Guideline on screening for esophageal adenocarcinoma in patients with chronic gastroesophageal reflux disease – reviewer comments and CTFPHC responses

Stakeholders and Clinical Experts

Reviewer 01 – Stakeholder

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes	Thank you
3. Is the guideline supported by the evidence?	Yes	Thank you
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	No	Thank you
5. Do you have any comments or suggestions to improve the guideline?	Comments: I didn't see any mention of self-sampling screening? I believe this is a newer test where patients swallow a sponge-like device and it is pulled back with a string? It may be good to list alarm symptoms in the synopsis or higher up so that these are not missed (or even repeat them).	Thank you – I have added the "Cytosponge or other swallowed devices" and "to the list of less invasive and less resource intensive screening procedures. Unfortunately we are limited to a word count of 2500 and the alarm symptoms were previously mentioned in the overview

		section. However, I have added them to the key points "This guideline does not apply to people exhibiting alarm symptoms for esophageal adenocarcinoma (e.g. dysphagia, odynophagia, recurrent vomiting, unexplained weight loss, anemia, loss of appetite or gastrointestinal bleeding) as clinicians should evaluate and manage those people accordingly.

Reviewer 02 – Stakeholder

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes Yes they are clear and consistent to the rationale of performing this guideline. The objective should respond to the hypothesis.	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes The patient group selected should allow for the study questions to be answered. This guideline does not apply to people exhibiting alarm symptoms for esophageal adenocarcinoma and other that should be refer to specialists. But target the primary care practitioners (PCPs).which is clearly defined.	Thank you
3. Is the guideline supported by the evidence?	Yes This guideline leads to the recommendation of not screening adults with chronic GERD for esophageal adenocarcinoma. This is a strong recommendation with very low certainty of evidence. Obviously, the PCPs would have to follow the standard of care or local guidelines	Thank you

	to consolidate the recommendations on the management of these patients.	
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	No I did a small literature search using similar key words as in this systematic review and I was unable to find higher evidence that the one presented here. Therefore, there is no information missing from this guideline. In the way it is presented it is easy to interpret for the PCP.	Thank you
5. Do you have any comments or suggestions to improve the guideline?	No, the guidelines presented here respond adequately to the questions raised by this protocol and for the population selected in this study. Therefore, I have no suggestions to improve this guideline.	Thank you

Reviewer 03 – Stakeholder

Question	**Reviewer comments**	**CTFPHC response**
1. Is the objective of the guideline clear?	Yes	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes- The target population is those with GERD symptoms for 12 months or longer. However, there is no discussion of frequency or severity of heartburn symptoms as a consideration on whether screening should be considered.	We have removed the reference to “12 months” as the GERD definitions in the included studies did not define a time period but were instead based on medical records of a diagnosis with GERD. The WG decided to adopt a wide definition because of the lack of consensual definition among authors, few using a standardized assessment tool and many poorly reporting intensity, frequency or duration of GERD. There is no clear threshold over which an individual becomes at risk.

3. Is the guideline supported by the evidence?	**Yes**	Thank you
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	No	Thank you
5. Do you have any comments or suggestions to improve the guideline?	The authors have mixed studies evaluating screening and therapy studies for Barrett's esophagus and early esophageal adenocarcinoma with the very limited data on EGD screening for esophageal adenocarcinoma. Examples include the 2nd paragraph of the screening section (lines 150-156), which mentions "endoscopic screening modalities" but does not state that the screenings were done to assess the ability to detect Barrett's esophagus and were not designed to show effectiveness as screening procedures to detect esophageal adenocarcinoma.	Agree – There was very little evidence looking at screening for EAC among GERD patients. We had to also consider indirect evidence comparing screening modalities. I have changed the following sections to reflect that the guideline is looking at screening for esophageal cancer AND precursor conditions (including Barrett's esophagus or dysplasia) **Key points:** • The task force recommends not routinely screening adults with chronic GERD for esophageal adenocarcinoma, Barrett's esophagus or dysplasia (precursor conditions) because no evidence of benefit was identified and there are uncertain harms, important resource implications and variable patient values and preferences. **Recommendation** "We recommend not screening adults (≥18 years) with chronic GERD for esophageal adenocarcinoma or precursor conditions (Barrett's esophagus or dysplasia) (strong recommendation; very low certainty of evidence)."

		Screening "…There were 5 randomized controlled trials (RCTs) (34-38) and one cohort study of screening for Barrett's esophagus (39) that compared endoscopic screening modalities…" **Conclusion** "The evidence reviewed for this guideline did not identify clinically meaningful benefits from screening for esophageal adenocarcinoma or precursor conditions in adults with chronic GERD with or without other risk factors.
	The same holds true for the treatment section. They cite studies evaluating the efficacy of Barrett's eradication, not GERD and totally blur any distinctions about treatment as it pertains to tissue being treated (Barrett's with/without dysplasia vs. adenocarcinoma). In addition, they state "very low certainty evidence" that ablation/resection reduces progression to esophageal adenocarcinoma. This is incorrect – there are now multiple randomized studies demonstrating the radiofrequency ablation in the setting of low and high grade dysplasia and photodynamic therapy for high grade dysplasia lower the risk of progression to adenocarcinoma. A clearer statement that screening is primarily for Barrett's esophagus, and treatments described herein have been primarily about Barrett's esophagus (usually	I have modified the Treatment section as follows: "Given the limited availability of direct evidence on screening effectiveness, the task force also examined the effectiveness of treatment for Barrett's esophagus, dysplasia or stage 1 esophageal adenocarcinoma" We stated "very low certainty evidence" due to the quality of the evidence not the direction or results of the evidence. I agree that the studies show a reduction in progression to high grade dysplasia or esophageal cancer. However, the certainty in this evidence is very low due to issues with very serious concerns on study limitations or

	with dysplasia) is appropriate to assist primary care practitioners in understanding the basis of this recommendation.	imprecision and serious concerns on inconsistency (modified GRADE quality assessment). **Screening** Changed to: "…There were 5 randomized controlled trials (RCTs) (34-38) and one cohort study of screening for Barrett's esophagus (39) that compared endoscopic screening modalities…" **Treatment** Changed to: "Results indicate that photodynamic therapy, radiofrequency ablation and endoscopic mucosal resection of Barrett's 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) (33). Possible reduction in progression to esophageal adenocarcinoma was also observed with photodynamic therapy (very low-certainty evidence) (33)."

Reviewer 04 – Stakeholder

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	**Yes**	Thank you

2. Are the patient groups to whom the guideline is meant to apply clearly described?	**Yes**	Thank you
3. Is the guideline supported by the evidence?	Yes - Overall, yes, the guideline is supported by the evidence, but please see my comment about medical treatments, that have not been mentioned in this document.	Thank you
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Yes - The evidence on medical treatments for GERD and/or Barrett's (for prevention of progression to dysplasia or esophageal adenocarcinoma) should also be briefly mentioned in this document	I have changed the Treatment section text to reflect that it also looks at medical treatments for GERD (see below). **Treatment** I have modified the Treatment section as follows: "Given the limited availability of direct evidence on screening effectiveness, the task force also examined the effectiveness of treatment for Barrett's esophagus, dysplasia or stage 1 esophageal adenocarcinoma"
5. Do you have any comments or suggestions to improve the guideline?	Lines 165-166. It reads "Due to the limited availability of direct evidence on the benefits and harms of screening, the task force sought linked evidence on the effectiveness of treatment (26)". Please specify the disease/population that the "treatment" refers to. Up to the previous paragraph the population is people with GERD, but it seems that in this paragraph the population is people with Barrett's esophagus and/or early premalignant lesions.	I have changed the Treatment section text to reflect that it also looks at treatment for the following conditions (see below) **Treatment** "Given the limited availability of direct evidence on screening effectiveness, the task force also examined the effectiveness of treatment for Barrett's esophagus, dysplasia or stage 1 esophageal adenocarcinoma" I have changed the scope of the guideline to reflect that we were looking at screening for

	In continuation to the above point, this reviewer understands why there is a need to assess if there are effective and safe treatments for Barrett's and premalignant lesions, in a guideline that deals with screening for esophageal adenocarcinoma. However, this is not clear to the readers. It might be worth adding a line or two in the beginning of the section on treatment of Barrett's/premalignant lesions, explaining that, since there is absence of direct strong evidence on the efficacy of screening people with GERD for esophageal adenocarcinoma, the committee had to look for indirect evidence: if there is no effective and safe treatment for premalignant/early lesions, then there is no justification for screening. Or something along these lines.	esophageal adenocarcinoma AND precursor condition (i.e. Barrett's esophagus or dysplasia). See changes to text below. **Key points:** • The task force recommends not routinely screening adults with chronic GERD for esophageal adenocarcinoma, Barrett's esophagus or dysplasia (precursor conditions) because no evidence of benefit was identified and there are uncertain harms, important resource implications and variable patient values and preferences. **Recommendation** "We recommend not screening adults (≥18 years) with chronic GERD for esophageal adenocarcinoma or precursor conditions (Barrett's esophagus or dysplasia) (strong recommendation; very low certainty of evidence)." **Screening** "…There were 5 randomized controlled trials (RCTs) (34-38) and one cohort study of screening for Barrett's esophagus (39) that compared endoscopic screening modalities…" **Conclusion** "The evidence reviewed for this guideline did not identify clinically meaningful benefits

	Only endoscopic treatments are addressed in this document. The SR conducted to support this guideline has also addressed medical treatments. The evidence on treatment of GERD with PPIs and treatment of Barrett's esophagus with PPIs and/or aspirin should also be described in the guideline document as potential treatments for prevention of progression to dysplasia or esophageal adenocarcinoma, even if the evidence is low or very low. See AspECT trial (Jankowski et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet 2018;392:400-408). This paper was published online in July 2018; therefore, it may have been published after the last literature search update, but given the importance of this RCT, it should be briefly assessed by GRADE and briefly discussed.	from screening for esophageal adenocarcinoma or precursor conditions in adults with chronic GERD with or without other risk factors. I have modified the Treatment section as follows: "Given the limited availability of direct evidence on screening effectiveness, the task force also examined the effectiveness of treatment for Barrett's esophagus, dysplasia or stage 1 esophageal adenocarcinoma" The ERSC was unable to include this trial as the treatment review was limited only to systematic reviews of RCTs. The study design limitation was based on WG discussions and resource constraints. However, I have included it in the following paragraph **Treatment** **"…** A recent RCT found improved outcomes for Barrett's esophagus treated with combination high dose proton pump inhibitors and aspirin (49).

