probably favors the comparison ○ Does not favor either the intervention or the	There was only one study (20) (with sufficient data) of *very low-certainty* which examined screening vs no screening for the outcomes of survival and stage of EAC. They reported no difference in long-term survival between screened and unscreened GERD patients despite screened patients being diagnosed at an earlier stage. Although risk factors such as age (≥50 years), male sex, family history, white race/ethnicity, abdominal obesity and smoking may increase the risk for esophageal adenocarcinoma, relevant trials and cohort studies did not include sufficient data within each category to support modifying our screening recommendation based on these factors, alone or in combination. Trials comparing sedated esophagogastroduodenoscopy versus unsedated transnasal esophagoscopy and unsedated transnasal versus unsedated transoral esophagogastroduodenoscopy reported one serious adverse event (0/209 and 1/59	

	comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	respectively) (27). Taken together, this would be an incidence of n=1/268 (approximately 4/1,000) serious adverse events for an elective procedure. Indirect evidence showed that treatment with photodynamic therapy, radiofrequency ablation and endoscopic mucosal resection of Barrett esophagus (with or without proton pump inhibitors) provide a statistically significant increase in eradication or clearance of dysplasia (very low to moderate-certainty evidence) (Appendix 4) (30). Possible reduction in progression to esophageal adenocarcinoma was also observed with photodynamic therapy (very low-certainty evidence). Mortality results were very limited (event rates of 0 to 3 per trial) (30). Possible reduction in progression to EAC was also observed with photodynamic therapy (very low-certainty evidence) (30). However, there was a statistically significant increase in stenosis and strictures for endoscopic mucosal resection compared to radiofrequency ablation (very low-certainty evidence) (30). A statistically significant increase in stricture formation occurred with photodynamic therapy plus omeprazole compared to omeprazole alone (very low-certainty evidence) (30).	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs **X Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings	A recommendation against screening reflects the status quo and would result in negligible costs and savings. Due to the low certainty evidence on the effectiveness of screening, no economic evaluation or systematic review of cost-effectiveness was conducted as part of this guideline. Screening GERD patients for EAC is not a routine part of care in Canada unless they have other risk factors (18,19). However, potential costs include physician services, opportunity costs, hospital/facility expenses and biopsy analysis (40-42). Recommendation in favour of screening: moderate costs (see information in right column).	The Ontario fee schedule (2015) lists oesophagoscopy, with or without biopsy(ies) as $128.29 and oesophagoscopy-gastroscopy, with or without duodenoscopy as $152.66 (elective) and $185.26 (for active bleeding). If

	○ Varies ○ Don't know	*(Recommendation against screening: status quo, judgment would be "don't know" or "negligible costs and savings")* Judgement (left column) is based on perspective of implementing screening program.	multiple biopsies are necessary or a brushing biopsy technique is used an additional $15.10 and $46.30 is added respectively (40). A study of EGD (without biopsy or intervention) in Canada found the average fee (± SD) was $114.19±$31.4 per procedure in 2009 (41). The median was $110.50 and ranged from $52.50 in Quebec to $213.33 for the Northwest Territories. However, costs also vary depending on the endoscopic modality (EGD, TNE, VCE, etc.), sedated or unsedated status and would increase

			if biopsy was performed (42). Additional costs include hospital/facility fees, biopsy analysis costs and would vary depending on screening or technique (42).
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** o Very low o Low o Moderate o High **x No included studies**	A cost-effectiveness systematic review was not completed.	

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies **x No included studies**	A cost-effectiveness systematic review was not completed.	

EQUITY	**What would be the impact on health equity?** ○ Reduced **X Probably reduced** ○ Probably no impact ○ Probably increased ○Increased ○ Varies ○ Don't know	Recommendation in favour of screening: Wait lists for endoscopy are perceived as long by Canadians therefore recommending in favour of screening may increase inequities by expanding wait lists and possibly creating a two-tiered system wherein those able to pay seek faster private services. *(Recommendation against screening: Screening is not currently conducted in Canada therefore not recommending screening represents the status quo and would not have an impact on equity.)* Judgement (left column) is based on perspective of implementing screening program.	A survey conducted in 2010 demonstrated that wait times to access endoscopy (EGD or colonoscopy) are already perceived as too long by many Canadians and do not meet accepted targets (43,44)
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No **X Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	There is currently no population level screening program for EAC in Canada. Given the lack of evidence on effectiveness and the system level costs, a population screening program may not be acceptable to stakeholders. EDG is currently performed by specialists and referred to from primary care. A population level screening program may increase waiting lists which may not be acceptable to health policy stakeholders.	A small US-based study (n=136) indicated that screening was acceptable to most adults, with a preference for sedated techniques (45).

