

The Road to a World-Unified Approach to the Management of Patients with Gastric Intestinal Metaplasia: A Review of Current Guidelines

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Abstract

Objective: During the last decade, the management of gastric intestinal metaplasia (GIM) has been addressed by several distinct international evidence-based guidelines. In this review we aimed to synthesize these guidelines and provide clinicians with a global perspective of the current recommendations for managing patients with GIM, as well as highlight evidence gaps that need to be addressed with future research. **Design:** We conducted a systematic review of the literature for guidelines and consensus statements published between January 2010 and February 2023 that address the diagnosis and management of GIM. **Results:** From 426 manuscripts identified, 15 guidelines were assessed. There was consistency across guidelines regarding the purpose of endoscopic surveillance of GIM (i.e., identify prevalent neoplastic lesions and stage gastric preneoplastic conditions) and that only patients with high-risk GIM phenotypes (e.g., corpus-extended GIM, OLGIM stages III/IV, incomplete GIM subtype), persistent refractory *H. pylori* infection, or first-degree family history of gastric cancer) merit regular-interval endoscopic surveillance, but not low-risk phenotypes, which comprise most patients with GIM. Not all guidelines are aligned on histological staging systems. If surveillance is indicated, most guidelines recommend a 3-year interval, but there is some variability. All guidelines recommend *H. pylori* eradication as the only non-endoscopic intervention for gastric cancer prevention, while some offer additional recommendations regarding lifestyle modifications. While most guidelines allude to the importance of high-quality endoscopy for endoscopic surveillance, few detail important metrics apart from stating that a systematic gastric biopsy protocol should be followed. Notably, most guidelines comment on the role of endoscopy for gastric cancer screening and detection of gastric precancerous conditions, but with high heterogeneity, limited guidance regarding implementation, and lack of robust evidence. **Conclusion:** Despite heterogeneous populations and practices, international guidelines are generally aligned on the importance of GIM as a precancerous condition and the need for a risk-stratified approach to endoscopic surveillance, as well as *H. pylori* eradication when present. There is room for harmonization of guidelines regarding 1) which populations merit index endoscopic screening for gastric cancer and GIM detection/staging; 2) objective metrics for high-quality endoscopy; 3) consensus on the need for histological staging; and 4) non-endoscopic interventions for gastric cancer prevention apart from *H. pylori* eradication alone. Robust studies, ideally in the form of randomized trials, are needed to bridge the ample evidence gaps that exist.

What is already known on this topic?

- Since 2010, several guidelines and expert consensus statements have been published worldwide providing evidence-based recommendations for the management of patients with gastric intestinal metaplasia (GIM), a precancerous condition associated with increased risk of gastric cancer.
- Likely due to heterogeneous populations, methods, and wording, controversy, confusion, and misperceptions remain in the management of patients with GIM, which might compromise the optimal care of these potentially high-risk patients.

What does this study add?

- We conducted a systematic review and synthesized all available, published international guidelines describing the management of patients with GIM and, herein, provide the first unified, global perspective for clinicians;
- Irrespective of the patient's country of origin or ethnicity, the index or surveillance endoscopy must include staging of GIM by performing endoscopic and histopathological mapping (risk stratification);
- Only individuals with a high-risk GIM phenotype (i.e., corpus-extended GIM, OLGIM stages III/IV, moderate-severe GIM, incomplete GIM subtype, persistent refractory *H. pylori* infection, or first-degree family history of gastric cancer) merit regular surveillance, with a 3-year interval unless multiple risk factors are present.
- Individuals with focal GIM changes limited to the antrum and no other risk factors for gastric cancer, do not require ongoing endoscopic surveillance follow-up;
- *H. pylori* testing (and its eradication if present) is unanimously recommended.

How does this study affect research, practice or policy?

- Clinical recommendations and policies must include risk stratification of gastric cancer among individuals with GIM.
- There is an opportunity to enhance the research agenda in this field to better define: populations who warrant screening; the optimal method for endoscopic surveillance (e.g., endoscopic staging, use of image enhancement, etc), and the optimal interval for surveillance; development of noninvasive diagnostic and prognostic biomarkers for GIM; assessment of interventions beyond *H. pylori* eradication to prevent gastric cancer; management of GIM in specific situations (e.g., autoimmune gastritis without *H. pylori*, hereditary syndromes); among others.

Introduction

Gastric adenocarcinoma (GC) is a preventable cancer. Approximately 970,000 new GC cases and nearly 760,000 related fatalities occurred in 2022. The International Agency for Research on Cancer (IARC) projects that the number of new GC cases will increase to 1.8 million with an associated 1.3 million deaths by 2040 if the current trajectory is maintained, making it clear that primary and secondary prevention efforts are of utmost importance (1,2).

Helicobacter pylori (*H. pylori*) eradication, healthy dietary habits, and smoking cessation are mainstays for primary GC prevention. However, primary prevention alone is insufficient for successfully decreasing GC burden and mortality, and effective secondary and tertiary prevention through strategies for early diagnosis is imperative (3, 4). In the majority of cases, intestinal-type GC develops through a cascade of gastric preneoplastic mucosal changes before neoplastic progression occurs. Furthermore, early gastric cancer (i.e., prior to submucosal invasion) can be cured through endoscopic or surgical resection, whereas there are no curative options for advanced-stage diagnoses. The slow stepwise progression and the opportunity for curative resection of early lesions underlie the rationale and effectiveness of secondary and tertiary prevention for combatting GC burden and mortality. These key concepts can be extrapolated, in theory, to all countries that have the appropriate infrastructure, and this is reflected in international guidelines for gastric intestinal metaplasia (GIM) diagnosis and management.

