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Title: Prevention of overuse: a view on upper gastrointestinal endoscopy.

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Dear dr. Wang and reviewers,

We kindly thank you and the reviewers for your valuable time and useful contributions. We thoroughly read and considered all comments.

Please find below a detailed point-to-point reply to the comments in blue font. Enclosed is the revised manuscript with all revisions marked in red, underlined font.

Kind regards,

Drs. Judith de Jong

Dr. Marten Lantinga

Prof. Dr. Joost Drenth

## Reviewer #1

This paper reviews the approach to the overuse of upper gastrointestinal endoscopy. It is very important issue. As authors state in their review there are some strategies and algorithms to avoid too much endoscopies. Nevertheless, only some of them could be widely implicated and accepted. Authors conclude that there is no single best strategy. Therefore, authors suggest for a future studies to look into combination of clinical assessment strategies. In general, the paper is very comprehensive and well written. I would be interested to have an author's approach to some issues:

- 1) Personally I would be interested what is authors' approach to repeated endoscopies. As the repeated endoscopies constitutes significant number of all upper endoscopic investigations. Should the approach be the same as for the first endoscopy or can we be more strict on indications for repeated endoscopy?

Repeat endoscopies are indeed a very important issue. While diagnostic yield of endoscopy in endoscopy naïve dyspeptic patients is known to be limited, clinically significant diagnoses at repeat endoscopy are even lower. Subsequent studies show that odds of finding clinically relevant abnormalities is extremely low (Guo *et al.* J Dig Dis 2013). As the reviewer suggests, we would recommend that other strategies to relieve symptoms should be emphasized in those patients. Repeat endoscopy should be reserved for patients in areas with high gastric cancer incidence, or with risk factors such as cigarette smoking, NSAID use, or antiplatelet use.

- 2) I believe, that the „H. pylori test and treat strategy“ must be emphasized as it is not only a way to avoid endoscopy, but also to prevent peptic ulcers and gastric cancer.

We thank the reviewer for this addition, as this is indeed one of the advantages of the H. pylori test and treat strategy. To make sure that this is emphasized, we added a sentence to the manuscript (page 17, line 394-396).

## Reviewer #2

This is a detailed review article on overuse of upper GI endoscopy in dyspepsia patients. This is interesting topic in terms of medical policy and structure of medical systems. However, there are some major issues:

- 1) Obviously it is well proved that endoscopy adds very little to further management of dyspepsia so no new information is given in this review. The important issue is the adherence of worldwide medical community to guidelines, credentials algorithms etc.

We agree with the reviewer that the role of endoscopy in the management of uncomplicated dyspepsia is already known to be limited. Therefore it is surprising that literature still

describes dyspepsia to be a common indication for endoscopy. These numbers suggest that even though its relevance is limited, endoscopy is frequently performed for (uncomplicated) dyspepsia. We therefore propose several strategies in this review to reduce these numbers. As the reviewer rightly points out, guideline adherence is of great importance. At page 6-7, line 125-186, we describe strategies that can assist in improvement of guideline adherence.

- 2) Of course in countries where endoscopy is too cheap it is more cost-effective to perform endoscopy to everybody instead of breath test only for HP.

Prices and availability of endoscopy do indeed vary between countries and affect cost-effectiveness. We found \$200 to be a threshold for cost-effectiveness of endoscopy as compared to H. pylori test and treat (page 17, line 387-389). While H. pylori urea breath test is a very reliable non-invasive test, it is also costly. H. pylori feces test is a good, more cost-effective alternative for both urea breath test and serology (Elwyn *et al.* Br J Gen Pract 2007).

- 3) Also endoscopy has a placebo action as well.

We acknowledge that endoscopy may have a placebo effect. For some patients endoscopy achieves considerable symptom relieve. The reassurance achieved by endoscopy is however short-term (Kerkhoven *et al.* Endoscopy 2006). We added a sentence about the placebo effect to the manuscript on page 5, line 81-82 for clarification. In addition, endoscopy for placebo effect comes at a high price considering the invasive nature of endoscopy, risk of complications, and limited availability in some areas. We feel that it should be carefully considered whether the advantage of a potential placebo effect outbalances the potential disadvantages of endoscopy. To our knowledge, guidelines therefore do not generally recommend endoscopy for reassurance of patients.

- 4) PPIs have been related to serious side effects especially in long term treatment so it is not advisable an empirical therapy with PPI. This issue needs further evidence and studies.