FEASIBILITY	**Is the intervention feasible to implement?** ○ No **X Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	The screening test (EGD) currently exists and is used for GERD patients who exhibit alarm symptoms (i.e. dysphagia, esophageal bleeding, vomiting). However, the wait times to access endoscopy (EGD or colonoscopy) are already perceived as too long by many Canadians (43,44). It also may be difficult to implement as the prevalence of GERD is estimated at 10-20% of the Canadian population (17).	

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	**Probably yes X**	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know X**	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know X**	
CERTAINTY OF EVIDENCE	**Very low X**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	**Important uncertainty or variability X**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	**Favors the comparison X**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs X**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies X**	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies X**	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	**Probably reduced X**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	**Probably no X**	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	**Probably no X**	Probably yes	Yes		Varies	Don't know	

Conclusions

Should we screen patients with chronic GERD for EAC and precancerous conditions (BE and dysplasia)?

TYPE OF RECOMMENDATION	**Strong recommendation against the intervention**	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	X	○	○	○	○

RECOMMENDATION	The Task Force does not recommend routinely screening adults with chronic GERD for EAC
JUSTIFICATION	Overall, very low-certainty evidence from one applicable observational study demonstrated no benefit of screening on survival (20). Very low-certainty evidence from the same observational study indicated that people who received a prior EGD had a statistically significant lower stage of diagnosis than those without a previous EGD. There was no direct evidence of harms of screening versus no screening. Indirect evidence showed n=1/268 serious adverse events in trials comparing unsedated and sedated screening techniques and statistically significant increased anxiety associated with unsedated endoscopy (very low-certainty evidence) (27). However, the mild additional discomfort seems to be well tolerated, given that 70 to 95% of participants stated they would undergo it again (27). Indirect evidence on treatment provided low to very low-certainty evidence with many results not meeting clinical or statistical significance. Some endoscopic ablation and endoscopic mucosal resection (with or without PPIs) may offer benefit in terms of eradication of dysplasia (30). Reduction in progression to esophageal adenocarcinoma was also observed with photodynamic therapy though the evidence was very low certainty. There was not enough data or certainty in the evidence to confirm an effect on mortality or harms (30). There is limited data and important variability around patient preferences as some indicated they would be hesitant to undergo screening given these potential risks while others placed greater importance on the possibility of earlier diagnosis (36,38,39). Additionally, the resources required to screen all adults with chronic GERD are substantial. Therefore, in the judgement of the task force the harms of screening outweigh the benefits and a strong recommendation against screening is warranted. This recommendation places a relatively higher priority on the potential harms of screening (including the resources that would be needed) and lack of evidence for any reduction in mortality, and places a lower priority on the potential to identify esophageal adenocarcinoma at an earlier stage.
SUBGROUP CONSIDERATIONS	A priori-defined subgroup analysis variables included age, sex, body mass index (BMI), smoking history, duration of chronic GERD, definition of chronic GERD, groupings of risk factors, and

	various ethnic groups. Although risk factors such as age (≥50 years), male sex, family history, white race/ethnicity, abdominal obesity and smoking may increase the risk for esophageal adenocarcinoma, relevant trials and cohort studies did not include sufficient data within each category to support modifying our screening recommendation based on these factors, alone or in combination.
IMPLEMENTATION CONSIDERATIONS	Clinicians should be aware of early alarm symptoms for EAC and diagnose these patients appropriately. Clinicians should be aware of early management protocols for GERD and BE. They should also apply clinical judgement for the investigation and management of those unresponsive to GERD treatment or with symptoms suggestive of other upper gastrointestinal disorders (e.g. dyspepsia).
MONITORING AND EVALUATION	This recommendation is against screening, therefore rates of upper gastrointestinal endoscopy for screening could be monitored to determine non-adherence.
RESEARCH PRIORITIES	There was only one observational study (with sufficient data) that examined whether screening compared to no screening improved outcomes and diagnosis (20). The limited use of a common definition for chronic GERD also reduced the generalizability of existing studies. EAC is the second most deadly cancer in Canada with a 5 year survival rate of 14% and prevalence is expected to increase over time (14,15). Ideally, high quality RCTs or cohort studies that examine screening versus no screening among GERD patients would provide the best evidence. However, due to the rarity of esophageal adenocarcinoma, the sample size needed for an RCT limits feasibility. Future studies may want to focus on higher risk individuals (e.g. abdominal obesity, family history, genetic mutations of p15) or screening procedures that are either less invasive or less resource intensive. Systematic reviews on newer forms of treatment (e.g. combined endoscopic mucosal resection and radiofrequency ablation, endoscopic submucosal dissection) are also lacking and

	would be useful to provide linked evidence for effectiveness of screening. Continuing to track the incidence of esophageal adenocarcinoma in Canada and known risk factors is also recommended.