The “Correa cascade” considers the occurrence of GC in a chronic state of mucosal inflammation, including the presence of atrophic changes and GIM. GIM in most cases occurs on a background of atrophy, although atrophic changes may not be clinically apparent in the setting of diffuse GIM (5). Conversely, atrophy may occur in the absence of GIM. Although moderate/severe gastric atrophy is also associated with an increased risk of GC, the endoscopic and histopathological staging and risk stratification for gastric atrophy as compared to GIM are subject to more interobserver, and even intra-observer, variability. Therefore, we have focused on guidance for GIM management as opposed to atrophy in the absence of confirmed GIM.

The prevalence of GIM when broadly considering all adults undergoing endoscopy with biopsies ranges from 5-30%, and is potentially even higher among individuals with additional risk factors (6,7) Despite this high prevalence and known association with GC, no specific guidelines existed for the management of GIM until 2012 and this was reflected by significant heterogeneity in clinical practice for GIM and low adherence to endoscopic surveillance and appropriate staging protocols.(8,9) To address this, scientific societies internationally independently evaluated the published literature according to predefined methodology (e.g., GRADE) to develop evidence-based guidance on the management of precancerous conditions, specifically GIM.

Currently, noninvasive biomarkers have not demonstrated sufficient, reproducible accuracy for GIM diagnosis. Endoscopy and histology thus remain the mainstay for diagnosis, surveillance, and staging of GIM. We hypothesize that the availability of multiple international guidelines with varying methodologies and presentation may confuse clinicians regarding GIM management, especially endoscopic surveillance, which invariably would impact clinical care.

We therefore conducted a systematic review and qualitative synthesis of all published and indexed evidence-based guidelines or expert consensus statements on GIM management, including which individuals should

receive screening for staging of the gastric mucosa for future risk determination; and which individuals should undergo GIM surveillance. This work primarily aims to provide clinicians worldwide with a comprehensive perspective, and secondarily to inform future guideline processes as well as the research agenda.

Methods

We performed a systematic review in PubMed on February 20th, 2024 with the following query: (guidelines OR statements OR consensus) AND (atrophy OR atrophic gastritis OR intestinal metaplasia OR precancerous OR premalignant OR preneoplasia OR dysplasia) AND (gastric OR stomach).

We limited the search to include publications between January 1 2010 and the search date. We also searched the complete list of references of the included articles and utilized experts' (authors) knowledge of other references to determine other guidelines that might have been missed during the electronic search. We included all guidelines and consensus statements that evaluated and discussed the diagnosis and management of GIM. Documents were considered "guidelines" or "consensus statements" as long as they were commissioned by an accredited international or national GI society (e.g. European Society for Gastrointestinal Endoscopy, American Gastroenterological Association) and described the methodological approach for delivering clinical recommendations or suggestions. We excluded documents that did not include GIM management. Hereafter, we use the term "guideline" to also encompass consensus statements and clinical practice updates, with differences in methodology acknowledged where appropriate.

From each guideline, the following information was abstracted and summarized:

- i) Scientific society(ies) supporting the guideline;
- ii) Year of publication and literature search dates;
- iii) Scope of the guideline (e.g., management of GIM only vs. other, e.g. *H. pylori* eradication);
- iv) Geographic region and population to which the guideline refers;
- v) Methodology (GRADE vs other);
- vi) Recommendations or discussions regarding upper gastrointestinal endoscopy (UGIE) screening for eligible populations to allow for the opportunistic identification of GC and/or gastric precancerous conditions (GIM);
- vii) Recommendations or suggestions regarding surveillance once GIM is diagnosed;
- viii) Recommended/suggested endoscopic surveillance intervals in those considered eligible for surveillance;
- ix) The recommended/suggested endoscopic approach (quality parameters) to optimize the detection of gastric precancer/cancer, and staging;
- x) The stated risk stratification parameters in patients with GIM, including histological staging systems, and respective definitions;
- xi) Recommendations/suggestions regarding potential therapeutic interventions for GC prevention once GIM is diagnosed (e.g., *H. pylori* testing / eradication; lifestyle modifications).

Intentionally, at least one author from each of the geographic regions encompassed was asked to co-author this manuscript. Each author was asked to critically review the summary for inconsistencies concerning their

region's published guidelines. The topics of endoscopic and histological diagnosis and staging of GIM are extensively described in prior literature and are not the focus of the article. An in-depth discussion of quality metrics in UGIE and population-based screening of GC and precancerous conditions is outside of the scope of this article, apart from identifying whether these aspects are included in international guidelines and summarizing the respective recommendations and guidance.

Results

A. Literature Search

The systematic literature search yielded 426 manuscripts, of which 411 were excluded based on title and abstract screening. No additional articles were identified through manual review of the references, and one was identified through co-authors' expert knowledge (16). A total of 16 articles met eligibility criteria and were included in this qualitative review (10-25).