Reviewer 05 – Stakeholder

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes - The purpose of the guideline as set out in the preamble and call out box – makes it	Thank you

	very clear to the intended reader (primary care provider).	
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes - both the patient groups and the intended intermediary (primary care providers) are very clear in the guideline.	Thank you
3. Is the guideline supported by the evidence?	Yes - Based on the strength of the evidence noted in the systematic reviews. The evidence is not strong – but it is the current evidence – so yes, the guideline is supported by the existing evidence.	Thank you
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Yes - None specific to screening – see comment 5 for other related prevention opportunities for primary care providers.	See below
5. Do you have any comments or suggestions to improve the guideline?	I am still thinking there is a good opportunity to screen GERD patients for risk factor status – smoking, alcohol consumption and abdominal obesity (also risk factors connected to several cancers including head and neck). Smoking status screening and cessation offering in particular would not only benefit primary and secondary prevention – it has been shown to improve treatment outcomes for patients diagnosed with cancer. Screening often presents a strong opportunity for motivational interviewing across all patient groups for risk factor modification. These are risks for both GERD and esophageal cancer.	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 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. Appendix III outlines upcoming RCTs which we will monitor to determine if subgroup analysis will be available.

Reviewers 06 – Other reviewer

Question	**Reviewer comments**	**CTFPHC response**

1. Is the objective of the guideline clear?	No (see below) - Key points need to be shortened to clearly define main points	Changed to: **Key points** • ~~The evidence reviewed for this guideline did not demonstrate a clear benefit from population level screening for esophageal adenocarcinoma or precursor conditions (i.e. Barrett's esophagus or dysplasia) in those with chronic gastroesophageal reflux disease (GERD).~~ • ~~We~~ The task force recommends not screening adults with chronic gastroesophageal reflux disease (GERD) for esophageal adenocarcinoma, Barrett's esophagus or dysplasia (precursor conditions) because available evidence did not demonstrate benefit, and there are uncertain harms, important resource implications and variable patient values and preferences. ~~(strong recommendation; very low certainty of evidence). evidence reviewed for this guideline did not demonstrate a clear benefit and there would be substantial costs associated with initiating a screening program~~ • ~~A systematic review on screening effectivenessthe effectiveness of screening~~ A retrospective cohort

	- Overview needs to clarify why EAC is increasing and ESCC is decreasing	study (very low certainty evidence) found that showed screening patients with chronic GERD identifiedshowed more cases with esophageal adenocarcinoma at an earlier-stage of esophageal adenocarcinoma at diagnosis but found no difference in long-term survival (all-cause mortality). when comparing those who previously received esophagogastroduodenoscopy to those who did not receive esophagogastroduodenoscopy (very low certainty of evidence). • There was no direct evidence available on harms of screening. Indirect evidence showed an increase in anxiety for unsedated endoscopic techniques but no increase in serious adverse events with any screening modality (very low certainty of evidence). • There was limited evidence and high variability in willingness to be screened due to individual patient values and preferences for screening: regarding their decision to screen for esophageal adenocarcinoma : some patients consistently favoured screening because of individual and familial risk factors, personal beliefs,

		and fear of missing an early diagnosis, while others were concerned with the invasiveness and risks of screening. • This guideline does not apply to people exhibiting alarm symptoms for esophageal adenocarcinoma (e.g. dysphagia, odynophagia, recurrent vomiting, unexplained weight loss, anemia, loss of appetite or gastrointestinal bleeding) or who are non-responsive to medical treatment, as clinicians should evaluate and manage ~~diagnose, refer and treat~~ those people accordingly. **Overview** Added This change may result from increases in adenocarcinoma-related risk factors (e.g. gastroesophageal reflux, obesity) and decreases in risk factors linked to squamous cell carcinoma (e.g. smoking) (2).
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes	
3. Is the guideline supported by the evidence?	Resource use section needs evidence	**Resource use** Changed to: "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. Potential costs include physician

		services, opportunity costs, hospital/facility expenses and biopsy analysis."
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Need to clarify evidence in "Screening section" where trials compared modalities but not screening vs no screening. Need to add reasons behind patient "stated/intended" refusal rates in Patient values and preferences section. Need to clarify feasibility, acceptability, cost and equity section	**Screening** Changed to: "Indirect evidence from comparisons of screening modalities indicated more anxiety for unsedated transnasal esophagoscopy compared to sedated esophagogastroduodenoscopy or video capsule esophagoscopy (swallowed device) (very low certainty evidence) (41-45) (Table 2). Trials comparing sedated esophagogastroduodenoscopy versus unsedated transnasal esophagoscopy (43) and unsedated transnasal versus unsedated transoral esophagogastroduodenoscopy (45) reported one serious adverse event (0/209 and 1/59 respectively) (31)." **Treatment** Changed to: In one trial, among 1,210 invited participants, 52% did not respond to the letter, 32% refused (no reason provided), 1% were ineligible, and 0.2% cited difficulty attending (42). Two other trials had high "stated or intended" refusal rates (45 of 105; 43% and 19 of 62; 31% respectively) due to anxiety, lack of interest, fear of gagging, unwilling to be study subjects, or reluctance to undergo transnasal procedures (46,50). **Feasibility, acceptability, cost and equity** Changed to:

	Need to clarify rationale section to clearly state evidence.	In the judgment of the task force, there are important feasibility and cost concerns, given that chronic GERD is a very common condition (10-20% of Canadians) (13,14). Canadian reports show that endoscopy wait times are perceived as too long and exceed recommended targets (53,54). Implementing screening would increase demand and could adversely affect equity. Given the limited and uncertain evidence of effectiveness, we believe screening all patients with GERD would not be feasible or acceptable and that it could inappropriately divert substantial health resources. **Rationale** Changed to: "The overall certainty of evidence was very low. One very low-certainty small retrospective cohort study compared screening to no screening and reported that, although patients with a prior esophagogastroduodenoscopy were statistically more likely to have a lower stage of adenocarcinoma at time of diagnosis, there were no statistically significant survival differences (40). One serious adverse event from screening was reported across two small trials, which compared screening modalities (very low-certainty). Preferences among chronic GERD patients appear variable. The systematic review indicated hesitancy to participate (32), while focus

		groups showed a moderate willingness to be screened (35). Additionally, screening all adults with chronic GERD would require substantial resources. “ … Because we did not identify direct evidence of benefit from screening on any critical or important outcome other than a statistically improved stage at diagnosis, without a difference in survival, the task force recommends against screening. The recommendation is strong because in its evidence to decision framework the task force placed a high value on the system-wide resources required to screen all chronic GERD patients without evidence of benefit (Appendix 2) (55).
5. Do you have any comments or suggestions to improve the guideline?	Remove the section on endoscopic surveillance (under monitoring and evaluation) as this is not applicable to the guideline Clarify that the recommendation is based on the evidence to decision framework.	Removed Changes to: The recommendation is strong because in ~~GRADE~~ its evidence to decision framework the task force place~~s~~d a high value on the system-wide resources required to screen all chronic GERD patients without evidence of ~~for esophageal adenocarcinoma or Barrett's esophagus in return for uncertain~~ benefit ~~(47,48).~~ (Appendix 2).

Peer Reviewers

Reviewer 01

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes • The title refers to "its precursors"; it may be clearer to specify Barrett's esophagus, instead. In practice, dysplasia (HGD or LGD or IDD) is included in the Barrett's esophagus documentation; virtually no-one will biopsy normal appearing esophageal squamous epithelium, so the finding of dysplasia is integral to the diagnosis & surveillance of BE.	We originally used the title of "…screening for EAC and Barrett's esophagus...", however it was decided that since Barrett's wasn't the only precursor it was not correct. Instead of listing Barrett's with or without dysplasia or EAC and its precursors we have now left it as "screening for esophageal adenocarcinoma". Then it is clarified in the text that this includes all precursors and specifically Barrett's esophagus.
	• As the guideline addresses recommendations on screening, it may be clearer if the first key point (page 1) is that which states "The task force recommends not routinely screening …"	Agree – moved point 4 to point 1
	• The 5th key point is that the guideline does not apply to people with alarm symptoms. In principle, this should be self-evident; investigation of symptoms is not screening. However, this exclusion should, also, apply to patients with treatment-nonresponsive GERD symptoms – most GERD guidelines recommend investigations in patients whose	Added patients with treatment-nonresponsive GERD • "This guideline does not apply to people with GERD exhibiting alarm symptoms for esophageal adenocarcinoma (e.g. dysphagia, odynophagia, recurrent vomiting, unexplained weight loss, anemia, loss of appetite or gastrointestinal bleeding) or non-responsive to

	GERD symptoms do not respond to therapy. Arguably, any EGD in a GERD patient could be considered as a screening test to document the presence or absence of BE or EAC.	medical treatment, as clinicians should evaluate and manage those people accordingly."
2. Are the patient groups to whom the guideline is meant to apply clearly described?	• It would be helpful to indicate, briefly, why chronic GERD is defined as symptoms for more than 12 months. • It would, also, be helpful (page 2) to specify that this applies to adult patients.	I have removed the reference to symptoms >12 months. We initially chose >12 months based on our first screening of articles, but have since amended the definition to be more inclusive (i.e. identified via electronic medical records), as this would otherwise exclude all studies from our systematic review. I have changed to: **Scope** The target population is adults with chronic GERD (~~symptoms for ≥12 months~~) …." **Screening** A systematic review found two retrospective cohort studies that assessed the effectiveness of screening versus no screening among chronic GERD patients (identified via electronic medical records) (40,41). Agree The target population is ~~individuals~~ adults with chronic GERD...
3. Is the guideline supported by the evidence?	• The available data do not provide any data to support screening. However,	I have changed the following sections to note that there was no statistical difference. We

	it is worth noting that the data are so sparse that they do not exclude potential benefit from screening. • Logically, if there is no demonstrable benefit from screening, one should be able to recommend against screening without invoking costs and patient acceptability.	also note the sample size (n=25 screened and n=130 unscreened) which shows the sparse data. **Screening** "…There was no statistically significant difference in long-term survival (adjusted hazard ratio (HR)=0.93 (95% CI, 0.58-1.50))…' The same study showed a statistically significant absolute effect of 156 more per 1,000 diagnosed with a lower stage of esophageal adenocarcinoma (stage 1 versus stages 2-4) among those with prior esophagogastroduodenoscopy (95% confidence interval from 5 to 486 more) (very low-certainty evidence). **Rationale** "…One very low-certainty small retrospective cohort study compared screening to no screening and reported that although patients with a prior esophagogastroduodenoscopy were statistically more likely to have a lower stage of adenocarcinoma at time of diagnosis, ~~this did not improve~~there were no statistically significant survival differences (40)." Agree – Removed from the initial sentence (was not rationale behind recommendation against) but kept cost and patient preferences as part of the reason the recommendation was strong. Changed to: **Rationale**

		"Because we did not identify direct evidence of benefit from screening on any critical or important outcome other than a statistically improved stage at diagnosis, without a difference in survival, the task force recommends against screening. The recommendation is strong because in its evidence to decision framework the task force placed a high value on the system-wide resources required to screen all chronic GERD patients without evidence of benefit (Appendix 2) (55)."
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	• As noted above, if it is considered to be important or necessary to specify that recommendation against screening does not apply to patients with alarm features, it would be important to emphasise that it does not apply to the investigations of other aspects of clinical GERD management, such as symptoms that are poorly responsive or unresponsive to medical therapy.	Added: **Scope** "The target population is adults with chronic GERD (symptoms for ≥12 months) but without alarm symptoms or non-responsive to medical treatment." **Recommendation** "This recommendation applies to adults ≥18 years with chronic GERD with or without other risk factors for esophageal adenocarcinoma or precursor conditions (Barrett's esophagus or dysplasia). It does not apply to people with GERD exhibiting alarm symptoms or to those non-responsive to medical treatment. ~~for esophageal adenocarcinoma."~~ **Considerations for implementation** Clinicians should be aware of alarm symptoms for esophageal adenocarcinoma and refer these patients, as well as those non-responsive to medical treatment, for diagnostic esophagogastroduodenoscopy.

