Gastroenterology 2020;158:693–702

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia

Samir Gupta,[1,2] Dan Li,[3,4] Hashem B. El Serag,[5] Perica Davitkov,[6,7] Osama Altayar,[8] Shahnaz Sultan,[9] Yngve Falck-Ytter,[10,11] and Reem A. Mustafa[12]

[1]Department of Veterans Affairs San Diego Healthcare System, San Diego, California; [2]Division of Gastroenterology and the Moores Cancer Center, University of California San Diego, La Jolla, California; [3]Department of Gastroenterology, Kaiser Permanente Santa Clara Medical Center, Santa Clara, California; [4]Division of Research, Kaiser Permanente Northern California, Oakland, California; [5]Department of Medicine, Baylor College of Medicine, Houston, Texas; [6]Veterans Administration, Northeast Ohio Healthcare System, Cleveland, Ohio; [7]Case Western Reserve University School of Medicine, Cleveland, Ohio; [8]Division of Gastroenterology, Washington University School of Medicine, St Louis, Missouri; [9]Minneapolis Veterans Affairs Healthcare System, University of Minnesota, Minneapolis, Minnesota; [10]Department of Veterans Affairs Cleveland Medical Center, Cleveland, Ohio; [11]Case Western Reserve University, Cleveland, Ohio; [12]Department of Internal Medicine, University of Kansas Medical Center, Kansas

See editorial on page 473.

Gastric cancer is the third leading cause of cancer death worldwide.[1] In 2018, 1,033,701 incident cases were diagnosed globally,[1] including 26,240 nationally in the United States.[2] The majority of gastric cancers in the United States are non-cardia gastric cancers, arising from the antrum, incisura, body, and/or fundus.[3] Chronic infection with *Helicobacter pylori* is the primary risk factor for (intestinal-type) non-cardia gastric cancer, with at least 80% of the global gastric cancer burden attributable to this pathogen.[4] Non-cardia intestinal-type cancer, the most common histologic subtype of gastric cancer, has been shown to follow a pattern of stepwise progression (ie, the Correa cascade), from normal mucosa to non-atrophic gastritis to atrophic gastritis to intestinal metaplasia to gastric adenocarcinoma.[5] Ability to identify precursor lesions on gastric biopsies has led to interest in developing screening and surveillance strategies for early detection and prevention of gastric cancer. In East Asia, population-based screening programs have been implemented in countries with particularly high gastric cancer incidence and mortality, such as Japan and Korea. These programs have resulted in higher detection rates of early gastric cancer, with substantially reduced mortality.[6,7] In low-incidence countries, such as the United States, population-wide screening has not been endorsed. However, interest remains in determining whether screening and surveillance targeted to specific populations based on histologic risk factors, race/ethnicity, immigration from countries with high gastric cancer incidence, and other factors may be warranted.

Gastric intestinal metaplasia (GIM) may represent the histologic step just before development of dysplasia. GIM has been considered as one specific marker to identify patients who might benefit from surveillance because it has been associated with increased risk for gastric cancer and is routinely encountered in clinical practice.[5] Surveys of US endoscopists have found wide variation in practice patterns in the management of GIM, even among physicians regularly caring for populations that could be at increased risk based on race/ethnicity and/or immigration status.[8] An evidence-based guideline supported by a comprehensive literature review for management of patients with GIM has not been previously published in the United States. Accordingly, we aimed to develop evidence-based guidelines to inform management of patients with GIM incidentally detected on gastric biopsies in routine clinical practice. A reader's understanding of this guideline will be optimized and enhanced by reading the accompanying 2 technical reviews (TRs), which provide an overview and synthesis of the evidence used to inform this guideline.[9,10]

Scope, Target Audience, and Definitions

This guideline focuses on recommendations for management of patients with GIM detected as part of routine upper endoscopy for reasons including workup of endoscopically identified gastropathy/presumed gastritis, dyspepsia, or exclusion of *H pylori*. Screening for gastric cancer (either population-wide or in select populations) and management of patients with dysplasia of the gastric mucosa, gastric adenocarcinoma, and/or autoimmune gastritis are beyond the scope of the current guideline. This guideline is intended to aid decision-making for patients who are undergoing upper endoscopy in North America. GIM is

Abbreviations used in this paper: **AGA, American Gastroenterological Association; ASGE, American Society of Gastrointestinal Endoscopy; CI, confidence interval; ESGE, European Society of Gastrointestinal Endoscopy; GIM, gastric intestinal metaplasia; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PICO, population, intervention, comparator, and outcome; RR, relative risk; TR, technical review.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.12.003

linked mainly to risk for non-cardia gastric cancer. For ease of presentation, we refer to non-cardia gastric cancer as "gastric cancer" throughout this article.