Seven of these 16 articles were from Europe, 5 were from the Americas (three from the USA, two from Latin America), and 4 were from the Asia-Pacific region (one from China, two from Japan, one from Taiwan). The 2012 and 2019 update of the European Society of Gastrointestinal Endoscopy (ESGE)/ European Helicobacter and Microbiota Study Group (EHMSG)/ European Society of Pathology (ESP) guidelines (MAPS I and MAPS II, respectively), the British Society of Gastroenterology (BSG) guidelines (2019), Italian (2019), Asociación Española de Gastroenterología/Sociedad Española de Endoscopia Digestiva and Sociedad Española de Anatomía Patológica (2021), Asociación Chilena de Endoscopia Digestiva/Sociedad Chilena de Gastroenterología (ACHED) (2014), American Gastroenterology Association (AGA) guidelines (2019), American Society of Gastrointestinal Endoscopy (ASGE, 2015), and Chinese guidelines (2023) were specifically dedicated to precancerous conditions including GIM management; whereas *H. pylori* management was the focus of Maastricht guidelines, Taipei, Kyoto, Brazilian, and the Japan Gastroenterological Endoscopy Society (JGES) guidelines, there were also statements/recommendations on GIM management. The Italian and Spanish guidelines are not adaptations of MAPS I and/or II, which is why they are considered separately in this review. The AGA Clinical Practice Update published in 2021 focuses on atrophic gastritis as a precancerous condition but provides guidance on GIM management including surveillance and is therefore included. All included guidelines used either GRADE methodology or a consensus approach. Nearly all the guidelines primarily addressing the management of precancerous conditions used GRADE methodology, with the exception of the Chinese Society of Gastroenterology (CSG), Cancer Collaboration Group of Chinese Society of Gastroenterology / Chinese Medical Association (CMA) guidelines, which used a consensus approach; by contrast, those that included GIM management as a secondary focus more often used a consensus approach (See Table 1). That said, the overall clinical guidance regarding GIM management did not differ substantially based on the robustness of the methodology (i.e., GRADE vs consensus).

B. Opportunistic detection of GIM during screening or diagnostic endoscopy

GIM is typically asymptomatic and can only be detected endoscopically as currently available noninvasive biomarkers have not demonstrated reliable accuracy for the diagnosis. Thus opportunities to diagnose GIM are either via screening UGIE in asymptomatic individuals (i.e., opportunistic detection) or via diagnostic UGIE in individuals with a clinical indication for endoscopy. None of the international guidelines recommend

screening for GIM per se; instead, screening is for early detection of GC. Some guidelines do, though, make clear statements that all endoscopies must include an assessment for the presence of precancerous changes, namely GIM. Many guidelines are aligned in the recommendation that a high-quality endoscopic exam with virtual (e.g., NBI, LCI, BLI) or conventional chromoendoscopy and endoscopic biopsies should be performed to enhance the endoscopic detection of GIM. One exception is the Japanese guideline which does not recommend gastric biopsies, instead relying solely on endoscopic detection and staging (see below). For those individuals diagnosed with GIM, many but not all guidelines also recommend the use of histologic staging systems, primarily OLGIM, and histologic subtyping of GIM given the implications for risk stratification (see below) – Table 2.

Guidelines that include opportunistic detection through endoscopic screening. As of this writing, the Japanese guideline, the Spanish guideline, the British guideline, and the Maastricht guideline offer recommendations regarding true population-based screening for GC. In Japan, references to GC risk stratification and potential non-invasive approaches are named. The Spanish guidelines recommend against the routine use of UGIE for GC screening in the general Spanish population given the low GC incidence overall, and suggest screening only for those with a family history of GC. This is similar to the recommendations of the German guideline and the Maastricht guideline. The Maastricht guideline, which is focused on *H. pylori* diagnosis and management, recommends that endoscopy with gastric biopsies be performed in asymptomatic individuals with a family history of GC starting at age 45 years and older. Neither the Spanish nor Maastricht guidelines call out other high-risk groups (e.g., early-generation immigrants from countries where GC is endemic). The 2019 British guidelines state there is insufficient evidence to support endoscopic screening in the overall low-risk UK population, but do provide a weak recommendation that UGIE screening with biopsies should be considered for individuals aged ≥ 50 years old with multiple risk factors for GC, notably rating the quality of evidence as low but achieving 100% consensus agreement. The Chilean guidelines stipulate that age ≥ 40 years old is sufficient for endoscopic screening for GC and its precancerous conditions considering that Chile is a high GC incidence country; however, the Chilean guidelines list an additional criterion that patients have at least one other clinical indication for endoscopy (e.g., abdominal pain) and thus, this cannot be considered true population-based screening. The Italian guideline recommends that a family history of GC and long-term PPI use warrants offering UGIE screening for precancerous conditions; clearly, though, many individuals warranting long-term PPI use may qualify for a diagnostic as opposed to a screening endoscopy. The ASGE guidelines on GIM management do not include recommendations on GC screening, but a separate document on race and ethnic considerations in UGIE more broadly mentions that endoscopic GC screening may be considered in certain high-risk populations in the US (e.g., immigrants from high-risk regions, first-degree family history) starting at age 40 years old; no other guidance, such as mucosal staging protocol nor subsequent intervals, is provided (26).

Guidelines that include opportunistic GIM detection through diagnostic endoscopy. The 2012 MAPS I guideline states that for *H. pylori* diagnosis and gastric mucosal staging, gastric samples from the antrum and corpus

should be obtained during a diagnostic upper endoscopy. This recommendation was reiterated and refined in the updated 2019 MAPS II guideline. It mandated that all first-time diagnostic endoscopies include gastric antrum and corpus biopsies, without mention of whether this is necessary for patients who have been noninvasively tested for *H. pylori* already or who are otherwise considered low-risk for GC. Similar to MAPS I/II, the Chinese guidelines recommend biopsies from the antrum and corpus to diagnose *H. pylori* and stage the gastric mucosa to determine the need for ongoing surveillance. The 2020 Japanese guidelines recommend endoscopic risk stratification using Kimura-Takemoto classification or virtual chromoendoscopy of GIM since advanced precancerous changes including GIM can be reliably detected endoscopically (27).