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Appendix 1C (1)

Subgroup Analysis[a]

A priori-defined subgroup analysis variables included age, sex, body mass index (BMI), smoking history, duration of chronic GERD, definition of chronic GERD, groupings of risk factors, and various ethnic groups. Due to the poor reporting of variables, we were not able to perform our a priori-defined subgroup analysis. We planned sensitivity analyses to restrict to those studies as being low risk of bias

[a] Text quoted directly from: Hamel C, Beck A, Thuku M, Stevens A, Skidmore B, Chatterjee A, Maziak D, Shea B, Hutton B, Little J, Moher D. 2018. Screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett esophagus) in patients with chronic gastroesophageal reflux disease with or without other risk factors: systematic review to inform a guideline of the Canadian Task Force on Preventive Health Care. Evidence Review Synthesis Centre: Ottawa Hospital Research Institute, Ottawa, Ontario. Available at: http://canadiantaskforce.ca/guidelines/published-guidelines/esophageal-adenocarcinoma/.

and based on the timing of publication. However only two studies, Chak, 2014 (2) and Jobe, 2006 (3), were considered low risk for the incidence of histologically confirmed BE and sensitivity analyses were not undertaken.

Potentially relevant, unpublished trials were identified from our grey literature search and may prove informative for any subsequent updates of this review (4-19). The ongoing BEST3 cluster randomized controlled trial in the UK involves 120 primary care practices with a planned sample of 9000 participants (4). The aims are to assess whether the Cytosponge test for patients with reflux symptoms will be effective in increasing the detection of BE in primary care compared to usual care, and to evaluate cost-effectiveness and patient acceptability. However, only the planned outcomes of the incidence of BE and adverse events may be relevant. Results are anticipated for late 2020.

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Appendix 1D

Outcome summary for reduction in progression to esophageal adenocarcinoma (or surrogate measure of eradication/clearance of dysplasia or Barrett esophagus) by non-surgical[a] treatment type