Methods

The steps undertaken in the development of this guideline were guided by the AGA guideline development process, which has been outlined elsewhere.[11] Briefly, the AGA process for developing clinical practice guidelines incorporates the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[11] and best practices, as outlined by the Academy of Medicine, formerly Institute of Medicine.[12]

Guideline Panel Composition, Funding, and Conflict of Interest

The guideline panel included gastroenterologists (S.G., D.L., and H.E.), guideline methodologist trainees (P.D. and O.A.), and GRADE experts (S.S., Y.F.Y., and R.A.M.). The guideline panel worked closely with TR team members who reviewed the evidence used to inform this guideline. Development of this guideline was wholly funded by the AGA, with no other additional outside funding.

Conflict of interest of all guideline panel members was managed according to AGA Institute Clinical Guidelines Committee policy. Before appointment to the panel, individuals completed conflict of interest forms and disclosed any and all relevant conflicts for 3 years before appointment. All conflict of interest forms can be accessed at AGA's National Office in Bethesda, MD.

Formulating Specific Clinical Questions

As described in detail in the TR documents accompanying this guideline, we developed 4 clinically relevant questions for management of GIM detected at routine endoscopy using the PICO format. The PICO format frames clinical questions by defining a specific population, intervention, comparator, and outcome. Our PICO questions were:

1. Among patients with GIM, does testing and treating for *H pylori* vs no testing and treatment affect patient important outcomes?
2. Among patients with GIM who are identified as low risk, does subsequent surveillance upper endoscopy vs no follow-up affect patient important outcomes?
3. Among patients with GIM who are identified as high risk, does subsequent surveillance upper endoscopy vs no follow-up affect patient important outcomes?
4. Among patients with GIM without dysplasia, does short-term follow-up (<1 year) with biopsies to determine the extent of GIM vs no short-term follow-up affect patient-important outcomes?

After finalizing the PICO questions, the TR team and the guideline panel prioritized patient-important outcomes critical and important for decision-making. Patient-important outcomes of interest included both benefits and harms, such as early gastric cancer detection, reduced morbidity/mortality from gastric cancer, complications associated with endoscopy, psychological outcomes (eg, anxiety and stress related to endoscopic surveillance, coping with a precancerous condition), and resource implications.

Evidence Review

A comprehensive list of direct and indirect evidence needed to inform the questions was developed (Table 1). The desired evidence included incidence and prevalence data for GIM, incidence of gastric cancer in individuals with GIM, and risk factors associated with progression to gastric cancer in patients with GIM compared with individuals without GIM. This "wish list of needed evidence" guided the systematic literature search. Given the paucity of robust direct data on GIM in the United States, evidence from all regions of the world was considered relevant in the evidence-gathering phase. Details related to the management and natural progression of dysplasia were considered outside the scope of this TR unless there was clear discernible clinical relevance to outcomes of GIM.

Development of Recommendations

Upon completion of the evidence synthesis, the guideline panel (S.G., D.L., and H.E.) worked with the TR team to understand the evidence. The panel established the following decision threshold to support surveillance: rate of progression to gastric cancer among individuals with GIM that exceeds 0.5%–1% annually.

During a face-to-face meeting followed by online communication and conference calls, the guideline panel developed recommendations based on the following elements of the GRADE evidence to decision framework: quality or certainty in the evidence, balance of benefits and harms, assumptions about patient values and preferences, and resource implications.

For each guideline statement, the strength of the recommendation and the quality of evidence to support the recommendation are provided (summarized in Tables 2 and 3, respectively). The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The term *AGA recommends* is used for strong recommendations, and *AGA suggests* is used for conditional recommendations. Table 3 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers. Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are its integral parts and serve to facilitate more accurate interpretation.

External Review

Draft recommendations were reviewed by all members of the panel and were made available online for public comment and sent out for external review. Subsequently, the document was revised to address pertinent comments, but no changes were made to the recommendations.