Guidelines that do not address opportunistic detection of GIM. The AGA guideline does not address endoscopic screening nor opportunistic detection during a diagnostic endoscopy for a non-screening indication. Instead, the document provides recommendations for the management of patients with already confirmed GIM, which is most often identified incidentally in the USA. The AGA guidelines acknowledge risk factors for GC, such as specific races and ethnicities, early-generation immigrant groups, and family history of GC, where an individualized approach may be considered.

In summary, there is high heterogeneity among guidelines regarding recommendations on the use of endoscopy for GC screening or opportunistic detection of GIM. It seems reasonable to consider that the index or surveillance endoscopy must include staging of GIM, if present. Revised or updated guidelines may consider clarifying these recommendations.

B. Individuals with established GIM diagnosis: surveillance vs no surveillance

All guidelines are aligned regarding the need to risk stratify patients with GIM to determine their need for ongoing surveillance, as well as in mandating *H. pylori* eradication if present.

All guidelines agree that patients with GIM are considered to have a high-risk phenotype if GIM affects both the gastric antrum (+/-incisura) and corpus (corpus-extended GIM), if there is moderate-severe GIM staged using OLGIM (i.e., OLGIM III/IV), if GIM is of the incomplete subtype (vs. complete subtype), and if there is a family history of GC in a first-degree relative. These are all factors consistently highlighted in the literature as the most important predictors of progression and may be used to identify individuals at the highest risk of GC, with most guidelines distinctly prioritizing histologic staging.

According to most guidelines, the presence of any high-risk phenotype is sufficient to identify those patients with GIM who merit surveillance. In contrast, the Spanish guidelines recommend surveillance for extensive GIM if at least one other risk factor, e.g. incomplete type or family history of GC, is present.

All guidelines are also aligned in their recommendations that patients with a low-risk GIM phenotype, which is substantially more common than the high-risk phenotype, do not require ongoing endoscopic surveillance. Most guidelines agree that the presence of antrum-limited GIM that is non-severe (OLGIM I-II) may not warrant surveillance, assuming adequate staging metrics during the index gastroscopy and the absence of high-risk qualifiers, including persistent *H. pylori* infection, incomplete GIM subtype, and family history of GC in a first-degree relative. However, factors such as tobacco smoking and dietary factors, which are associated with GC, are not fully accounted for as risk stratification metrics. In patients with limited, mild GIM but with additional risk factors for gastric cancer (e.g., family history or high-risk race/ethnicity), MAPS II, BSG, China, Chilean and the AGA guidelines recommend endoscopic surveillance, whereas this is not mentioned in the Japanese, Taipei and Brazilian guidelines. However, the Japanese guideline recommends surveillance regardless of the extent of GIM because of the high GC incidence in the population and the relative availability of endoscopy.

Most guidelines do not provide guidance on how to properly risk stratify patients if information is missing. For example, if patients have insufficient biopsies (e.g., only antrum) then complete histological staging is not possible. That said, the AGA guidelines, MAPS I/II, and the Spanish guidelines do provide guidance on short-interval endoscopy (<12 months) for risk stratification purposes if the quality of the initial exam is questionable.

In summary, advanced stages of GIM (i.e GIM affecting both the gastric antrum (+/-incisura) and corpus (corpus-extended GIM), if there is moderate-severe GIM staged using OLGIM (i.e., OLGIM III/IV) or if the GIM is of the incomplete subtype) are considered the phenotype of interest for endoscopic surveillance to detect early neoplasia, whereas low-risk GIM phenotypes generally do not warrant surveillance in the absence of additional risk factors for advanced gastric neoplasia.

C. Approach to endoscopic surveillance

When surveillance is recommended, all guidelines recommend endoscopy as the only acceptable modality given the insufficient performance of currently available noninvasive biomarkers and biomarker panels. Few guidelines detail upper endoscopy quality metrics—e.g., mucosal cleansing protocol, visualization technique (high-definition white light +/- virtual or conventional chromoendoscopy), photodocumentation, or withdrawal time—within the guideline document, except for the BSG guidelines. Most guidelines do provide suggestions for the biopsy protocol, albeit with heterogeneity. Most guidelines suggest that biopsies from the antrum/incisura and corpus be obtained separately following a systematic protocol (5) to allow for histological staging, while targeted biopsies should also be obtained separately for lesions suspicious for advanced pathology. However, MAPS II states that the benefit of performing biopsies in patients under surveillance is not established, and biopsies should only be performed if any irregular area / suspicious lesion is identified.

Figure 1 summarizes these approaches. Some guidelines have accompanying articles (e.g., AGA, Spanish society) that detail quality metrics in upper endoscopy with specific sections on best practices for the detection and surveillance of preneoplastic conditions (28,29).

In summary, practice guidelines vary with respect to details and approach to the endoscopic surveillance exam.