		Conclusion "This guideline does not apply to people exhibiting alarm symptoms or non-responsive to medical treatment ~~for esophageal adenocarcinoma~~ who should be evaluated, referred and managed accordingly."
5. Do you have any comments or suggestions to improve the guideline?	Comments: • The adverse event rate quoted for screening is rather high in the context of routine diagnostic upper endoscopy which generally has rather lower adverse event rates (Borgaonkar M et al. Can J Gastroenterol 2012;26:71-78). • The conclusion indicates the absence of benefits … in chronic GERD with or without other risk factors. The data on other risk factors (age, sex, BMI,	I have added the raw data to Table 2 and referenced this in the rationale: **Rationale** One serious adverse event from screening was reported across two small trials, which compared screening modalities (very low certainty). Table 2 shows the breakdown of each trial and that there was only 1 serious adverse event in a patient undergoing unsedated transnasal endoscopy. Also it indicates that there is very low certainty of evidence. 290 **Table 2:** Outcome summary of harms prior to and during screening for esophageal adenocarcinoma among individuals with chronic 291 GERD (by screening modality) **Outcome** | **No of studies (Reference)** | **Screening Modality** | | **Risk Ratio (95% CI)** | **Absolute Difference per 1,000 (95% confidence interval)** | **Absolute Risk Increase** | **Certainty of Evidence** Life threatening, severe, or medically significant consequences | 1 (44) | Standard sedated esophagogastro-duodenoscopy (EGD): 0/61 | Unsedated transnasal esophagoscopy (TNE)[a]: 0/148 | Not estimable due to zero count in both arms. Serious adverse events were assessed 1 and 30 days after the procedure. No serious adverse events were reported in any of the study arms. | | | Very low[b] | 1 (46) | Unsedated transoral EGD: 0/34 | Unsedated TNE: 1/25 | Not estimable due to zero count in comparison group. Authors reported 0 of 34 participants had serious, or medically significant consequences with unsedated transoral EGD and 1 of 25 with unsedated TNE. | | | Very low[c] I have added this to Appendix 3. We did not have enough space in the article (word limit = 2500) to discuss. **Appendix III**

	etc) was not clearly articulated or the absence of absence was not reviewed in detail. • The implications of the AspECT Study results (Jankowski J et al) should, perhaps, be more explicit – addressed, perhaps, in the Gaps in Knowledge and in the treatment section. Recognizing that it was not included in the systematic reviews, it is, nonetheless, a large prospective RCT which shows benefit from treating Barrett's esophagus (BE) and, hence, potential benefit from diagnosing BE, whether at screening or at routine endoscopy (with a commitment to identifying prevalent BE). • The absence of data on the effect of risk factors for EAC on screening benefits (or harms) is a gap that needs to be addressed.	I have moved the section on the AspECT study from Monitoring and evaluation to the Treatment section **Treatment** A recent RCT found improved outcomes for Barrett's esophagus treated with combination high dose proton pump inhibitors and aspirin (49). I have changed the Gaps in knowledge section to state: Ideally, there would be well-designed RCTs conducted to examine screening versus no screening among chronic GERD patients. Barriers to feasibility, however, include the low prevalence of esophageal adenocarcinoma and the limited ability to identify GERD patients most likely to progress. I have also added Appendix 3 which discusses the lack of data available for subgroup analysis by risk factor (see above).

Reviewer 02

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes	Thanks

2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes	Thanks
3. Is the guideline supported by the evidence?	Yes	Thanks
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Yes 1. Images to show what video capsule, cytosponge, transnasal endoscopy look like 2. Description of how these techniques are used (e.g. cytosponge is a capsule that is swallowed by the patient and then via string, pulled back out of the patient's mouth). Not all physicians reading the recommendations will know what these tests are. 3. Even though the task force does not want to review the cost effectiveness analysis for screening, it provides a strong argument for avoiding screening too.	1. We have decided not to add images as they can easily be found on internet and the Task Force does not usually provide any. Some of these techniques (e.g. cytosponge) are still experimental and under patent and we cannot get involved in their promotion. 2. See above 3. The TF used the GRADE Evidence to Decision framework (ETD) to determine weigh the harms and benefits of screening for esophageal cancer (see Appendix 2). In this framework the certainty of the evidence was very low for all outcomes in KQ1 (unable to determine the certainty of the effect estimate). There was also no statistical or clinically meaningful benefit found for any of the critical or important outcomes and therefore the recommendation was against screening. We also considered cost (discussed in the ETD) which resulted in the

		TF recommending strongly against screening. This was mentioned in the rationale section of the guideline (see highlighted area below) **Rationale** "Because we did not identify direct evidence of benefit from screening on any critical or important outcome other than a statistically improved stage at diagnosis, without a difference in survival, the task force recommends against screening. The recommendation is strong because in its evidence to decision framework the task force placed a high value on the system-wide resources required to screen all chronic GERD patients without evidence of benefit (Appendix 2) (55).in return for uncertain benefit (Appendix 2) (55)."
5. Do you have any comments or suggestions to improve the guideline?	In main document, it is important to mention the gold standard therapy for esophageal cancer is esophagectomy. Page 4 (treatment) does not mention this at all. If we are going to mention early stage cancer, and side effects of endoscopic therapy, we need to make sure the reader does not assume alternate is un available.	I have added: "This review focused on endoscopic techniques, but esophagectomy is standard care for localized esophageal cancer beyond very early stages (5,48)." - (Referenced: 1. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016;111(1):30-50. - 2. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, ESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice

	Also, I am concerned that the quality of evidence is being focused on to the point of suggesting EMR and RFA are poor therapy choices. I think its important to reference ACG guidelines from 2016 that found strong recommendations for the use of EMR, RFA for early stage esophageal cancer. Similar comments are made about endoscopic therapy for dysplastic Barrett's in the appendix (page 8 and 24). I would mention the alternative is to endoscopic therapy for dysplastic Barrett's is esophagectomy. Lack of this comment leaves the reader to presume that 'no treatment' is a justifiable option. Not all primary care physicians are going to recognize that esophagectomy is still offered to patients who are assessed for endoscopic therapy (RFA or EMR) but have concerning features (lymphovascular invasion for e.g.). It is intuitive that preventing esophagectomy would mean improved quality of life, but data is sparse. It may be worth mentioning that as again, the impression left is that RFA and EMR are poor choices with significant side effect profile.	Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016 Sep;27(suppl 5):50-7.) The treatment evidence was from a review of systematic reviews which did not show a statistically significant reduction in mortality. However, I have softened the language to reflect the fact that the event rate was very low. Mortality results were very limited (event rates of 0 to 3 per trial) (33). I have left pages 8 and 24 as is since this is what was discussed during the Evidence to Decision framework review. But I have added a footnote to the 2 tables in the Appendices that look at treatment benefits and harms. "Outcome summary for reduction in progression to esophageal adenocarcinoma (or surrogate measure of eradication/clearance of dysplasia or Barrett's esophagus) by non-surgical[a] treatment type" [a] This review focused on early (non-surgical) techniques used in treatment of Barrett's esophagus, dysplasia or stage 1 esophageal adenocarcinoma. However, esophagectomy

		is the standard treatment for more advanced or high risk cases.

Reviewer 03

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes	Thanks
2. Are the patient groups to whom the guideline is meant to apply clearly described?	No This can be defined more accurately, given that the risk of EAC in those with chronic GERD is not uniform and increases with age and other co-existent risk factors such as smoking, obesity and family history.	The Task Force defined subgroups for which the risk of EAC was greater (i.e. age, sex, body mass index (BMI), smoking history, duration of chronic GERD, definition of chronic GERD, groupings of risk factors, and various ethnic groups). However, due to the poor reporting of variables, we were not able to perform our a priori-defined subgroup analysis. I have added the above note to Appendix III as well as a list of ongoing studies which may allow for subgroup analysis by risk factor.
3. Is the guideline supported by the evidence?	No: Several recent studies that have been published are not included in this document to inform recommendations. Examples : 1. The documents cites one study (ref 40) showing the lack of effect of a prior EGD on EAC outcomes. However it ignores several other publications on this issue, which were all included in a recently published *SRM in Gastroenterology 2018 (Codipilly DC et al*) which clearly showed	1. Thanks - This study was identified during our pre-publication search (not found in original search as published in 2018). We will be adding this trial to our review of reviews (KQ3).

	benefit of lower EAC related and all cause mortality. EAC was also detected at earlier stages in this study. This important study needs to be included, cited and factored into decision making. 2. Studies on patient tolerance with screening are misinterpreted and taken out of context. While there may be a statistically significant increase in anxiety in those undergoing uTNE compared to sEGD, these scores are clinically acceptable. Infact a large majority of patients in these cited studies preferred uTNE to sEGD for screening. I am the senior author on several of these cited publications.	2. I have reviewed the 5 included RCTs and determined that they do indeed indicate tolerability and potentially even preference for uTNE in some cases. I have made the following changes to highlight that while there was a statistically significant difference between modalities, in many cases both would be considered tolerable by patients. (a) Removed from key points: •~~Very low certainty evidence also showed an increase in anxiety for unsedated endoscopic techniques and an incidence of less than 4/1,000 serious adverse events in two small trials of both sedated and unsedated techniques.~~ (b) Added to text: ~~Indirect~~ Evidence from ~~comparisons of screening modalities~~T<u>two trials comparing sedated esophagogastroduodenoscopy versus unsedated transnasal esophagoscopy (43) and unsedated transnasal versus unsedated transoral esophagogastroduodenoscopy (45) reported one serious adverse event (following transnasal endoscopy)) (31). In three RCTs</u> ~~indicated more anxiety for~~ unsedated transnasal esophagoscopy <u>was associated with</u>

	3. While doing volunteer focus groups is laudable, three other studies that are missed are those assessing attitudes to screening in the community and preferences for uTNE versus sEGD which showed strong interest in this area particularly for minimally invasive techniques such as uTNE and others in development. *a. Blevins CH et al, Comparative Assessment of Patient Preferences and Tolerability in Barrett Esophagus Screening: Results From a Randomized Trial. J Clin Gastroenterol. 2018 Nov/Dec;52(10):880-884. PMC6056346.* *b.Gupta M, et al, Screening for Barrett's esophagus: results from a population-based survey. Dig Dis Sci. 2014 Aug;59(8):1831-50.* *c. Freeman M, Offman J, Walter FM, Sasieni P, Smith SG. Acceptability of the Cytosponge procedure for detecting*	statistically significant higher anxiety compared to sedated esophagogastroduodenoscopy (during procedure) or video capsule esophagoscopy (before and during procedure) (very low certainty evidence) (41-45) (Table 2). However, the mild additional discomfort seems to be well tolerated given that 70 to 95% of participants stated they would undergo it again. ~~Trials comparing sedated esophagogastroduodenoscopy versus unsedated transnasal esophagoscopy (43) and unsedated transnasal versus unsedated transoral esophagogastroduodenoscopy (45) reported one serious adverse event (0/209 and 1/59 respectively) (31).~~ (c) I have moved the "Life threatening, severe, or medically significant consequences" up to the first row of table 2 (before anxiety) 3. (a) -This article was very recent and published outside of the last pre-publication search date (October 29, 2018). However, it would meet the inclusion criteria for KQ1. They used the same population as the Sami 2015 trial which was included for KQ1. We will reference this new trial in the systematic