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
Progression to esophageal adenocarcinoma (EAC)	(Rees, 2010) (1), 1 RCT: (Heath, 2007) (2)	Celecoxib[b]: 3/49 versus Placebo: 3/51	OR=1.04 (0.20 to 5.44)	2 per 1,000 more progressed to EAC at one-year with Celecoxib (from 46 fewer to 195 more)	-	0.2	AMSTAR: Low[c] Modified GRADE: Very low[d]
	(Rees, 2010) (1), 1 RCT: (Overholt, 2005) (3)	PDT + Omeprazole[e]: 18/138 versus Omeprazole[e]: 20/70	OR=0.38 (0.18 to 0.77)	154 per 1,000 fewer progressed to EAC at latest time point (up to 2 years) with PDT+Omeprazole (from 50 to 219 fewer)	15.4	-	AMSTAR: Low[c] Modified GRADE: Very low to low[f]
	(Li, 2008) (4), 1 RCT: (Overholt, 2007) (5)	PDT + Omeprazole[e]: [g]21/138 versus Omeprazole: 20/70	RR=0.53[h] (0.31 to 0.91)	134 per 1,000 fewer progressed to EAC at 5 years with PDT+Omeprazole (from 26 to 197 fewer)	13.4	-	AMSTAR: Critically low[i] Modified GRADE: Very low to low[f]
	(Rees, 2010) (1), 1 RCT (Shaheen, 2009) (6)	RFA + PPI: 1/84 versus PPI: 4/43	OR=0.12 (0.01 to 1.09)	81 per 1,000 fewer progressed to EAC at 5 years or latest time point with RFA+PPI (from 92 fewer to 8 more)	8.1	-	AMSTAR: Low[c] Modified GRADE: Low[j]
	(Rees, 2010) (1),	Anti-reflux surgery[k]: 2/53 versus	OR=0.75 (0.10 to 5.53)	12 per 1,000 fewer progressed to EAC with anti-reflux surgery	1.2	-	AMSTAR: Low[c] Modified GRADE: Very low[l]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	1 RCT (Parrilla, 2003) (7)	H2 receptor agonist/ Omeprazole[e]: 2/40		(from 45 fewer to 175 more)			
	(Fayter, 2010), (8), 1 RCT (Mackenzie, 2007) (9)	ALA-PDT with varying doses of light and comparing red or green light	Narrative summary: Patients with high grade dysplasia receiving high-dose ALA–PDT (60 mg/kg) and high-dose red light (1000 J/cm) had a significant decrease in cancer risk at 36 months follow-up compared with treatment groups with lower doses of photosensitiser and/or lower light doses at 36 months (3% risk vs 24% risk).				AMSTAR: Critically low[i] Modified GRADE: Very low[m]
	(Fayter, 2010) (8), 2 RCTs (Mackenzie, 2007, Mackenzie, 2009) (9,10)	ALA-PDT with red light and ALA with green light at 30 or 60 mg/kg	Narrative summary: ALA red light was associated with lower rates of adenocarcinoma than green light (8% vs 45%, $p < 0.05$). 60-mg ALA red light was more successful than 30-mg ALA red light ($p = 0.03$) and then 30-mg ALA green light ($p = 0.005$).				AMSTAR: Critically low[i] Modified GRADE: Very low to low[n]
	(Qumseya, 2017) (11), 1 RCT (Phoa, 2014) (12)	RFA: 1/68 versus Surveillance: 6/68	RR[h]=0.17 (0.02 to 1.35)	73 per 1,000 fewer progressed to EAC with RFA (cumulative progression over the follow-up period) (from 86 fewer to 31 more)	7.4	-	AMSTAR: Low[c] Modified GRADE: Very low[o]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	(Almond, 2014) (13), 3 RCTs (Zopf, 2001, Hage, 2004, Ragunath, 2005) (14-16)	PDT: 1/20 versus APC+PPI: 0/17	Not estimable	Not estimable	-	Not estimable	AMSTAR: Critically low[i] Modified GRADE: Very low[p]
Eradication/ clearance of dysplasia	(Rees, 2010) (1), 2 RCTs (Overholt, 2005, Ackroyd, 2000) (3,17)	PDT+Omeprazole[e]: [g]87/156 versus Omeprazole[e]: [g]10/88	Pooled OR=9.13 (4.42 to 18.86)	426 per 1,000 more had complete eradication of dysplasia at 2 years with PDT + Omeprazole (from 248 to 594 more)	-	42.6	AMSTAR: Low[c] Modified GRADE: Very low to low[f]
	(Li, 2008) (4), 1 RCT (Ackroyd, 2000) (17)	PDT+Omeprazole[e]: [g]18/18 versus Omeprazole[e]: [g]6/18	RR[h]=2.85 (1.52 to 5.33)	617 per 1,000 more had eradication of dysplasia with PDT + Omeprazole (from 173 to 1,000 more)	-	61.7	AMSTAR: Critically low[i] Modified GRADE: Very low to low[f]
	(Li, 2008) (4), 1 RCT, (Overholt, 2005) (3)	PDT+Omeprazole[e]: 81/138 versus Omeprazole[e]: 10/70	RR[h]=4.11 (2.28 to 7.42)	444 per 1,000 more had eradication of dysplasia with PDT + Omeprazole (from 183 to 917 more)	-	44.4	AMSTAR: Critically low[i] Modified GRADE: Very low to low[f]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	(Rees, 2010) (1), 1 RCT (Shaheen, 2009) (6)	RFA+PPI: 72/84 versus PPI: 9/43	OR=22.67 (8.72 to 58.94)	648 per 1,000 more had complete clearance of dysplasia at 12 months with RFA+PPI (from 488 to 730 more)	-	64.8	AMSTAR: Low[c] Modified GRADE: Low[j]