D. Surveillance intervals

While there is generally agreement regarding who warrants surveillance, there is notable heterogeneity regarding recommended surveillance intervals. Surveillance every 3 years for patients with any high-risk GIM phenotype is the most commonly recommended (7 out of 16 guidelines) (see Figure 2). If there is a family history of GC in a first-degree relative, MAPS II, the BSG, and the Chinese guidelines suggest a shorter interval to be considered; whereas, the Chilean, Brazilian, Japanese and Taiwanese guidelines also suggest an interval shorter than 3 years to be considered, but additional criteria for who qualifies for the shortened interval are not provided.

The AGA, on the other hand, recommends that an up to 5-year surveillance interval may also be acceptable, but no additional information regarding who might qualify for this extended interval is provided; notably, the AGA Clinical Practice Update advocates for a 3-year interval in individuals with advanced atrophic gastritis with or without GIM.

In summary, international guidelines vary with respect to evidence-based guidance regarding appropriate endoscopic surveillance intervals among individuals with GIM enrolled in surveillance. Surveillance is generally suggested every 3 years, but the South American and Asian guidelines favor a lower threshold for more intensive surveillance in patients with additional risk factors, while the US guidelines allow for potentially longer intervals.

E. Non-endoscopic therapeutic interventions

Other than surveillance, there is no definitive endoscopic management for GIM in the absence of visible neoplastic lesions. The mainstay non-endoscopic interventions for patients with GIM is testing for *H. pylori* infection either through histology or other noninvasive non-serological methods, and confirming eradication after treatment in those who are positive; this is a strong recommendation in all guidelines. GIM can progress even once *H. pylori* is successfully eradicated, and this fact is acknowledged in most guidelines.

There is more heterogeneity regarding non-endoscopic non-*H. pylori* interventions in patients with GIM for GC risk/mortality reduction. MAPS II and the Chinese guidelines suggest offering low-dose aspirin to patients at higher risk of GC who also have a cardiovascular indication, whereas the German guidelines advise against the use of aspirin if the sole indication is GC prevention. The Chinese recommendations also refer to the supplementation of certain vitamins/minerals, including selenium and folate, and garlic. The Maastricht guidelines state that medical and special dietary chemoprevention cannot be recommended in patients with severe GIM (or severe atrophy) post-*H. pylori* eradication in the absence of sufficient evidence for benefit. None of the other guidelines offered guidance for any other noninvasive interventions for individuals with GIM.

F. Specific situations

Management of individuals with GIM in special situations, e.g., post-partial gastrectomy and hereditary syndromes (e.g. Lynch syndrome, Familial Adenomatous Polyposis) is not addressed in general. Many guidelines offer limited guidance for patients with autoimmune gastritis diagnosed with GIM and patients diagnosed with gastric neoplasia (dysplasia/GC); a full discussion of which is beyond the scope of this document.

Discussion

Reducing the global burden of GC is a shared goal worldwide. Most GCs have precursor conditions and lesions that can be detected endoscopically and histologically, which facilitates opportunities for prevention and curative resection of early GC. Population-based screening for GC is not recommended outside of a few East Asian countries (30). That said, several international societies including from Europe and the Americas acknowledge the potential impact of *targeted* screening for high-risk groups, albeit with varying definitions of what qualifies as “high-risk”, which most certainly reflects the limited literature. Current studies are conducted to determine the role of endoscopy and other measures for screening in Europe (e.g. Towards Gastric Cancer Screening Implementation in the European Union (TOGAS EU4H–2022–PJ–01)). Endoscopic screening for early GC detection and prevention (e.g., resection of dysplasia) must be balanced with the fact that endoscopy in most countries is a limited resource, is costly, invasive, inconvenient for patients, and poses small but measurable risk.

GIM is a defined precancerous condition that is amenable to surveillance for early GC detection. However, most patients with GIM are at low risk of progression and the risk/burden of endoscopy likely outweighs the theoretical benefit of detecting early neoplasia in these patients. Accordingly, clinicians must be equipped with clear evidence-based guidance to ensure that resources are appropriately allocated to patients with GIM who are high-risk while minimizing the burden and potentially unnecessary anxiety among patients with GIM who are low-risk. Furthermore, there is a push to maximize the sustainability of endoscopy for cancer prevention by optimizing the populations for which it is recommended, and ensuring each exam generates the highest-quality information to minimize unnecessary repeat procedures (31,32). The presence of GIM, along with the determination of a high vs. low-risk phenotype, is the most consistent marker for GC risk, and thus appropriate endoscopic surveillance and adjunct therapeutic interventions (e.g., *H. pylori* eradication, smoking cessation) allow an invaluable opportunity for efficient secondary prevention of GC. For these reasons, we aimed to generate a document that summarizes and compares the currently published guidelines and consensus documents on GIM management.

We conclude that **international guidelines are aligned in two main recommendations regarding 1) the need for risk-stratified surveillance (as opposed to universal surveillance) and 2) mandatory *H. pylori* eradication in patients with GIM.** Otherwise, there was heterogeneity regarding recommendations for opportunistic detection of GIM during UGIE, the execution of risk stratification (i.e., use of histological staging systems such as OLGIM), the approach to the endoscopic exam with respect to defined quality metrics and gastric sampling protocols, surveillance intervals, and adjunctive modalities for noninvasive interventions for GC risk reduction in patients with GIM (e.g., chemoprevention agents apart from *H. pylori* eradication; diet modifications and supplementation). This heterogeneity reflects the current gaps in evidence and lack of robust, high-quality data, as well as the heterogeneity of the populations served by each of the guidelines. Indeed, it is expected that guidelines serving high-GC incidence populations (e.g., Latin America, Asia-Pacific)

may favor a stricter approach, for example shorter endoscopic intervals, while those serving low-GC incidence populations may favor a less aggressive approach. However, this may not be appropriate particularly given that there are no compelling data to support clinicians changing their practice of surveillance according to their country of practice or patient ethnicity independent of other risk parameters (33).