	Barrett's oesophagus: a qualitative study. BMJ Open. 2017 Mar 1;7(3):e013901. doi: 10.1136/bmjopen-2016-013901. PubMed PMID: 28255095; PubMed Central PMCID: PMC5353314.	review (KQ1) (b) Was only a sample of general adults and no one was offered screening or a test, just a survey, much like the Freeman study. This study will also be mentioned in the Discussion section of the report. (c) We had excluded this article because they weren't offered the Cytosponge and our inclusion criteria stated the participants must "have been offered, received, or allocated to receive screening". This study is more hypothetical, in that they were asked if they offered, what would they do. This study will be mentioned in the Discussion section of the systematic review (to be posted on the Task Force website.
	4. The recommendations ignore substantial data on the safety and tolerability of uTNE for BE/EAC screening. In particular data from this SRM needs to be discussed and factored in. *Sami SS, et al. Performance characteristics of unsedated ultrathin video endoscopy in the assessment of the upper GI tract: systematic review and meta-analysis. Gastrointest Endosc. 2015 Nov;82(5):782-92. doi:10.1016/j.gie.2015.07.016. Epub 2015 Sep 12. Review. PubMed PMID: 26371850.*	4. This article was not included in the review of patient values and preferences as our study design criteria excluded systematic reviews. However, studies within this SR would have been screened to determine if any were applicable. Since our population was restricted to GERD patients only many studies were not applicable. I have noted in the Screening section that uTNE tolerability was within accepted levels. ~~Indirect~~ Evidence from ~~comparisons of screening modalities~~~~T~~two trials

	5. Cost effectiveness data for the screening of BE/EAC in those with chronic GERD have not been included or cited. Several studies have been published in this realm. All have shown that a strategy of screening for BE/EAC in those with chronic GERD is cost effective compared to a strategy of not screening. A few examples (this list is not all inclusive) are : *a. Honing J, Kievit W, Bookelaar J, Peters Y, Iyer PG, Siersema PD. Endosheathultrathin transnasal endoscopy is a cost-effective method for screening for Barrett's esophagus in patients with GERD symptoms. Gastrointest Endosc. 2018 Oct 29 PubMed PMID: 30385112.* *b. Heberle CR, Omidvari AH, Ali A, Kroep S, Kong CY, Inadomi JM, Rubenstein JH, Tramontano AC, Dowling EC, Hazelton WD, Luebeck EG, Lansdorp-Vogelaar I, Hur C. Cost Effectiveness of Screening Patients With Gastroesophageal Reflux Disease for Barrett's Esophagus With a Minimally Invasive Cell Sampling Device. Clin Gastroenterol Hepatol. 2017 Sep;15(9):1397-1404.e7. PMCID:*	comparing sedated esophagogastroduodenoscopy versus unsedated transnasal esophagoscopy (43) and unsedated transnasal versus unsedated transoral esophagogastroduodenoscopy (45) reported one serious adverse event (following transnasal endoscopy)) (31). In three RCTs ~~indicated more anxiety for~~ unsedated transnasal esophagoscopy was associated with statistically significant higher anxiety compared to sedated esophagogastroduodenoscopy (during procedure) or video capsule esophagoscopy (before and during procedure) (very low certainty evidence) (41-45) (Table 2). However, the mild additional discomfort seems to be well tolerated given that 70 to 95% of participants stated they would undergo it again. ~~Trials comparing sedated esophagogastroduodenoscopy versus unsedated transnasal esophagoscopy (43) and unsedated transnasal versus unsedated transoral esophagogastroduodenoscopy (45) reported one serious adverse event (0/209 and 1/59 respectively) (31).~~ 5. Due to the low certainty evidence on the effectiveness of screening, no economic

	PMC5827938. *c. Rubenstein JH, Inadomi JM, Brill JV, Eisen GM. Cost utility of screening for Barrett's esophagus with esophageal capsule endoscopy versus conventional upper endoscopy. Clin Gastroenterol Hepatol. 2007 Mar;5(3):312-8. PubMed PMID: 17368230.* *d. Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. Ann Intern Med. 2003 Feb 4;138(3):176-86. PubMed PMID: 12558356.* 6. While I agree that data on endoscopic therapy affecting EAC cancer related mortality is lacking (likely due to the relatively low incidence of EAC compared to other commoner cancers such as lung or colon), there are data on these technologies which have been missed and are relevant to these recommendations. These include both efficacy and cost effectiveness data on endoscopic therapy for BE related dysplasia and carcinoma. These strategies are now the standard of care in the management of BE related dysplasia and carcinoma. I have included some example of studies which should be included.	evaluation or systematic review of cost-effectiveness was conducted as part of this guideline. 6. The first study by Kroep et al., was a modelling study and not within our inclusion criteria. We did include (a) Desai et al, 2017 (b) Qumsya, et al, 2016 and (c) Chadwick, et al. 2013 (see KQ3 treatment overview sent with guideline). This report will be available alongside the guideline on the Task Force website. Data from these reviews are also available in

	Kroep S, Heberle CR, Curtius K, Kong CY, Lansdorp-Vogelaar I, Ali A, Wolf WA, Shaheen NJ, Spechler SJ, Rubenstein JH, Nishioka NS, Meltzer SJ, Hazelton WD, van Ballegooijen M, Tramontano AC, Gazelle GS, Luebeck EG, Inadomi JM, Hur C. <u>*SRMs on efficacy and complications.*</u> *a: Desai M, Saligram S, Gupta N, Vennalaganti P, Bansal A, Choudhary A, Vennelaganti S, He J, Titi M, Maselli R, Qumseya B, Olyaee M, Waxman I, Repici A, Hassan C, Sharma P. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointest Endosc. 2017 Mar;85(3):482-495.e4. doi:10.1016/j.gie.2016.09.022. Epub 2016 Sep 23. Review. PubMed PMID: 27670227.* *b: Qumseya BJ, Wani S, Desai M, Qumseya A, Bain P, Sharma P, Wolfsen H. Adverse Events After Radiofrequency Ablation in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2016 Aug;14(8):1086-1095.e6. doi: 10.1016/j.cgh.2016.04.001. Epub 2016 Apr 9. Review. PubMed PMID: 27068041.* *c: Chadwick G, Groene O, Markar SR, Hoare J, Cromwell D, Hanna GB. Systematic review comparing radiofrequency ablation and complete endoscopic resection in*	the Appendices (Tables IV and V). As treatment data was considered indirect evidence for the effectiveness of screening and there is a word limit in our guideline article we could not include all the data results in the text. (d) Orman et al, 2013 was excluded due to "Not comparing one management/treatment strategy to another management/treatment strategy or to no management/treatment". Cost-effectiveness Due to the low certainty evidence on the effectiveness of screening, no economic evaluation or systematic review of cost-effectiveness of treatment was conducted as part of this guideline.

	treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events. Gastrointest Endosc. 2014 May;79(5):718-731.e3. doi:10.1016/j.gie.2013.11.030. Epub 2014 Jan 23. Review. PubMed PMID: 24462170. *d: Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013 Oct;11(10):1245-55. doi: 1016/j.cgh.2013.03.039. Epub 2013 May 2. Review. PubMed PMID: 23644385; PubMed Central PMCID: PMC3870150* *<u>Cost effectiveness analyses on endoscopic therapy</u>* *1: Pollit V, Graham D, Leonard C, Filby A, McMaster J, Mealing SJ, Lovat LB, Haidry RJ. A cost-effectiveness analysis of endoscopic eradication therapy (EET) for management of dysplasia arising in patients with Barrett's esophagus in the United Kingdom. Curr Med Res Opin. 2018 Nov 27:1-29. doi:10.1080/03007995.2018.1552407. [Epub ahead of print] PubMed PMID: 30479169.* *2: Esteban JM, González-Carro P, Gornals JB, Collados C, Álvarez M, Pérez-Mitru A, Serip S. Economic evaluation of endoscopic radiofrequency ablation for the treatment of dysplastic Barrett's esophagus in Spain. Rev Esp Enferm Dig. 2018 Mar;110(3):145-154.*	

	doi: 10.17235/reed.2017.5087/2017. PubMed PMID: 29168641. *3: Filby A, Taylor M, Lipman G, Lovat L, Haidry R. Cost-effectiveness analysis of endoscopic eradication therapy for treatment of high-grade dysplasia in Barrett's esophagus. J Comp Eff Res. 2017 Jul;6(5):425-436. doi: 10.2217/cer-2016-0089. Epub 2017 May 25. PubMed PMID: 28541099.* *4: Phoa KN, Rosmolen WD, Weusten BLAM, Bisschops R, Schoon EJ, Das S, Ragunath K, Fullarton G, DiPietro M, Ravi N, Tijssen JGP, Dijkgraaf MGW, Bergman JJGHM; SURF investigators. The cost-effectiveness of radiofrequency ablation for Barrett's esophagus with low-grade dysplasia: results from a randomized controlled trial (SURF trial). Gastrointest Endosc. 2017 Jul;86(1):120-129.e2. doi: 10.1016/j.gie.2016.12.001. Epub 2016 Dec 9. PubMed PMID: 27956164.* 7. The statement that these recommendations are aligned with those of other GI societies is not accurate. While all societies do suggest against screening a general population with GERD, they do suggest screening for those with multiple risk factors. This includes the BSG, AGA, ACG, ACP and ASGE.	7. I have changed the Other Guidelines section to state: "~~This task force recommendation is aligned with previous guidance from t~~The Canadian Association of Gastroenterology, British Society of Gastroenterology and American Gastroenterological Association ~~guidelines which~~ all ~~do not~~ recommend against routine screening among chronic GERD patients (4,57,58). ~~Most Other~~ Many other guidelines ~~including the American College of Gastroenterology and the National Institute for Health Care Excellence point to~~ suggest screening among patients with GERD who have multiple risk factors, but ~~also~~ do not recommend population-level screening (5,59) (Table 3). Due to the lack of information on subgroups (i.e. risk factors) we were unable to make a recommendation for this population. We have added more information in Appendix 3.