	(Pandey, 2018) (18), 1 RCT (Shaheen, 2009) (6)	RFA+PPI: 38/42 versus PPI: 5/22	RR[h]=3.98 (1.83 to 8.66)	677 per 1,000 more had complete eradication of dysplasia with RFA+PPI (from 189 to 1,000more)	-	67.7	AMSTAR: Critically low[i] Modified GRADE: Very low[q]
	(Pandey, 2018) (18), 1 RCT (Phoa, 2014) (12)	RFA: 62/63 versus Surveillance (endoscopic): 19/68	RR[h]=3.52 (2.40 to 5.17)	704 per 1,000 more had complete eradication of dysplasia with RFA (from 391 to 1,000 more)	-	70.4	AMSTAR: Critically low[i] Modified GRADE: Very low to low[r]
	(Rees, 2010) (1), 1 RCT (Parrilla, 2003) (7)	Anti-reflux surgery[k]: 5/58 versus H2 receptor agonist/ Omeprazole[e]: 3/43	OR=1.26 (0.28 to 5.58)	17 per 1,000 more had complete eradication of dysplasia at 5 years with anti-reflux surgery (from 49 fewer to 225 more)	-	1.7	AMSTAR: Low[c] Modified GRADE: Very low[l]
	(Rees, 2010) (1),	PDT: [g]10/13 versus APC + PPI: 6/9	OR=1.67 (0.25 to 11.07)	103 per 1,000 more had complete eradication of	-	10.3	AMSTAR: Low[c] Modified GRADE: Very low[s]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	1 RCT (Ragunath, 2005) (16)			dysplasia at 12 months with PDT (from 333 fewer to 290 more)			
	(Almond, 2014) (13), 1 RCT (Hage, 2004) (15)	PDT: 5/5 versus APC+PPI: 3/3	RR[h]=1.00 (0.64 to 1.56)	0 per 1,000 fewer had complete eradication of dysplasia at 12 months with PDT (from 360 fewer to 560 more)	0		AMSTAR: Critically low[i] Modified GRADE: Very low[t]
	(Almond, 2014) (13), 1 RCT (Ragunath, 2005) (16)	PDT: [g]8/11 versus APC+PPI: 6/9	RR[h]=1.09 (0.61 to 1.96)	60 per 1,000 more had complete eradication of dysplasia at 12 months with PDT (from 260 fewer to 640 more)		6.0	AMSTAR: Critically low[i] Modified GRADE: Very low[u]
	(Chadwick, 2014) (19), 1 RCT (van Vilsteren, 2011) (20)	EMR: 25/25 versus RFA: 21/22	RR[h]=1.05 (0.93 to 1.18)	48 per 1,000 more had complete eradication of dysplasia at end of follow-up with EMR (from 67 fewer to 172 more)	-	37.9	AMSTAR: Critically low[i] Modified GRADE: Very low[q]
Complete eradication/ ablation of	(Rees, 2010) (1), 2 RCTs (Overholt,	PDT+Omeprazole[e] : 72/138 versus	OR=14.18 (5.38 to 37.37)	450 more per 1,000 had complete eradication of BE at 5 years with PDT+Omeprazole	-	45.0	AMSTAR: Low[c] Modified GRADE: Very low to low[f]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
Barrett esophagus	2005, Overholt, 2007) (3,5)	Omeprazole[e]: 5/70		(from 221 to 670 more)			
	(Rees, 2010) (1), 1 RCT (Bright, 2007) (21)	Anti-reflux surgery[k] + APC: 14/20 versus Anti-reflux surgery[k]: 0/20	OR=91.46 (4.77 to 1,754.50)	Not estimable	-	Not estimable	AMSTAR: Low[c] Modified GRADE: Very low[m]
	(Rees, 2010) (1), 1 RCT (Parrilla, 2003) (7)	Anti-reflux surgery[k]: 0/53 versus H2 receptor antagonist/ Omeprazole: 0/40	Not estimable	Not estimable	Not estimable	Not estimable	AMSTAR: Low[c] Modified GRADE: Very low[m]
	(Li, 2008) (4), 3 RCTs (Hage, 2004, Kelty, 2004, Hage, 2005) (15,22,23)	PDT : 22/80 versus APC+PPI: 36/61	Pooled RR[h]=0.51 (0.34 to 0.77)	289 fewer per 1,000 had histologically complete ablation of BE with PDT (from 136 to 390 fewer)	28.9	-	AMSTAR: Critically low[i] Modified GRADE: Very low[v]
	(Rees, 2010) (1), 3 RCTs (Hage, 2004,	PDT: [g]35/68 versus APC+PPI : [g]41/59	Pooled OR=0.31 (0.00 to 32.60)	[w]Moderate baseline risk: 284 per 1,000 fewer had complete eradication of BE	Moderate baseline risk: 28.4	-	AMSTAR: Low[c] Modified GRADE: Very low[x]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	Ragunath, 2005, Kelty, 2004) (15,16,22)			at 12 months with PDT (from --- to 315 more) ; [w]High baseline risk: 61 per 1,000 fewer had complete eradication of BE at 12 months with PDT (from --- to 29 more)	High baseline risk: 6.1		