Certainly, the prevalence of gastric precancerous conditions, and likewise GC, is higher in certain populations based on country of origin and ethnicity, and the risk of developing GC overall (and mortality) is higher in early-generation immigrants from high GC to low GC regions (34-35). However, among individuals already diagnosed with precancerous conditions the risk of progression to GC is independent of the country of origin and ethnicity (33), meaning that other factors (e.g., GIM subtype, persistent *H. pylori*, family history) should be used to determine the need and intervals for surveillance. Thus, the variations in recommendations, especially regarding the surveillance interval, across international guidelines may relate to perceived risk of progression but lacks strong evidence. For example, the Chilean guidelines recommend a 1-year surveillance interval in patients with OLGIM III/IV, whereas the Spanish guidelines recommend surveillance only if there is at least one additional risk factor for progression (e.g., family history of GC), and the AGA suggests that up to a 5-year interval may be appropriate.

Other nuances when considering recommendations for GIM management in the context of each guideline and the population served relate to the respective healthcare infrastructure and resource availability, age of the population, as well as cultural, lifestyle, and dietary practices. The training of the clinical providers including the endoscopists and pathologists and their familiarity with GIM detection and staging is also of relevance. For example, broadly speaking, endoscopists in the USA have lower familiarity with GIM detection and endoscopic staging vs endoscopists from high GC incidence countries, particularly Japan and South Korea where routine population-based screening occurs. In the USA, histological staging with OLGIM and GIM subtyping are not routine practice, particularly compared to many European and Latin American countries. The primary benefit of endoscopic surveillance is the opportunity for early detection of neoplasia and curative resection, which has substantial implications for GC mortality reduction. However, the success of endoscopic surveillance hinges on the accurate detection of precancerous and cancerous lesions. Considering that the endoscopic miss rate for early GC based on a meta-analysis is approximately 10%, and may be higher in less experienced hands, interventions are needed to improve and standardize the endoscopic surveillance exam. To this end, few guidelines stipulated quality metrics that must be achieved to qualify as a high-quality upper endoscopic exam, although the importance of such metrics is becoming increasingly appreciated. In 2024, the AGA published its first consensus report providing 'best practice advice' statements for how to perform a high-quality upper GI endoscopy and included metrics specific for the GIM surveillance exam, which complements the AGA guideline on GIM management published in 2020 (28). Similarly, the Spanish GI society also published a supplemental document on quality metrics in upper endoscopy to accompany the guideline, which lacked such metrics (. The ESGE addresses appropriate biopsy sampling according to MAPS guidelines as a quality criterion together with others to define the quality of an upper endoscopy (29,32).

Accurate endoscopic and histological staging of GIM is critical, as this is a primary determinant for the branchpoint of whether or not to recommend endoscopic surveillance. While there was consistency regarding which factors (e.g., OLGIM III/IV, incomplete GIM subtype, anatomic extension) constitute a high-risk phenotype, there was heterogeneity regarding which metrics are routinely recommended. For example, in the USA, there is no guideline recommendation for pathologists to perform OLGIM staging or to report the histologic subtype when GIM is present, and therefore this information is rarely available for clinical decision-making. In addition, there was heterogeneity regarding the 'weight' of each risk stratification parameter. Family history and OLGIM III/IV generally hold the most weight and in some guidelines warrant a shorter than 3-year surveillance interval; however, other guidelines, such as the Spanish guidelines, recommended surveillance in patients with extensive GIM *only if* additional risk factors are present (e.g., incomplete GIM, family history of GIM), or if there was a prior or current history of gastric neoplasia. This heterogeneity stems both from the lack of robust evidence, as no randomized clinical trials exist, and from the diverse classifications that determine the presence of this phenotype (36-38). More robust and precise risk stratification markers (e.g., tissue-based markers) could improve risk stratification and, ideally, consistency across guidelines.

Fortunately, most people with GIM who originate from low GC-risk countries fall into an overall low-risk phenotype and may not warrant or benefit from endoscopic surveillance; accordingly, most guidelines are aligned in the recommendation against surveillance in patients with low-risk GIM phenotype. The two exceptions are the Chilean and Japanese guidelines, which recommend that all individuals with GIM should be surveilled once diagnosed. This universal recommendation reflects the high GC incidence and mortality in these countries and the acknowledgment that mild antrum-limited GIM still does carry some, albeit very low, level of elevated GC risk; however, the sustainability of such an approach has been called into question given that endoscopy is a limited and costly resource. Among patients with GIM, GIM is extensive in 7-25% based on studies from low GC incidence countries and 16-26% based on studies from high-incidence areas (5,39-40). The true prevalence of incomplete GIM vs. complete GIM (vs. mixed) is not known and studies are highly variable in their reporting; that said, incomplete GIM is more common in patients with extensive GIM and prior or current *H. pylori* infection. Notably, all of the guidelines that mention histological subtyping of GIM consider the presence of incomplete GIM as sufficient for categorizing someone as high-risk and warranting endoscopic surveillance, yet the merits of this classification are based solely on observational studies (and meta-analyses of these studies) that are subject to bias, although studies consistently demonstrate several-fold higher risk of GC compared to patients with complete-type GIM only.