	The guidelines should suggest who with chronic GERD who may benefit from screening for BE taking into account those risk factors which may increase yield and effectiveness.	
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Guidance needs to be provided to the practitioners on which patient with chronic GERD could benefit from BE/EAC screening: not just anyone with chronic GERD, since the risk is not uniform.	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. Unfortunately a lack of available evidence did not allow for these to be undertaken. We have identified potentially relevant unpublished trials which may allow for future analysis. We have added more information in Appendix 3.
5. Do you have any comments or suggestions to improve the guideline?	A BE content expert needs to be part of the panel writing these guidelines. The absence of one leads to the obvious result of missing large portions of the evidence in this area.	We included the following clinical experts (non-voting) in our Working Group: 1. Dr. Paul J. Belletrutti – Gastroenterologist, Clinical Associate Professor of Medicine Therapeutic Endoscopy, University of Calgary Research Interest: Application and evaluation of advanced endoscopic techniques including endoscopic ultrasound and esophageal ablation for Barrett's esophagus 2. Dr. Laura Targownik – Gastroenterologist, Section Head for Gastroenterology, Division

		of Internal Medicine at the University of Manitoba 3. Dr. Harminder Singh – Gastroenterologist, Max Rady College of Medicine, Internal Medicine, Rady Faculty of Health Sciences, University of Manitoba

CMAJ Peer Reviewers

Reviewers – Editors

Reviewer comments	CTFPHC response
1. As per letter above (and in light of the reviewers' comments below), please address the issue of other risk factors in conjunction with GERD and their impact on risk of esophageal cancer, and how this affects application of the guideline recommendation. It is critical that this information be included, otherwise the guideline may be viewed as unrealistic by clinicians (a special subsection in the Recommendations section would be a good place to do this.]	We have removed the "with or without other risk factors" from the text portion added a new section to Recommendations: Recommendation: We recommend not screening adults (≥18 years) with chronic GERD, ~~with or without other risk factors,~~ for esophageal adenocarcinoma or precursor conditions (Barrett's esophagus or dysplasia) (strong recommendation; very low-certainty evidence). Although risk factors such as age (over 50), 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 (see Appendix 3) (31) We have removed "with or without other risk factors" from the text portion of the conclusion and added a sentence on risk factors instead.

	Conclusion: The evidence reviewed for this guideline did not identify clinically meaningful benefits from screening for esophageal adenocarcinoma or precursor conditions in adults with chronic GERD. It also did not provide sufficient data within risk factor categories (e.g., older age (≥50 years), male sex, abdominal obesity) to support modifying our screening recommendation based on these factors, alone or in combination. ~~with or without other risk factors.~~ Comments: There are some data on associations of individual risk factors with EAC, from epidemiological studies : • Barrett's: RR=11.3[1] (varies according to the presence and grade of dysplasia) • Age: Approximately 10 times more cases in 50 years and over (all esophageal subtypes)[2] • GERD (daily): RR=7.4[3] • Males: RR= 6.87[4] (Canada) • Family history: RR=5.5[5] • White ethnicity: RR=5.0[6] • Abdominal obesity: RR=2.5[7] • Smoking (present or past): RR= 2.0[6]

[1] Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011 Oct 13;365(15):1375-83.
[2] Zeng Y, Ruan W, Liu J, Liang W, He J, et al,. Esophageal cancer in patients under 50: a SEER analysis. J Thorac Dis. 2018 May; 10(5): 2542–50.
[3] Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 2010 Nov;32(10):1222-7.
[4] Xie SH, Lagergren J. A global assessment of the male predominance in esophageal adenocarcinoma. Oncotarget 2016 Jun 21; 7(25): 38876–83.
[5] Tofani CJ, Gandhi K, Spataro J, Yoo J, Murphy, M, et al. Esophageal adenocarcinoma in a first-degree relative increases risk for esophageal adenocarcinoma in patients with Barrett's esophagus. United European Gastroenterol J 2019; 7(2) 225–9.
[6] Short MW, Burgers KG, Fry VT. Esophageal Cancer. Am Fam Physician. 2017 Jan 1;95(1):22-8.
[7] Singh S, Sharma AN, Murad MH, Buttar NS, El–Serag HB, et al. Central Adiposity Is Associated With Increased Risk of Esophageal Inflammation, Metaplasia, and Adenocarcinoma: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2013 Nov; 11(11): 1399-1412.

	• Potential risk associated with: low fruit and vegetable consumption, duration of GERD, hiatal hernia, length of Barrett's segment and protective role of H.pylori, aspirin and statins, etc.[8] However, no study (including Rubinstein's)[9] was able to report the effects of such risk factors, single or in combination, on the outcomes of screening. Therefore we weren't able to draw any conclusions. We have also added to the Key Points, Scope and Recommendations sections to more accurately describe that our target population does not include those previously diagnosed with Barrett's esophagus (BE) as they are often already undergoing endoscopic surveillance. Although this is a risk factor, these patients would not be in the screening population to which our guideline applies. Key Points • This guideline on screening does not apply to people exhibiting alarm symptoms that may be caused by~~for~~ esophageal adenocarcinoma (e.g., dysphagia, odynophagia, recurrent vomiting, unexplained weight loss, anemia, loss of appetite or gastrointestinal bleeding) or those diagnosed with Barrett's esophagus (with or without dysplasia)~~as clinicians should evaluate and manage these people accordingly~~. Scope The target population ~~is~~ consists of adults with chronic GERD~~,~~ and exclude~~ing~~ those with alarm symptoms and those diagnosed with Barrett's esophagus (with or without dysplasia). Recommendation

[8] Coleman HG, Xie SH, Lagergren J. Esophageal Cancer The Epidemiology of Esophageal Adenocarcinoma. Gastroenterology 2018; 154(2): 390-405.
[9] Rubenstein JH, Sonnenberg A, Davis J, McMahon L, Inadomi JM. Effect of a prior endoscopy on outcomes of esophageal adenocarcinoma among United States veterans. Gastrointest Endosc 2008 Nov;68(5):849-55.

	This recommendation does not apply to people exhibiting alarm symptoms or those diagnosed with Barrett's esophagus (with or without dysplasia).
2. Please be clear as to the definition of GERD that clinicians should be using (please see reviewer #2's comments).	Comments: For the definition of chronic GERD, we have now clarified that chronic GERD was initially defined by the task force as symptoms of GERD for ≥12 months (with no specific frequency); or proton pump inhibitor (or other pharmacotherapy) use for GERD for ≥12 months. However, it was later expanded to allow for any article on "chronic GERD" based on study author criteria. Due to the lack of reporting, the included studies are not clear on how GERD was defined and many do not include information on duration of GERD. The "Screening" section now states these study limitations. This was also outlined in the "Gaps in knowledge" section where the lack of consistent reporting limited the generalizability of studies. Added to the Scope section: Chronic GERD was initially defined by the task force as symptoms of GERD for ≥12 months (with no specific frequency); or proton pump inhibitor (or other pharmacotherapy) use for GERD for ≥12 months. However, it was later expanded to allow for any study on "chronic GERD" based on study author criteria. Added to the Screening section A systematic review found two retrospective cohort studies…The severity or duration of GERD was not defined in either study. Five randomized controlled trials (RCTs) (42-46) and one cohort study (47)… When reported, the definition of GERD varied among studies;

	some did not report duration (43,46,47), proton pump inhibitor use (43,46) and none used the Montreal definition. Added to the Gaps in knowledge section The limited use of a common definition for chronic GERD (i.e. severity, duration, use of medication) reduces the generalizability of existing studies.
3. "Monitoring and evaluation" should be a subsection of the Considerations for implementation section	The section heading of "Monitoring and evaluation" is the standard Task Force guideline format agreed with CMAJ and therefore will remain as is.

Reviewer 01

Reviewer comments	**CTFPHC response**
1. It is clearly shown that GERD is only one of the factors recognized risk conditions for adenocarcinoma In this perspective, the paragraph "other guidelines" must be reconsidered because it is too simplified. It is true that some guidelines suggest not screening the general population (not our question) and patients with GERD without alarm symptoms, but most of them take into consideration the screening for adenocarcinoma and Barret esophagus on the basis of the duration of illness. A number of guidelines suggest screening among GERD patients with multiple risk factors. The assessment of the role of other risk factors (well listed in the paper) is considered only in the short Appendix III, confined to the difficulties of this evaluation due to poor reporting of the variables in the studies. [Editor's note: we suggest that you include some information in the guideline itself as to how the recommendation fits in with the patient with more than GERD as a risk factor, drawing on the literature you found, perhaps in a special subsection of the Recommendation	Other guidelines has been edited to read: The Canadian Association of Gastroenterology, British Society of Gastroenterology and American Gastroenterological Association all recommend against routine screening among unselected chronic GERD patients (4,56,57). ~~Many other~~ Some guidelines (4,5,57-59) suggest screening among patients with GERD who have multiple risk factors ~~but those guidelines similarly do not recommend population-level screening~~ (Table 3). These recommendations are not based on screening studies but instead use epidemiological data showing a correlation between specific risk factors (e.g., older age (≥50 years), male sex, abdominal obesity) and the development of Barrett's esophagus or esophageal adenocarcinoma (4-10). Some guidelines have also incorporated economic modelling studies (5,61,62) or expert opinion (4) in addition to risk factor analysis. Studies of Barrett's esophagus cohorts show surveillance may provide a small survival benefit (63-68). However, this benefit might be predominantly the effect of lead-time bias, and patients with a prior diagnosis of Barrett's esophagus were excluded from our guideline.

section. More information on the recommendations of other guidelines in this scenario could be placed in the Other Guidelines section.] From a practical point of view, in primary care, it remains completely unsolved the main question: a lean female 45 years old patient, not smoker, with diagnosis by three years has a similar risk to an obese male 60 years old patient, smoker, with 10 years of disease? I believe that, for a utility in primary care. it is necessary an evaluation of the risk stratification to avoid to confuse different typologies of patients on the basis of incompleteness of available data.	We have removed the "with or without other risk factors" from the text portion added a new section to Recommendations: Recommendation: We recommend not screening adults (≥18 years) with chronic GERD, ~~with or without other risk factors,~~ for esophageal adenocarcinoma or precursor conditions (Barrett's esophagus or dysplasia) (strong recommendation; very low-certainty evidence). Although risk factors such as age (over 50), 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 (see Appendix 3) (31). We have removed "with or without other risk factors" from the text portion of the conclusion and added a sentence on risk factors instead. Conclusion: The evidence reviewed for this guideline did not identify clinically meaningful benefits from screening for esophageal adenocarcinoma or precursor conditions in adults with chronic GERD. It also did not provide sufficient data within risk factor categories (e.g., older age, male sex, abdominal obesity) to support modifying our screening recommendation based on these factors, alone or in combination. ~~with or without other risk factors.~~
2. I finally believe that the classification of very low evidence to the recommendation cannot support a level of strong recommendation. [Editor's note: Please be clear as to how that is possible.]	We have added to the Rationale section As referenced in a previous guideline (57,58) "when there is an absence of evidence to provide confidence that there is benefit from implementing a new prevention service and there is high certainty that scarce health care resources would be expended, the task force

	may make a strong recommendation against service implementation. This is consistent with the GRADE approach (56), in which strong recommendations are sometimes made with low-certainty evidence combined with high certainty of harm or resource implications, and with the value that the task force places on using scarce primary care resources wisely".