The reviewer raised a relevant issue. A recent meta-analysis summarized studies of long-term side effects of PPI treatment (reference 71). It was concluded that evidence of these side-effects is not very robust, and, as the reviewer suggests, more studies are needed to establish a causal relationship. We added a line in the manuscript to emphasize reviewers point (page 18, line 422-423). On the contrary, short-term PPI use in a symptomatic population is known to be safe and well tolerated. Benefits often outweigh potential mild side effects of short-term use. Dyspepsia and acid-related symptoms may negatively influence quality of life. As both are often self-limiting or may be solved by lifestyle interventions, a short trial of PPI use may assist in bridging this period, without need of endoscopy. However, we agree that PPI use

should be closely monitored to prevent inappropriate long-term use, which we aim to emphasize with our statement on page 18, line 425-429.

- 5) In contrast to Asian countries, where there are currently screening endoscopic strategies for prevention of gastric cancer, no such screening programs exist in the west, and this is the reason of very low incidence of diagnosis of early gastric cancer in the west, where cancer is mainly diagnosed in advanced stages. Gastric cancer in early stages is asymptomatic and the alarm symptoms the authors reported, are symptoms of advanced gastric cancer. In the modern era of ESD we have to force medical systems to introduce screening programs in order to increase the incidence of diagnosis of early gastric cancer.

We thank the reviewer for highlighting the important point of screening for gastric cancer. Currently, gastric cancer screening is standard practice in several countries with high incidence of gastric cancer, such as Japan and Korea. Intervals and initiation age differ between screening programs, but observational studies show a decline in gastric cancer mortality when screening is performed. In low incidence countries, screening is generally not advised by guidelines due to its limited yield and subsequent cost-ineffectiveness.

Gastric cancer screening is an important issue and should be done justice by being extensively researched. As the focus of this review is directed at endoscopies not referred for according to guidelines, screening falls outside the scope of this review. The strategies are therefore not applicable for patients for whom screening is advised by current guidelines. We will clarify this by rephrasing line 72 on page 5, and adding line 121-123 on page 6.

- 6) The authors stated in page 6 second paragraph of <<clinical assessment>>: <<studies consistently failed to detect improved cancer detection rates>>. To my opinion this is not due to endoscopy but due to low quality of endoscopic practice in the West mainly based on white light endoscopy and low training of western endoscopists to modern magnifying techniques and so an average endoscopist has no experience to recognize the early gastric cancer, which can be misdiagnosed as erosion.

We agree with the reviewer that low incidence of gastric cancer deprives western endoscopists from extensive practice in recognition of gastric cancer. A meta-analysis that gives interesting insight in this matter was published in 2015 (Veitch *et al.* Nat. Rev Gastroenterol. Hepatol. 2015). The following table shows miss rates of gastric cancer in Western and Asian countries. It should be noted that the Asian series included early gastric neoplasia in their analysis. Miss rate after 3 years was under 10% in all but one (14%) Western studies. Against a low incidence of gastric cancer, these are still low absolute numbers. Continuing improvement and evaluation of endoscopist training is however pivotal. It would be interesting to study ways to improve recognition of gastric cancer in low-incidence areas in future studies.

<b>Table 1   Missed upper gastrointestinal cancers within 3 years of gastroscopy</b>						
Anatomic site	<3 year miss rate (%) <sup>*</sup>	Country	Population (n)	Time period	Study design	Reference
Stomach	18/129 (13.9)	UK	–	1994–1999	Surgical series, retrospective	Amin <i>et al.</i> (2002) <sup>3</sup>
Stomach	13/284 (4.6) <sup>†</sup>	Finland	–	1996–2001	Retrospective, link to cancer registry	Voutilainen <i>et al.</i> (2005) <sup>7</sup>
Stomach	188/730 (25.8)	Japan	51,411	1990–1995	Retrospective, link to cancer registry	Hosokawa <i>et al.</i> (2007) <sup>14</sup>
Stomach	6/74 (8.1)	UK	9,764	2005–2008	Retrospective	Vradelis <i>et al.</i> (2011) <sup>8</sup>
Stomach	1083/3,498 (40.0)	Korea	765,813	2002–2005	Screening programme	Choi <i>et al.</i> (2011) <sup>13</sup>
Stomach	128/5,473 (2.3)	UK	5 million <sup>§</sup>	Before 2012	Nested case control	Menon <i>et al.</i> (2012) <sup>10</sup>
Early gastric cancer/HGIN	23/103 (22.2)	China	44,500	2010–2011	Retrospective	Ren <i>et al.</i> (2013) <sup>15</sup>
Early gastric cancer	52/284 (18.3)	Korea	–	2006–2013	Retrospective	Cho <i>et al.</i> (2014) <sup>16</sup>
Stomach and oesophagus	5/94 (5.3)	USA	–	2000–2010	Retrospective	Khalil <i>et al.</i> (2014) <sup>5</sup>
Oesophagus and stomach	30/305 (9.8)	UK	–	1994–2001	Retrospective	Yalamarthy <i>et al.</i> (2004) <sup>9</sup>
Oesophagus	10/110 (9.1)	USA	–	1997–2001	Retrospective, link to cancer registry	Bloomfield <i>et al.</i> (2005) <sup>4</sup>
Oesophagus, stomach and duodenum	55/706 (7.8)	Australia	28,064	1990–2004	Retrospective, link to cancer registry	Raftopoulos <i>et al.</i> (2010) <sup>6</sup>
<sup>*</sup> Numbers represent the amount of cancers detected that had been missed at a gastroscopy 3 years earlier, compared with the total number of cancers diagnosed in the study. <sup>†</sup> Gastroscopy within 3.5 years. <sup>§</sup> Primary care database. Abbreviations: –, not available; HGIN, high-grade intraepithelial neoplasia.						