ALA-PDT = Aminolevulinic acid – photodynamic therapy; AMSTAR= A MeaSurement Tool to Assess systematic Reviews; APC=Argon plasma coagulation; BE=Barrett esophagus; EAC=Esophageal adenocarcinoma; EMR=Endoscopic mucosal resection; GRADE= Grading of Recommendations Assessment, Development and Evaluation system); OR=Odds ratio; PDT=Photodynamic therapy; PPI= Proton pump inhibitors; RFA=Radiofrequency ablation; RR=Relative risk.

[a] This review focused on early (non-surgical) techniques used in treatment of Barrett esophagus, dysplasia or stage 1 esophageal adenocarcinoma. However, esophagectomy is the standard treatment for more advanced or high risk cases.

[b] Nonsteroidal anti-inflammatory drug (NSAID).

[c] An AMSTAR (A MeaSurement Tool to Assess systematic Reviews) assessment of low was given due to one critical flaw with or without non-critical weaknesses. The review had a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

[d] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations was rated as serious and imprecision was rated as very serious.

[e] Proton pump inhibitor.

[f] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low to low-certainty was given because study limitations and imprecision were rated as serious and indirectness was rated as unclear.

[g] Discordant results found.

[h] The effect estimate was not reported in the original review or report but calculated by the research team.

[i] An AMSTAR assessment of critically low was given because the systematic review had more than one critical flaw with or without non-critical weaknesses. The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

[j] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of low-certainty was given because study limitations and imprecision were rated as serious.

[k] Nissen fundoplication.

[l] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations and imprecision were rated as very serious and indirectness was rated as unclear.
[m] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations was rated as very serious, imprecision was rated as serious and indirectness was rated as unclear.
[n] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low to low-certainty was given because study limitations was rated as very serious to serious, imprecision was rated as serious and indirectness was rated as unclear.
[o] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because imprecision was rated as very serious and other considerations (i.e. publication bias) was rated as serious and study limitations was rated as unclear.
[p] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations, imprecision and other considerations (i.e. publication bias and grey literature searches) were rated as serious and indirectness was rated as unclear.
[q] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations, imprecision and other considerations (i.e. publication bias and grey literature searches) were rated as serious.
[r] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low to low-certainty was given because imprecision and other considerations (publication bias, small studies) were rated as serious and study limitations was rated as unclear.
[s] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations was rated as serious, and imprecision was rated as very serious and indirectness was rated as unclear.
[t] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations and imprecision were rated as very serious and other considerations (i.e. publication bias, grey literature search) was rated as serious and indirectness was rated as unclear.
[u] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations and other considerations (publication bias, grey literature search) were rated as serious, and imprecision were rated as very serious and indirectness was rated as unclear.
[v] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations was rated as very serious, imprecision and other considerations (i.e. publication bias and grey literature searches) were rated as serious, and indirectness was rated as unclear.
[w] The Absolute Risk Difference (ARD) was not estimable for the pooled estimate because the lower 95% CI was 0.00. The calculated ARDs are therefore, shown according to moderate and high baseline control group rates.
[x] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations and inconsistency were rated as serious, imprecision was rated as very serious and indirectness was rated as unclear.

Further details on methodology and results can be found in:
(a) Hamel C, Ahmadzai N, Beck A, Thuku M, Skidmore B, Pussegoda K, et al. Screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patients with chronic gastroesophageal reflux disease with or without other risk factors: two systematic reviews and one overview of reviews to inform a guideline of the Canadian Task Force on Preventive Health Care (CTFPHC). Syst Rev 2020;9(20):https://doi.org/10.1186/s13643-020-1275-2.
(b) Ahmadzai N, Hamel C, Thuku M, Pussegoda K, Beck A, Skidmore B, et al. Benefits and Harms of Treatment Options for Esophageal Adenocarcinoma and Precancerous Conditions: An Overview of Systematic Reviews. Ottawa, Ontario: Ottawa Hospital Research Institute; 2018 available at http://canadiantaskforce.ca/guidelines/published-guidelines/esophageal-adenocarcinoma/.

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Appendix 1E:

Outcome summary for harms of treatment for Barrett esophagus, dysplasia or stage 1 esophageal adenocarcinoma by treatment type[a]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
Stricture formation	(Rees, 2010) (1), 1 RCT (Overholt, 2005) (2)	PDT + Omeprazole[b]: 49/138 versus Omeprazole[b]: 0/70	OR=77.98 (4.73 to 1286.52)	Not estimable	-	Not estimable	AMSTAR: Low[c] Modified GRADE: Very low to low[d]
	(Rees, 2010) (1), 1 RCT (Shaheen, 2009) (3)	RFA + PPI: 5/84 versus PPI: 0/43	OR=6.02 (0.33 to 111.44)	Not estimable	-	Not estimable	AMSTAR: Low[c] Modified GRADE: Very low[e]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	(Pandey, 2018) (4), 1 RCT (Phoa, 2014) (5)	RFA versus Surveillance (endoscopic)	Narrative summary: 8 events were reported, but data was not presented per arm.				AMSTAR: Critically low[f]Modified GRADE: Very low to low[g]
	(Rees, 1010) (1), 1 RCT (Mackenzie, 2008) (6)	PDT using 5-ALA: 1/16 versus PDT using Photofrin: 6/16	OR=0.11 (0.01 to 1.07	Not calculated as the data was from an abstract	Not estimable	-	AMSTAR: Low[c] Modified GRADE: Very low[h]
	(Fayter, 2010) (7), 1 RCT (Kelty, 2004a) (8)	ALA–PDT with varying doses of light and comparing red or green light	Narrative summary: No patients developed strictures.				AMSTAR: Critically low[f] Modified GRADE: Very low to low[i]
	(Rees, 2010) (1), 1 RCT (Sharma, 2006) (9)	APC + PPI: 1/19 versus MPEC+PPI: 0/12	OR=2.03 (0.08 to 53.87)	Not estimable	-	Not estimable	AMSTAR: Low[c] Modified GRADE: Very low[j]
	(Rees, 2010) (1), 3 RCTs (Hage, 2004, Kelty, 2004b,	PDT: [k]2/73 versus APC + PPI: [k]4/61	Pooled OR=0.51 (0.11 to 2.44)	31 per 1,000 fewer developed strictures with PDT (from 58 fewer to 81 more)	3.1	-	AMSTAR: Low[c] Modified GRADE: Very low[j]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	Ragunath, 2005) (10-12)						
	(Almond, 2014) (13), 1 RCT (Ragunath, 2005) (12)	PDT: [k]2/11 versus APC+PPI: [k]1/9	RR[l]=1.64 (0.18 to 15.26)	71 per 1,000 more developed strictures with PDT (from 91 fewer to 1,000 more)	-	7.1	AMSTAR: Critically low[f] Modified GRADE: Very low[m]
	(Desai, 2017) (14), 1 RCT (van Vilsteren, 2011) (15)	EMR: 22/25 versus RFA: 3/22	RR[l]=6.45 (2.23 to 18.66)	743 per 1,000 more developed strictures with EMR (from 168 to 1,000 more)	-	74.3	AMSTAR: Critically low[f] Modified GRADE: Very low[n]
Bleeding	(Desai, 2017) (14), 1 RCT (van Vilsteren, 2011) (15)	EMR: [k]5/25 versus RFA: [k]2/22	RR[l]=2.20 (0.47 to 10.23)	109 per 1,000 more had acute bleeding with EMR (treated endoscopically) (from 48 fewer to 839 more)	-	10.9	AMSTAR: Critically low[f] Modified GRADE: Very low[m]
	(Desai, 2017) (14), 1 RCT (van Vilsteren, 2011) (15)	EMR: [j]6/25 versus RFA: [j]3/22	RR[l]=1.76 (0.50 to 6.22)	104 per 1,000 more had bleeding with EMR (from 68 fewer to 712 more)	-	10.4	AMSTAR: Critically low[f] Modified GRADE: Very low[o]
	(Pandey, 2018) (4),	RFA+PPI versus	Narrative summary: One event (1/84) was reported, but data was not presented per arm.				AMSTAR: Critically low[f]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	1 RCT (Shaheen, 2009) (3)	PPI					Modified GRADE: Very low[p]
	(Pandey, 2018) (4), 1 RCT (Phoa, 2014) (5)	RFA versus Surveillance (endoscopic)	One event in total (1/68) was reported, but data was not presented per arm.				AMSTAR: Critically low[f] Modified GRADE: Very low to low[g]
Perforations	(Fayter, 2010) (7), 1 RCT (Kelty, 2004a) (8)	ALA–PDT at 30 mg/kg or 60 mg/kg at 4- or 6-hour incubation times or with fractionated illumination	Narrative summary: Reported no major side effects in terms of perforations.				AMSTAR: Critically low[f] Modified GRADE: Very low to low[d]
	(Chadwick, 2014) (16), 1 RCT (van Vilsteren, 2011) (15)	EMR: 1/25 versus RFA: 0/22	RR[l]=2.65 (0.11 to 62.00)	Not estimable	-	Not estimable	AMSTAR: Critically low[f] Modified GRADE: Very low[p]
	(Pandey, 2018) (4), 1 RCT (Shaheen, 2009) (3)	RFA+PPI versus PPI	Narrative summary: No instances of perforation were reported in among thel 84 patients				AMSTAR: Critically low[f] Modified GRADE: Very low[p]