Reviewer 02

Reviewer comments	**CTFPHC response**
1. The authors unconditionally recommend against endoscopic screening of chronic GERD patients, based on very low quality evidence as they admit. The end point of screening is actually precursors of esophageal adenocarcinoma (Barrett's esophagus) rather than cancer itself. Available literature, that the authors do not list in their reference list, suggests that early diagnosis of adenocarcinoma or high grade dysplasia in Barrett's esophagus leads to better outcomes. Please see references below: a. Tramontano AC, Sheehan DF, Yeh JM, et al. The Impact of a Prior Diagnosis of Barrett's Esophagus on Esophageal Adenocarcinoma Survival. Am J Gastroenterol 2017;112:1256-1264. b. Codipilly DC, Chandar AK, Singh S, et al. The Effect of Endoscopic Surveillance in Patients with Barrett's Esophagus: A Systematic Review and Meta-analysis. Gastroenterology 2018. c. Wenker TN, Tan MC, Liu Y, et al. Prior Diagnosis of Barrett's Esophagus Is Infrequent, but Associated with Improved Esophageal Adenocarcinoma Survival. Dig Dis Sci 2018;63:3112-3119.	We have edited the Key Points, Scope and Recommendations sections to more accurately reflect that our target population does not include those previously diagnosed with Barrett's esophagus (BE) as they are often already undergoing endoscopic surveillance. Although this is a risk factor, these patients would not be in the screening population to which our guideline applies. Key Points • This guideline on screening does not apply to people exhibiting alarm symptoms that may be caused by~~for~~ esophageal adenocarcinoma (e.g., dysphagia, odynophagia, recurrent vomiting, unexplained weight loss, anemia, loss of appetite or gastrointestinal bleeding) or those diagnosed with Barrett's esophagus (with or without dysplasia)~~as clinicians should evaluate and manage these people accordingly~~. Scope The target population ~~is~~ consists of adults with chronic GERD~~,~~ and excludes~~ing~~ those with alarm symptoms and those diagnosed with Barrett's esophagus (with or without dysplasia). Recommendation

d. Hur C, Miller M, Kong CY, et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer 2013;119:1149-58. e. Fountoulakis A, Zafirellis KD, Dolan K, et al. Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. Br J Surg 2004;91:997-1003. f. Cooper GS, Kou TD, Chak A. Receipt of previous diagnoses and endoscopy and outcome from esophageal adenocarcinoma: a population-based study with temporal trends. Am J Gastroenterol 2009;104:1356-62. g.Verbeek RE, Leenders M, Ten Kate FJ, et al. Surveillance of Barrett's esophagus and mortality from esophageal adenocarcinoma: a population-based cohort study. Am J Gastroenterol 2014;109:1215-22. h. Kastelein F, van Olphen SH, Steyerberg EW, et al. Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. Gut 2016;65:548-54. i.Kastelein F, van Olphen S, Steyerberg EW, et al. Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis. Gut 2015;64:864-71.	This recommendation does not apply to people exhibiting alarm symptoms or those diagnosed with Barrett's esophagus (with or without dysplasia). We have also added to the Other guidelines section to show how the Task Force differs from other guideline developers in methodology: The Canadian Association of Gastroenterology, British Society of Gastroenterology and American Gastroenterological Association all recommend against routine screening among unselected chronic GERD patients (4,56,57). ~~Many other~~ Some guidelines (4,5,57-59) suggest screening among patients with GERD who have multiple risk factors ~~but those guidelines similarly do not recommend population-level screening~~ (Table 3). These recommendations are not based on screening studies but instead use epidemiological data showing a correlation between specific risk factors (e.g., older age (≥50 years), male sex, abdominal obesity) and the development of Barrett's esophagus or esophageal adenocarcinoma (4-10). Some guidelines have also incorporated economic modelling studies (5,61,62) or expert opinion (4) in addition to risk factor analysis. Studies of Barrett's esophagus cohorts show surveillance may provide a small survival benefit (63-68). However, this benefit might be predominantly the effect of lead-time bias, and patients with a prior diagnosis of Barrett's esophagus were excluded from our guideline. Based on our population definition the following literature was not applicable to our screening recommendation as it only includes patients already under surveillance for BE. a. Tramontano AC, Sheehan DF, Yeh JM, et al. The Impact of a Prior Diagnosis of Barrett's Esophagus on Esophageal Adenocarcinoma Survival. Am J Gastroenterol 2017;112:1256-1264

	b. Codipilly DC, Chandar AK, Singh S, et al. The Effect of Endoscopic Surveillance in Patients with Barrett's Esophagus: A Systematic Review and Meta-analysis. Gastroenterology 2018. c. Wenker TN, Tan MC, Liu Y, et al. Prior Diagnosis of Barrett's Esophagus Is Infrequent, but Associated with Improved Esophageal Adenocarcinoma Survival. Dig Dis Sci 2018;63:3112-3119. e. Fountoulakis A, Zafirellis KD, Dolan K, et al. Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. Br J Surg 2004;91:997-1003. g.Verbeek RE, Leenders M, Ten Kate FJ, et al. Surveillance of Barrett's esophagus and mortality from esophageal adenocarcinoma: a population-based cohort study. Am J Gastroenterol 2014;109:1215-22. h. Kastelein F, van Olphen SH, Steyerberg EW, et al. Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. Gut 2016;65:548-54 i. Kastelein F, van Olphen S, Steyerberg EW, et al. Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis. Gut 2015;64:864-71. The following study shows a link between different risk factors and development of BE or EAC. However, the task force requires evidence that **screening** among these high risk populations also results in an improvement in morbidity and mortality, which this study did not provide. d. Hur C, Miller M, Kong CY, et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer 2013;119:1149-58.

	In the following study, only 22.4% of patients had a GERD diagnosis, and we don't know how many of these individuals were also under BE surveillance. Because of the way the information is presented in this study, we would not be able to include it, as the population is not representative. As per our protocol we sent two separate emails to the authors over two weeks to see if they could provide more detailed results. Unfortunately, we received no reply and are therefore unable to include this study. f. Cooper GS, Kou TD, Chak A. Receipt of previous diagnoses and endoscopy and outcome from esophageal adenocarcinoma: a population-based study with temporal trends. Am J Gastroenterol 2009;104:1356-62. We were unable to find evidence to allow for a screening recommendation for GERD patients (without previously diagnosed BE) based on risk factors.
2. There is ample data suggesting that management of early stage dysplasia within Barrett's esophagus leads to reduction in cancer. Examples below. a. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277-88. b. Small AJ, Araujo JL, Leggett CL, et al. Radiofrequency Ablation Is Associated With Decreased Neoplastic Progression in Patients With Barrett's Esophagus and Confirmed Low-Grade Dysplasia. Gastroenterology 2015;149:567-76 e3; quiz e13-4.	We agree that treatment data shows a statistically significant improvement in management of BE and dysplasia. The study by Shaheen, et al., 2009 was included in our overview of systematic reviews on treatment on BE, dysplasia or early stage EAC. It is referenced in the table in Appendix IV showing a statistically significant decrease in progression to EAC and improved eradication/clearance of dysplasia and/or eradication/ablation of BE. The study by Small et al., 2015 was reviewed but excluded from our overview of systematic reviews on treatment as it was not a randomized controlled trial (criteria for inclusion from our protocol). Based on these (and other) results, the guideline text states: **"In terms of potential treatment benefit, results indicate that photodynamic therapy, radiofrequency ablation and endoscopic mucosal resection of Barrett's esophagus (with or without proton pump inhibitors) provide a statistically significant increase in**

	eradication or clearance of dysplasia (very low to low-certainty evidence) (Appendix 4) (33)…. We have added: Overall, very uncertain evidence showed that these treatments improve eradication/ clearance of dysplasia but the benefit is unknown for mortality.
3. The current norm in esophageal screening endoscopy in chronic GERD is against population screening, but instead, targeted screening of populations at risk, including male gender, long standing reflux symptoms, obesity, etc. Any guideline that discusses screening in this context needs to address these target populations, which would be at a disadvantage if denied screening. See references below. [Please see editor's notes for reviewer #1] a. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology 2011;140:e18-52; quiz e13. b. Shaheen NJ, Weinberg DS, Denberg TD, et al. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. Ann Intern Med 2012;157:808-16. c. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014;63:7-42. d. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016;111:30-50; quiz 51. e. Whiteman DC, Appleyard M, Bahin FF, et al. Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma. J Gastroenterol Hepatol 2015;30:804-20.	We have added to the Other guidelines section to show how the Task Force differs from other guideline developers in methodology: The Canadian Association of Gastroenterology, British Society of Gastroenterology and American Gastroenterological Association all recommend against routine screening among unselected chronic GERD patients (4,56,57). ~~Many other~~ Some guidelines (4,5,57-59) suggest screening among patients with GERD who have multiple risk factors ~~but those guidelines similarly do not recommend population-level screening~~ (Table 3). These recommendations are not based on screening studies but instead use epidemiological data showing a correlation between specific risk factors (e.g., older age (≥50 years), male sex, abdominal obesity) and the development of Barrett's esophagus or esophageal adenocarcinoma (4-10). Some guidelines have also incorporated economic modelling studies (5,61,62) or expert opinion (4) in addition to risk factor analysis. Studies of Barrett's esophagus cohorts show surveillance may provide a small survival benefit (63-68). However, this benefit might be predominantly the effect of lead-time bias, and patients with a prior diagnosis of Barrett's esophagus were excluded from our guideline. The following guidelines are referenced in the section "Some guidelines suggest screening among patients with GERD who have multiple risk factors…": a. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the

f. Fock KM, Talley N, Goh KL, et al. Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus. Gut 2016;65:1402-15. g. Huerta-Iga F, Bielsa-Fernandez MV, Remes-Troche JM, et al. Diagnosis and treatment of gastroesophageal reflux disease: recommendations of the Asociacion Mexicana de Gastroenterologia. Rev Gastroenterol Mex 2016;81:208-222. h.Sharma P, Katzka DA, Gupta N, et al. Quality indicators for the management of Barrett's esophagus, dysplasia, and esophageal adenocarcinoma: international consensus recommendations from the American Gastroenterological Association Symposium. Gastroenterology 2015;149:1599-606.	management of Barrett's esophagus. Gastroenterology 2011;140:e18-52; quiz e13. c. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014;63:7-42. d. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016;111:30-50; quiz 51. The following papers do not provide recommendations (screened out a priori due to narrative review/report) and therefore have not been added to Table 3. b. Shaheen NJ, Weinberg DS, Denberg TD, et al. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. Ann Intern Med 2012;157:808-16. e. Whiteman DC, Appleyard M, Bahin FF, et al. Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma. J Gastroenterol Hepatol 2015;30:804-20. The following guideline is only available in Spanish and therefore was screened out a priori: g. Huerta-Iga F, Bielsa-Fernandez MV, Remes-Troche JM, et al. Diagnosis and treatment of gastroesophageal reflux disease: recommendations of the Asociacion Mexicana de Gastroenterologia. Rev Gastroenterol Mex 2016;81:208-222. The following guideline was screened out a priori due to study design (narrative review or report):

	f. Fock KM, Talley N, Goh KL, et al. Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus. Gut 2016;65:1402-15. The following guideline was not included as the recommendations involved surveillance and management of BE (not screening). It was also screened out a priori due to study design (narrative review/report) h. Sharma P, Katzka DA, Gupta N, et al. Quality indicators for the management of Barrett's esophagus, dysplasia, and esophageal adenocarcinoma: international consensus recommendations from the American Gastroenterological Association Symposium. Gastroenterology 2015;149:1599-606.
4. The only risk the authors report from screening procedures is anxiety.	Other risks of screening are reported in the following different sections of the guideline (see bolded text): Methods: "Ultimately, there were three critical outcomes: all-cause mortality~~,~~, cancer-related mortality~~,~~ and **life threatening severe or medically significant ~~consequences~~complications of screening**; and five important outcomes: incidence of esophageal adenocarcinoma (by stage); **quality of life**; **psychological effects; additional major and minor medical procedures; and overdiagnosis."** We have modified the screening sections to make it more clear: Screening: No included studies reported or provided applicable data on cause-specific mortality, **quality of life, additional medical procedures, or overdiagnosis**.