Unmet needs. Randomized trials on GC screening, gastric precancer surveillance, and intervention strategies are lacking, and this stands in stark contrast to colorectal cancer screening and post-polypectomy colonoscopy surveillance, as well as esophageal adenocarcinoma screening and Barrett's esophagus surveillance. Generating robust evidence is a critical unmet need, particularly as it relates to endoscopic

surveillance intervals and developing, validating and positioning risk stratification metrics with high discrimination values. Specific research priority areas include noninvasive and also tissue-based biomarkers for diagnosis, staging, and prognosis, of GIM the improved uptake and consistency of adherence to guidelines, the development of quality metrics linked to patient-specific outcomes (e.g., gastric neoplasia detection rate), leveraging non-invasive therapeutic interventions for halting or reversing GIM progression (e.g., diet modifications; chemoprevention) apart from *H. pylori* eradication, leveraging newer technologies such as artificial intelligence and image-enhanced endoscopy to improve the detection of gastric preneoplasia/neoplasia, and specific guidance regarding GIM management in special situations such as hereditary syndromes, post-surgical stomach, after endoscopic resection of neoplasia, and in autoimmune gastritis.

This is the first systematic review of all position statements regarding GIM. At the time of this writing, new guidelines are being updated or developed in the USA, Germany, and by ESGE (MAPS III), but are not yet publicly available. Reassuringly, GIM guidelines have demonstrated increased uptake in clinical practice during the last decade. For example, retrospective studies from the USA (41), reported that *H. pylori* diagnosis, multiple biopsies, and the recommendation for surveillance significantly increased among US doctors following the 2019 AGA guideline. Also, in Europe, the ESGE considered biopsy sampling according to the so-called MAPS protocol as a minor but relevant quality parameter (32).

In conclusion, irrespective of the country of origin when performing an UGIE, the best care must include staging of GIM by performing histopathological mapping. In most guidelines, only individuals at a higher risk (corpus extended GIM, OLGIM stages III/IV, incomplete GIM subtype, persistent *H. pylori* infection, or first-degree family history of gastric cancer) merit regular surveillance at a 3-year interval if no concurrent risk factors are present. Importantly, the most common group, those individuals with focal GIM changes limited to the antrum and no other risk factors for GC, do not require follow-up in most cases, but there are exceptions. *H. pylori* testing (and its eradication if present) is unanimously recommended and should be synergistically suggested for primary prevention of GC.

Contributoship

MDR, SS and EEO developed the protocol, conducted the review, and revised the final draft of the manuscript. All the authors collected data, provided input for the protocol and revise the draft of the manuscript, approving the final version. MDR, SS and EEO are the guarantors.

Conflicts of Interest

No conflicts of interest are declared by Mário Dinis-Ribeiro, Shailja Shah, Hashem B El-Serag, Matthew Banks, Noriya Uedo, Hisao Tajiri, Luiz G Coelho, Diogo Libanio, Edith Lahner, Antonio Rollan, Jing-Yuan Fang, Leticia Moreira, Jan Bornschein, Ernst J Kuipers, Emad El-Omar. Peter Malfertheiner is a member of advisory board/lecturer of Aboca, Alfasiigma, Allergosan, Bayer, Biocodex, Menarini advisory boards/lectures.

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This manuscript did not involve animal experiences or patients' data or interventions.

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Figure Legends

Figure 1 – Synthesis of most commonly accepted biopsies protocols according to endoscopic findings. In the presence of GIM, targeted biopsies should be performed; whereas in its absence, random biopsies in antrum and corpus are acceptable (with the incisura angularis biopsy being optimal but optional (5)).

Figure 2 – Algorithm synthesizing the major recommendations for managing individuals with GIM according to country of origin when applicable. Both ESGE guidelines, and three US guidance documents are included (two AGA, one ASGE). **Patients with gastric cancer should still have endoscopic and histologic staging of the surrounding mucosa for additional risk stratification

Table 1 – Description of included guidelines and consensus documents according to their main purpose/scope and geographic region

Purpose/scope	Year of publication (search period)	Region	Society/ies supporting	Methodology utilized
Dedicated to precancerous conditions including GIM				
MAPS I (10), MAPSII (11)	2012, 2019 (March 2018)	Europe	ESGE, EHMSG, ESP	GRADE
UK (12)	2019 (Feb 2019)	Europe	BSG	GRADE
Italian (13)	2019 (Feb 2019)	Europe	AIGO, SIED, SIGE, SIMI	GRADE
USA (14,15,16)	2015, 2019, 2021 (March 2014, Sept 2018, March 2021)	North America	AGA, ASGE	GRADE (14,16) / Consensus (15)
Chile (17)	2014 (2013)	South America	ACHED, SCHG	GRADE
China (18)	2023 (December 2022)	Asia	CSG (Cancer Col Group), CMA	Consensus
Gastric cancer screening				
German (19)	2019 (March 2017)	Europe	DGVS	Oxford
Spain (20)	2021 (July 2019)	Europe	AEG, SEED, SEAP	GRADE
Japan (21)	2020 (Feb 2017)	Asia	JGES	GRADE
<i>H. pylori</i>				
Maastricht VI (22)	2022 (Dec 2020)	International	EHMSG	Consensus
Kyoto (23)	2015 (Dec 2013)	International	None	Consensus
Taipei (24)	2020 (July 2019)	Asia	APAHAM	Consensus
Brazil (25)	2018 (March 2017)	South America	NBEHPM	Consensus