Outcome	(Systematic review) (reference), No. and design of original studies (references)	Treatment type	Effect estimate (95% CI)	Absolute Risk Difference per 1,000 (95% confidence interval)	Absolute Risk Reduction, %	Absolute Risk Increase, %	Certainty of systematic review evidence
	(Pandey, 2018) (4), 1 RCT (Phoa, 2014) (5)	RFA versus Surveillance (endoscopic)	Narrative summary: No instances of perforation were reported among the 68 patients.				AMSTAR: Critically low[f] Modified GRADE: Very low to low[g]
Stenosis requiring treatment	(Chadwick, 2014) (16), 1 RCT (van Vilsteren, 2011) (15)	EMR: 22/25 versus RFA: 3/21	RR[l]=6.16 (2.14 to 17.74)	737 per 1,000 more developed stenosis (requiring treatment) with EMR: (from 163 to 1,000 more)	-	74.3	AMSTAR: Critically low[f] Modified GRADE: Very low[p]

5-ALA: Aminolevulinic acid; AMSTAR= A MeaSurement Tool to Assess systematic Reviews; APC=Argon plasma coagulation; EMR=Endoscopic mucosal resection; GRADE= Grading of Recommendations Assessment, Development and Evaluation system); MPEC=Multipolar electrocoagulation; OR=Odds ratio; PDT=Photodynamic therapy; PPI= Proton pump inhibitors; RFA=Radiofrequency ablation; RR=Relative risk.

[a] This review focused on early (non-surgical) techniques used in treatment of Barrett esophagus, dysplasia or stage 1 esophageal adenocarcinoma. However, esophagectomy is the standard treatment for more advanced or high risk cases.

[b] Proton pump inhibitor.

[c] An AMSTAR (A MeaSurement Tool to Assess systematic Reviews) assessment of low was given due to one critical flaw with or without non-critical weaknesses. The review had a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

[d] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low to low-certainty was given because study limitations and imprecision were rated as serious and indirectness was rated as unclear.

[e] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations was rated as serious and imprecision was rated as very serious.

[f] An AMSTAR assessment of critically low was given because the systematic review had more than one critical flaw with or without non-critical weaknesses. The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

[g] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low to low-certainty was given because imprecision and other considerations (publication bias, unpublished literature search) were rated as serious and study limitations was rated as unclear.

[h] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations was rated as very serious, imprecision was rated as serious and indirectness was rated as unclear.
[i] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low to low-certainty was given because study limitations was rated as very serious to serious, imprecision was rated as serious and indirectness was rated as unclear.
[j] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations was rated as serious, imprecision was rated as very serious and indirectness was rated as unclear.
[k] Discordant results found.
[l] The effect estimate was not reported in the original review or report but calculated by the research team
[m] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low certainty was given because study limitations and other considerations (publication bias, grey and/or comprehensive literature search) were rated as serious and imprecision was rated as very serious.
[n] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations, imprecision and other considerations (comprehensive search) were rated as serious.
[o] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations, and other considerations (comprehensive search) were rated as serious and imprecision was rated as very serious.
[p] A modified GRADE assessment (Grading of Recommendations Assessment, Development and Evaluation system) of very low-certainty was given because study limitations, imprecision and other considerations (publication bias, unpublished literature and/or comprehensive search) were rated as serious.

Further details on methodology and results can be found in:
(a) Hamel C, Ahmadzai N, Beck A, Thuku M, Skidmore B, Pussegoda K, et al. Screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patients with chronic gastroesophageal reflux disease with or without other risk factors: two systematic reviews and one overview of reviews to inform a guideline of the Canadian Task Force on Preventive Health Care (CTFPHC). Syst Rev 2020;9(20):https://doi.org/10.1186/s13643-020-1275-2.
(b) Ahmadzai N, Hamel C, Thuku M, Pussegoda K, Beck A, Skidmore B, et al. Benefits and Harms of Treatment Options for Esophageal Adenocarcinoma and Precancerous Conditions: An Overview of Systematic Reviews. Ottawa, Ontario: Ottawa Hospital Research Institute; 2018 available at http://canadiantaskforce.ca/guidelines/published-guidelines/esophageal-adenocarcinoma/.

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Appendix 1F: Esophageal cancer topography and morphology codes for Figure 1

Esophageal cancer topography codes: C15.0 to C15.9 (ICD-10) and 150.0-150.9 (ICD-9).

Esophageal adenocarcinoma includes the following morphology codes: 8140 to 8141, 8143 to 8145, 8190 to 8231, 8260 to 8263, 8310, 8401, 8480 to 8490, 8550 to 8551, 8570 to 8574, and 8576.

Esophageal squamous cell carcinoma includes the following morphology codes: 8050 to 8078 and 8083 to 8084.
Data source: Canadian Cancer Registry and National Cancer Incidence Reporting System databases at Statistics Canada.
Analysis by: Centre for Surveillance and Applied Research, Public Health Agency of Canada.