	… ~~Evaluation of screening harms found evidence~~Harms of screening were evaluated in four RCTs (42,44-46). Evidence from two trials comparing sedated esophagogastroduodenoscopy versus unsedated transnasal esophagoscopy (N = 209) and unsedated transnasal versus unsedated transoral esophagogastroduodenoscopy (N = 59) reported **one serious adverse event (following transnasal endoscopy)**. In three RCTs, unsedated transnasal esophagoscopy was associated with statistically significant higher anxiety (harm) compared to sedated esophagogastroduodenoscopy (during procedure) or video capsule esophagoscopy (before and during procedure) (very low-certainty evidence) (42,44,45) (Table 2). Rationale: **One serious adverse event** from screening was reported across two small trials, which compared screening modalities (very low-certainty).

Reviewer 03

Reviewer comments	CTFPHC response
1. (a) I essentially agree with the main conclusion that screening of chronic GERD patients should not be offered to patients but the one main concern that I do have is that what constitutes a chronic GERD patient is not well defined. The guideline needs some improvement in this area. This in itself is no easy task.	For the definition of chronic GERD, we have now clarified that chronic GERD was initially defined by the task force as symptoms of GERD for ≥12 months (with no specific frequency); or proton pump inhibitor (or other pharmacotherapy) use for GERD for ≥12 months. However, it was later expanded to allow for any article on "chronic GERD" based on study author criteria. Due to the lack of reporting, the included studies are not clear on how GERD was defined and many do not include information on duration of GERD. The "Screening" section now states these study limitations. This was also outlined in the "Gaps in knowledge" section where a lack of consistency in definition of GERD decreased the generalizability of studies.

	Added to the Scope section: Chronic GERD was initially defined by the task force as symptoms of GERD for ≥12 months (with no specific frequency); or proton pump inhibitor (or other pharmacotherapy) use for GERD for ≥12 months. However, it was later expanded to allow for any study on "chronic GERD" based on study author criteria. Added to the Screening section A systematic review found two retrospective cohort studies… The severity or duration of GERD was not defined in either study. Five randomized controlled trials (RCTs) (42-46) and one cohort study (47)… . When reported, the definition of GERD varied among studies; some did not report duration (43,46,47) or proton pump inhibitor use (43,46) and none used the Montreal definition. Added to the Gaps in knowledge section The limited use of a common definition for chronic GERD (i.e. severity, duration, use of medication) reduces the generalizability of existing studies.
1(b) For the definition of GERD the Montreal definition of GERD is a pivotal paper. (Vakil N, Veldhuyzen van Zanten S, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006 Aug;101(8):1900-20. PMID: 16928254) Generally a GERD diagnosis can be made when patients suffer from dominant symptoms of heartburn and regurgitation. This is separate from the clinical entity dyspepsia where usually epigastric pain or discomfort symptoms play a bigger role. That said epigastric (or retrosternal pain) and heartburn can be a feature of reflux disease, but they should not be the dominant symptom(s). The problem for primary care is that there is significant overlap between GERD and Dyspepsia. The Canadian Dyspepsia working	We have clarified in the Overview section: GERD (Montreal definition (a global Delphi consensus) is a common condition where reflux of stomach contents (acid regurgitation) causes troublesome symptoms (e.g., ~~acid regurgitation~~, heartburn, waterbrash) ~~or complications~~ (11). **It should be distinguished from dyspepsia, which is a syndrome characterized predominantly by epigastric pain** of at least 1 month (12). We have also referenced the latest ACG/CAG guidelines on dyspepsia (see above - 12. Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG Clinical Guideline: Management of Dyspepsia. Am J Gastroenterol 2017 Sep;112(9):1484.)

group, of which this reviewer was a member, has an all-inclusive dyspepsia definition, which includes GERD symptoms. (Veldhuyzen van Zanten SJO, Flook N, Chiba N, Armstrong D, Barkun A, Bradette M, Thomson A, Bursey F, Blackshaw P, Frail D, Sinclair P. An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ 2000 Jun 13;162 (12 Suppl):S3-23. PMID: 10870511)	We have discussed the issue of significant overlap between dyspepsia and GERD as well as the basis for this and other exclusion criteria described by our guideline (i.e. those with alarm symptoms). It is the opinion of the Task Force that the evaluation of conditions (including dyspepsia, non-response to GERD treatment or any other upper GI issue) is beyond the scope of the guideline. These conditions or symptoms were also not listed in the population exclusion criteria as outlined in our protocol. Therefore, studies may have included patients with dyspepsia or those non-responsive to PPIs. However, we did explicitly set out to exclude those with "alarm symptoms" for EAC as well as those with Barrett's esophagus (with or without dysplasia) and defined them in the protocol. If patients with dyspepsia or other upper GI conditions display these alarm symptoms physicians should evaluate and manage these people accordingly. Based on the above statements, the Task Force has decided not to explicitly exclude those with dyspepsia or those non-responsive to GERD in our scope or recommendation statement. However, we do feel it is important to add to the "Considerations for Implementation" section that clinical judgement should be used in these situations. For dyspepsia and for all other potential upper GI disorders/symptoms clinicians should determine if a diagnostic work-up is needed (including EGD). The 2017 ACG and CAG guidelines use a definition of predominant epigastric pain (>=1 month) to help distinguish it from GERD. They also conditionally recommend that dyspepsia patients ≥60 years undergo EGD to exclude organic pathology (itself a recommendation based on very low quality evidence). Similarly, patients that are non-responsive to GERD treatment may need investigation to determine if they have an underlying non-GERD related condition. However, in these situations **screening** in not indicated and the presence of other GI symptoms does not change the recommendation.

	We have changed the Key Points, Scope, Recommendation, Considerations for Implementation and Conclusion sections based on the above statement: Key Points: • This guideline on screening does not apply to people exhibiting alarm symptoms that may be caused by~~for~~ esophageal adenocarcinoma (e.g., dysphagia, odynophagia, recurrent vomiting, unexplained weight loss, anemia, loss of appetite or gastrointestinal bleeding) or those diagnosed with Barrett's esophagus (with or without dysplasia)~~as clinicians should evaluate and manage these people accordingly~~. Scope The target population ~~is~~ consists of adults with chronic GERD~~,~~ and excludes~~ing~~ those with alarm symptoms and those diagnosed with Barrett's esophagus (with or without dysplasia). Recommendation This recommendation does not apply to people exhibiting alarm symptoms or those diagnosed with Barrett's esophagus (with or without dysplasia) ~~or to those non-responsive to GERD treatment~~. Consideration for Implementation Clinicians should be aware of alarm symptoms for esophageal adenocarcinoma and evaluate, refer and manage ~~these~~ patients ~~as well as those non-responsive to medical treatment, for diagnostic esophagogastroduodenoscopy~~ accordingly. 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). Conclusions

	The evidence reviewed for this guideline did not identify clinically meaningful benefits from screening for esophageal adenocarcinoma or precursor conditions in adults with chronic GERD. It also did not provide sufficient data within risk factor categories (e.g., older age (≥50 years), male sex, abdominal obesity) to support modifying our screening recommendation based on these factors, alone or in combination. ~~with or without other risk factors.~~ The~~is~~ task force provides a strong recommendation ~~indicates~~ that clinicians should not offer screening to adults with chronic GERD~~such people~~. This guideline does not apply to people exhibiting alarm symptoms or those diagnosed with Barrett's esophagus (with or without dysplasia) ~~or those non-responsive to medical treatment,~~ who should be evaluated, referred and managed accordingly. The exclusion of patients with alarm symptoms is detailed in multiple locations throughout the guideline (i.e. Key points, Scope, Recommendations, Considerations for Implementation and Conclusions sections) and therefore it was thought as unnecessary to also be specified in the title. Title: Guideline on screening for esophageal adenocarcinoma in patients with chronic gastroesophageal reflux disease ~~without alarm symptoms~~
1(c) In this reviewer's opinion, the diagnosis of GERD warrants dominant symptoms of heartburn and regurgitation as well as a response to acid suppression. In reality, it is often not clear or was never defined why chronic PPI users were started on the PPI. Where I see a problem for family physicians is how to deal with a patient who is a chronic user of a PPI and who has proven to be a responder (in the sense that heartburn and regurgitation are completely controlled or much improved). Certainly, a patient who has been a long-term PPI user for GERD symptoms should be considered a chronic GERD	We have added to the Scope section to show that the definition of chronic GERD includes PPI/other pharmaceutical users (without current GERD symptoms). Added to the Scope section: "Chronic GERD was initially defined by the task force as symptoms of GERD for ≥12 months (with no specific frequency); **or proton pump inhibitor (or other pharmacotherapy) use for GERD for ≥12 months.**

patient, even if the patient is asymptomatic while taken the PPI, and it should be more specifically stated in the manuscript. Many patients with true GERD need their current PPI because they have recurrence of GERD symptoms after the discontinuation of the medication and a substantial proportion do need BID dosing for symptom control. So a patient fits the criteria for being a chronic GERD patient if they have frequent or recurring symptoms of heartburn and acid regurgitation and these should be the dominant symptoms They also need to be responsive to acid suppressive therapy , that is to H2 blockers or now much more common to proton pump inhibitors. Also patients, who are well controlled while taking acid suppressive therapy long term, and have proven to themselves (and the prescriber) that they need their current PPI because they have recurrence of GERD symptoms after the discontinuation of the medication, should be considered to be a chronic GERD patient.	However, it was later expanded to allow for any study on “chronic GERD” based on study author criteria.