ESGE (European Society of Gastrointestinal Endoscopy), EHMSG (European Helicobacter Microbiota Study Group), ESP (European Society of Pathology), BSG (British Society of Gastroenterology), AIGO (Society of Hospital Gastroenterologists and Digestive Endoscopists), SIED (Italian Society of Digestive Endoscopy), SIGE (Italian Society of Gastroenterology), SIMI (Italian Society of Internal Medicine), AGA (American Gastroenterology Association), ACHED (Asociacion Chilena de Endoscopia Digestiva), SCHG (Sociedad Chilena de Gastroenterología CSG (Chinese Society of Gastroenterology, Cancer Collaboration Group of Chinese Society of Gastroenterology), CMA (Chinese Medical Association), DGVS (...), JGES (Japanese Gastroenterological Endoscopy Society), AEG (Asociación Española de Gastroenterología), SEED (Sociedad Española de Endoscopia Digestiva), SEAP (Sociedad Española de Anatomía Patológica), APAHAM (Asian Pacific Alliance on Helicobacter and Microbiota, NBEHPM (Brazilian Nucleus for the Study of Helicobacter pylori and Microbiota)

Table 2 – Recommendations for opportunistic diagnosis, surveillance and therapeutic interventions in individuals with GIM according to the diverse guidelines/consensus and their scope and region

Name of guideline	Opportunistic endoscopic diagnosis	Surveillance recommended? (interval, method)				Therapy?	
		<i>Corpus extended GIM or OLGIMIII/IV</i>	<i>Incomplete GIM</i>	<i>Family history</i>	<i>Mild GIM only in antrum AND no other factors</i>	Hp	Other
Dedicated to precancerous conditions including GIM							
MAPS I (10), MAPSII (11)	NA but implicit (using HQ endoscopy including virtual chromoendoscopy; OLGIM or extension for histological staging)	Yes, 3 y UGIE + targeted biopsies	Yes (in MAPSII) 3 y UGIE + targeted biopsies	Yes 1-2 y (according to the GIM stage) UGIE + targeted biopsies	No	Yes	Low dose aspirin ?
UK (12)	Yes (using HQ endoscopy including virtual chromoendoscopy; OLGIM or extension for histological staging) In high-risk individuals (defined as age ≥ 50 with multiple risk factors for GC, e.g., male, smokers, pernicious anemia, first-degree family history of GC);	Yes 3 y UGIE + targeted biopsies	Yes 3 y UGIE + targeted biopsies	Yes 1-3 y (according to the GIM stage) UGIE + targeted biopsies	No	Yes	No
Italy (13)	Yes (using HQ endoscopy including virtual chromoendoscopy; OLGIM or extension for histological staging) In high-risk individuals (defined as family history of GC, long-term PPI use, anemia, long-standing dyspepsia)	Yes 3 y UGIE + biopsies	Yes 3 y UGIE + biopsies	Yes 3 y UGIE + biopsies	No	Yes	NA

USA (13,14,16)	Yes (using HQ endoscopy including virtual chromoendoscopy; OLGIM or extension for histological staging) The ASGE comments that endoscopic screening may be considered in 1 st generation US immigrants from high-risk regions aged ≥40 years, particularly if there is a first-degree family history of GC (26)	Yes 3-5 y UGIE + biopsies	Yes 3-5 y UGIE + biopsies	Yes no specific interval UGIE + biopsies	No	Yes	NA
Chile (17)	Yes (using HQ endoscopy including virtual chromoendoscopy; OLGIM or extension used for histological staging) In individuals with family history of GC, or aged > 40 years with abdominal pain	Yes 1 y UGIE + biopsies	NA	Yes 5 years UGIE + biopsies	Yes 3 y UGIE + biopsies	Yes	NA
China (18)	NA but implicit using HQ endoscopy including virtual chromoendoscopy; OLGIM or extension used for histological staging	Yes 3 y UGIE + targeted biopsies	Yes 3 y UGIE + targeted biopsies	Yes 3 y UGIE + targeted biopsies	No	Yes	Vitamins, selenium, garlic, folate; Low-dose aspirin?
Gastric cancer screening							
Germany (19)	NA but implicit	Yes 3 y UGIE + biopsies	Not included	Yes no specific interval	No	Yes	NA
Spain (20)	Yes (using HQ endoscopy including virtual chromoendoscopy; OLGIM	Yes 3y ONLY if incomplete IM or family history	Yes 3y if OLGIM III/IV UGIE + biopsies	Yes 3y UGIE + biopsies	No	Yes	No

	or extension used for histological staging) In high-risk individuals with family history aged > 40 years	UGIE + biopsies					
Japan (21)	Yes (using HQ endoscopy including virtual chromoendoscopy and endoscopic staging only)	Yes 1-3 y UGIE no reference to biopsies	Not included	Not addressed	Yes	Yes	No
<i>H. pylori</i>							
Maastricht VI (22)	NA but implicit	Yes 3 y UGIE + biopsies	NC	NA	No	Yes	No
Kyoto (23)	NA but implicit	Yes no interval specified UGIE + biopsies	NC	NA	No	Yes	NA
Taipei (24)	NA but implicit	Yes 2-3 y UGIE + biopsies	NC	NA	No	Yes	NA
Brazilian (25)	NA but implicit	Yes 2 y UGIE + biopsies	NC	NA	No	Yes	NA

UGIE – upper gastrointestinal endoscopy, GC – Gastric cancer; Hp – *H. pylori*; HQ – high quality; NA – not addressed; NC – Not considered