- 7) I can't understand <<true indication for UGI endoscopy>>. What about screening for gastric cancer? So the strategies <<test and treat>> and <<empirical treatment>> may be not beneficial in countries where endoscopy is overall available and cheap and also it is not beneficial for screening gastric cancer.

We rephrased the sentence on page 10, line 234-235, as we agree that 'true indication' is not the appropriate terminology in this context and certainly does not concern screening populations. In populations where screening is performed, patients may receive endoscopy before H. pylori can be tested or PPI can be tried. However, even in countries that have national screening programs, such as Japan, the value of H. pylori test and treat is increasingly recognized. Programs are initiated to screen young patients for H. pylori by urine or feces test, and eradicate if positive. This new focus on cancer prevention, rather than early detection, may result in even better mortality reduction rates.

### Reviewer #3

The study deals with one of the problems most GI units face worldwide, which is the overuse of upper GI endoscopy referrals. The authors revise the current evidence and offer several options to reduce this.

- 1) Sometimes the manuscript is a bit redundant. An increase in the number of Tables or Figures could help the reader.

We thank the reviewer for this excellent suggestion. A table with an overview of included studies was added to the manuscript on pages 8, 10, 12-13, and 14.

- 2) The authors could be a bit more precise when make suggestions on how the interested reader could put in practice these recommendations.

We acknowledge that more precise suggestions, such as a step-to-step approach or algorithm, would help interested readers with implementation of these strategies. We are however impeded to do so by existing variations in clinical practice between countries and settings. In addition, rigid recommendations are less suitable for a patient centered approach, considering inter-patient differences and physician's clinical views. We feel that collaboration of the most important elements of all strategies, i.e. local adaption of guidelines by a local core group, use of a directional algorithm prior to referral, liberal use of *H. pylori* diagnostics, and short trial of PPI, may be capable of reducing upper GI endoscopies in most situations. For these strategies to succeed and have a lasting effect, commitment and willingness to change are important factors. Regional meetings of a committed core group could contribute to successful implementation.

- 3) The authors could also offer additional options, since I suspect the four offered are being implemented in many centers with no major impact.

In this review we chose to emphasize these four for several reasons. Use of guidelines is the basis of appropriate care. However, passive dissemination of guidelines, as is often exhibited, may not reach a sufficient audience, which may be improved by active implementation (see also page 8, lines 165-177). Use of clinical assessment strategies may help guideline adherence, once properly implemented. The open-access system is an example of a referral pathway that may be improved by the use of algorithms. *H. pylori* detection and treatment is highly important for symptom relief, as well as prevention of gastric cancer and peptic ulcers. However, often *H. pylori* diagnostics are performed in addition to endoscopy. We aim to show that *H. pylori* diagnostics can be used to reduce endoscopies. PPIs may be controversial in treatment of dyspepsia, considering the limited efficacy and fear of negative effects associated with long-term use. However, the literature we found shows that a reduction of endoscopies can still be achieved by a short trial of PPI. We hope to advocate the short term use of these safe and efficient drugs, instead of prompt endoscopy.

In addition to these reasons, we were limited by the data available in literature. While we may deduce which additional strategies could be useful, we have no evidence to prove its efficacy. Therefore, we limited this review to strategies that were evidence based. However, in our search we found strategies used for other types of overuse, i.e. laboratory orders, urine catheters, and (cardiac) imaging. Examples of strategies were automatic feedback systems, financial incentive programs, use of eHealth, and use of biomarkers or other non-invasive tests. Unfortunately no studies are yet available using these strategies to reduce upper GI endoscopy. Hopefully future studies will seize the opportunity to explore these strategies. We are trying to contribute to a larger variety of strategies with the TRIODE trial, using a patient education tool, that is currently recruiting patients (see page 19, final paragraph).

Additional revisions

- 1) We added Marten A Lantinga as co-author, considering his extensive contributions to drafting and revising the manuscript.
- 2) Several textual changes were made as recommended by the language editor.
- 3) Several textual changes were made in the abstract for clarification purposes.

All revisions are marked red and underlined.