2. I must admit, and this is perhaps a personal bias, that I hesitate not recommending screening at all across the board to all chronic GERD patients, even though there is some, although not conclusive, evidence to screen for Barrett's esophagus in males who have chronic GERD. The recommendation is mainly based on lack of evidence that there is a mortality benefit. It is unlikely that that evidence or lack thereof will be forth coming given how prevalent GERD is. The ACG guidelines published in 2015 comment that, "Screening for Barrett's esophagus may be considered in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux disease and two or more risk factors (such as obesity and smoking) for Barrett's esophagus or esophageal adenocarcinoma". ACG made that a strong recommendation for which there was felt to be a moderate level of evidence. ACG recommended that this be discussed with patients who have more risk factors. I DO agree with the general recommendation to not off screen but I wonder whether the point about screening for Barrett's in patients with several risk factors and who are male, should at least be mentioned in the discussion.	We have removed the "with or without other risk factors" from the text portion added a new section to Recommendations: Recommendation: We recommend not screening adults (≥18 years) with chronic GERD, ~~with or without other risk factors,~~ for esophageal adenocarcinoma or precursor conditions (Barrett's esophagus or dysplasia) (strong recommendation; very low-certainty evidence). Although risk factors such as age (over 50), 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 (see Appendix 3) (31). Comments: There are some data on associations of individual risk factors with EAC, from epidemiological studies : • Barrett's: RR=11.3[10] (varies according to the presence and grade of dysplasia) • Age: Approximately 10 times more cases in 50 years and over (all esophageal subtypes)[11] • GERD (daily): RR=7.4[12] • Males: RR= 6.87[13] (Canada) • Family history: RR=5.5[14]

[10] Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011 Oct 13;365(15):1375-83.
[11] Zeng Y, Ruan W, Liu J, Liang W, He J, et al,. Esophageal cancer in patients under 50: a SEER analysis. J Thorac Dis. 2018 May; 10(5): 2542–50.
[12] Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 2010 Nov;32(10):1222-7.
[13] Xie SH, Lagergren J. A global assessment of the male predominance in esophageal adenocarcinoma. Oncotarget 2016 Jun 21; 7(25): 38876–83.
[14] Tofani CJ, Gandhi K, Spataro J, Yoo J, Murphy, M, et al. Esophageal adenocarcinoma in a first-degree relative increases risk for esophageal adenocarcinoma in patients with Barrett's esophagus. United European Gastroenterol J 2019; 7(2) 225–9.

	• White ethnicity: RR=5.0[15] • Abdominal obesity: RR=2.5[16] • Smoking (present or past): RR= 2.0[15] • Potential risk associated with: low fruit and vegetable consumption, duration of GERD, hiatal hernia, length of Barrett's segment and protective role of H.pylori, aspirin and statins, etc.[17] However, no study (including Rubinstein's)[18] was able to report the effects of such risk factors, single or in combination, on the outcomes of screening. Therefore we weren't able to draw any conclusion. We have also added to the Other guidelines section to show how the Task Force differs from other guideline developers in methodology: The Canadian Association of Gastroenterology, British Society of Gastroenterology and American Gastroenterological Association all recommend against routine screening among unselected chronic GERD patients (4,56,57). ~~Many other~~ Some guidelines (4,5,57-59) suggest screening among patients with GERD who have multiple risk factors ~~but those guidelines similarly do not recommend population-level screening~~ (Table 3). These recommendations are not based on screening studies but instead use epidemiological data showing a correlation between specific risk factors (e.g., older age (≥50 years), male sex, abdominal obesity) and the development of Barrett's esophagus or esophageal adenocarcinoma (4-10). Some guidelines have also incorporated economic modelling studies (5,61,62) or expert opinion (4) in addition to risk factor analysis. Studies of

[15] Short MW, Burgers KG, Fry VT. Esophageal Cancer. Am Fam Physician. 2017 Jan 1;95(1):22-8.
[16] Singh S, Sharma AN, Murad MH, Buttar NS, El–Serag HB, et al. Central Adiposity Is Associated With Increased Risk of Esophageal Inflammation, Metaplasia, and Adenocarcinoma: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2013 Nov; 11(11): 1399-1412.
[17] Coleman HG, Xie SH, Lagergren J. Esophageal Cancer The Epidemiology of Esophageal Adenocarcinoma. Gastroenterology 2018; 154(2): 390-405.
[18] Rubenstein JH, Sonnenberg A, Davis J, McMahon L, Inadomi JM. Effect of a prior endoscopy on outcomes of esophageal adenocarcinoma among United States veterans. Gastrointest Endosc 2008 Nov;68(5):849-55.

	Barrett's esophagus cohorts show surveillance may provide a small survival benefit (63-68). However, this benefit might be predominantly the effect of lead-time bias, and patients with a prior diagnosis of Barrett's esophagus were excluded from our guideline. We have added to the Key Points, Scope and Recommendation sections to more accurately describe that our target population does not include those previously diagnosed with Barrett's esophagus (BE) as they are often already undergoing endoscopic surveillance. Key Points: • This guideline on screening does not apply to people exhibiting alarm symptoms that may be caused by~~for~~ esophageal adenocarcinoma (e.g., dysphagia, odynophagia, recurrent vomiting, unexplained weight loss, anemia, loss of appetite or gastrointestinal bleeding) or those diagnosed with Barrett's esophagus (with or without dysplasia)~~as clinicians should evaluate and manage these people accordingly~~. Scope The target population ~~is~~ consists of adults with chronic GERD~~,~~ and exclude~~s~~~~ing~~ those with alarm symptoms and those diagnosed with Barrett's esophagus (with or without dysplasia). Recommendation This recommendation does not apply to people exhibiting alarm symptoms or those diagnosed with Barrett's esophagus (with or without dysplasia) ~~or to those non-responsive to GERD treatment~~. Consideration for Implementation Clinicians should be aware of alarm symptoms for esophageal adenocarcinoma and evaluate, refer and manage ~~these~~ patients ~~as well as those non-responsive to medical treatment, for diagnostic esophagogastroduodenoscopy~~ accordingly. 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). We have removed "with or without other risk factors" from the text portion of the conclusion and added a line Conclusions The evidence reviewed for this guideline did not identify clinically meaningful benefits from screening for esophageal adenocarcinoma or precursor conditions in adults with chronic GERD. It also did not provide sufficient data within risk factor categories (e.g., older age (≥50 years), male sex, abdominal obesity) to support modifying our screening recommendation based on these factors, alone or in combination. ~~with or without other risk factors.~~ The~~is~~ task force provides a strong recommendation is~~ndicates~~ that clinicians should not offer screening to adults with chronic GERD~~such people~~. This guideline does not apply to people exhibiting alarm symptoms or those diagnosed with Barrett's esophagus (with or without dysplasia) ~~or those non-responsive to medical treatment,~~ who should be evaluated, referred and managed accordingly.
3. (a) The risk of esophageal adenocarcinoma is very low in patients below the age of 50 so some of the guidelines, which have addressed screening for Barrett's esophagus, have used that age (or now 60 years) as one of the criteria to consider screening. In the review, most of the studies have a very small sample size making it impossible to draw any meaningful conclusions. However, the large RCT ASPECT trial by Jankowski and co-workers, which was recently published in the Lancet, showed that patients diagnosed with Barrett's esophagus greater than one centimeter in length, derived benefit from a PPI given twice a day, that is in a high dose, in that it delayed progression to dysplasia and esophageal adenocarcinoma. In	We agree that the ASPECT trial, if confirmed, may encourage screening for BE. BE patients in the ASPECT trial were most likely not diagnosed via screening, however, and therefore not part of our population inclusion criteria. We have added to the Recommendations section to highlight that there was no data to allow for a screening recommendation based on risk factors: Recommendation:

that light, it is likely that the push to screen for Barrett's esophagus for which the target population is the chronic GERD patient will continue and I am not sure that the current guideline will really be able to completely negate screening in these patients.	Although risk factors such as age (over 50), 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 (see Appendix 3) (31). We also mention the ASPECT trial in the Gaps in Knowledge section "For example, a recent RCT (n=2,557) found improvement in time to all-cause mortality, esophageal adenocarcinoma, or high-grade dysplasia for Barrett's esophagus treated with combination high dose proton pump inhibitors and aspirin (49). However, this RCT did not meet our review inclusion criteria (41) as it is yet to be included in a systematic review."
3 (b) I think this is still is important as there's clear evidence that the incidence of esophageal adenocarcinoma has risen significantly over the past twenty years and up until now there is no real evidence that the risk has been levelling off. The most likely risk factor that explains this trend is obesity.	We have included Figure 1 which shows the large increase in EAC since the 1980's. We also state: "Incidence has shifted over the past 40 years with rates of adenocarcinoma increasing and squamous cell carcinoma falling (Figure 1) (3). This change may result from increases in adenocarcinoma-related risk factors (e.g., gastroesophageal reflux, obesity) and decreases in risk factors linked to squamous cell carcinoma (e.g., smoking) (2)." We have included obesity (particularly abdominal obesity) in our list of risk factors which were identified a priori. However, no data were found to allow for a screening recommendation based on these risk factors, alone or in combination.
4. To summarize, I am slightly uncomfortable with the blank recommendation to not offer gastroscopy to all these patients. Are we comfortable to prescribe PPIs sometimes for decades in GERD patients and never take a look, especially if there are risk factors such as male gender, obesity in smoking? This in the light that there has been marked increase in esophageal adenocarcinoma incidence over	We have removed the "with or without other risk factors" from the text portion added a new section to Recommendations: Recommendation: We recommend not screening adults (≥18 years) with chronic GERD, ~~with or without other risk factors,~~ for esophageal adenocarcinoma or

the past 20 years. The reality is that gastroscopy is a relatively straightforward and generally safe procedure. When we wait until there are alarm symptoms it is often too late.	precursor conditions (Barrett's esophagus or dysplasia) (strong recommendation; very low-certainty evidence). Although risk factors such as age (over 50), 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 (see Appendix 3) (31).
5. I agree but it should be stressed perhaps more clearly in the conclusion that the recommendation not to screen is because there essentially is no evidence in support of it. This said, as upper GI symptoms are so common it is highly unlikely that a screening trial that specifically address the screening question will ever be conducted.	We have edited the Conclusions section to read: Conclusions The evidence reviewed for this guideline did not identify clinically meaningful benefits from screening for esophageal adenocarcinoma or precursor conditions in adults with chronic GERD. It also did not provide sufficient data within risk factor categories (e.g., older age (≥50 years), male sex, abdominal obesity) to support modifying our screening recommendation based on these factors, alone or in combination. ~~with or without other risk factors.~~ The~~is~~ task force provides a strong recommendation is~~ndicates~~ that clinicians should not offer screening to adults with chronic GERD~~such people~~. This guideline does not apply to people exhibiting alarm symptoms or those diagnosed with Barrett's esophagus (with or without dysplasia) ~~or those non-responsive to medical treatment,~~ who should be evaluated, referred and managed accordingly. We also state in the Gaps in knowledge section: "Ideally, there would be well-designed RCTs ~~conducted to~~ examining~~e~~ the effects of screening versus no screening among chronic GERD patients. Barriers to feasibility, however, include the low prevalence of esophageal adenocarcinoma and ~~the~~ limited ~~ability to identify~~ probability that GERD patients ~~most likely to~~ will progress to cancer."