Recommendations

A summary of all the recommendations in this guideline is provided in Table 4.

Recommendation 1. In patients with GIM, the AGA recommends testing for *H pylori* followed by eradication over no testing and eradication. *Strong recommendation, moderate quality of evidence.*

Rationale: *H pylori* is an established gastric carcinogen, accounting for up to 89% of non-cardia gastric cancers

Table 1. PICO Questions, Outcomes, and Evidence Needed to Inform PICO Questions

PICO question	Patient-important outcomes	Evidence needed to inform PICO questions
1. Among patients with GIM, does testing for *H pylori* and treating if positive vs no testing affect patient-important outcomes? 2. Among patients with GIM who are identified as low risk, does subsequent upper endoscopic surveillance vs no follow-up affect patient-important outcomes? 3. Among patients with GIM who are identified as high risk, does subsequent upper endoscopic surveillance vs no follow-up affect patient-important outcomes? 4. Among patients with GIM without dysplasia does short-term upper endoscopic follow-up (<1 year) to determine the extent (using biopsies) of GIM vs no short-term follow-up affect patient-important outcomes?	Early cancer detection Reduced gastric cancer morbidity/mortality Endoscopy complications Costs Psychological harms	Incidence and prevalence of GIM in the US population Incidence of stomach cancer in the general population Prevalence of concurrent gastric cancer in patients with GIM Incidence of gastric cancer in patients with GIM after GIM diagnosis Risk of progression to gastric cancer in patients with GIM Subgroups: Family history of gastric cancer, race/ethnicity, smoking status, histologic features, extent of GIM, biomarkers Potential adverse consequences of performing surveillance upper endoscopy for patients with GIM Benefits of performing surveillance upper endoscopy for patients with GIM

worldwide.[4] As outlined in the TR, 22 studies, including 7 randomized controlled trials and 3 cohort studies, were used to inform recommendations on whether *H pylori* diagnosed in the setting of histologically detected GIM should be eradicated.[9] The TR found that *H pylori* eradication (compared with placebo) among individuals with or without GIM in the absence of gastric neoplasia was associated with a 32% pooled relative risk (RR) reduction in incident gastric cancer risk (RR, 0.68; 95% confidence interval [CI], 0.48–0.96). *H pylori* eradication (compared with placebo) among individuals with or without GIM was also associated with a 33% pooled RR reduction in risk for gastric cancer mortality (RR, 0.67; 95% CI, 0.38–1.17). Analyses of gastric cancer among individuals with *H pylori* infection and confirmed GIM showed a qualitatively similar RR reduction for incident gastric cancer associated with eradication of *H pylori* (RR, 0.76; 95% CI, 0.36–1.61). Results from the studies identified in the TR's comprehensive systematic review were insufficient to assess the impact of *H pylori* eradication on gastric cancer mortality restricted to individuals with confirmed GIM (see Table 3 in Gawron et al,[9] for the this evidence profile summarizes the body and quality of evidence that informed this recommendation).

Overall, the known strong association of *H pylori* with risk for incident gastric cancer and the TR's findings, which reinforce the evidence of reduced risk for incident gastric cancer after *H pylori* eradication, supports the AGA recommendation to test for and eradicate *H pylori* in individuals with incidentally detected GIM. The quality of evidence to support this recommendation was rated as moderate, in part because of the lack of data on impact of *H pylori* eradication in individuals with confirmed GIM. In addition, the trial that had the largest influence on the pooled estimate was limited by attrition bias and was conducted in an indigenous Chinese population, which may have different risk of gastric cancer. Confirming eradication of *H pylori* is recommended, given high known *H pylori* eradication failure rates using current therapies, but the method of testing for *H pylori* and strategies for confirming eradication are outside scope of the current guideline and are covered elsewhere.[13]

Recommendation 2. In patients with GIM the AGA suggests against routine use of endoscopic surveillance. *Conditional recommendation, very low quality of evidence*
Comment: Patients with GIM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance.
Patients with GIM specifically at higher risk of gastric cancer include those with:

- **Incomplete vs complete GIM**
- **Extensive vs limited GIM**
- **Family history of gastric cancer**

Patients at overall increased risk for gastric cancer include:

- **Racial/ethnic minorities**
- **Immigrants from high incidence regions**

Comment: Patients with GIM who put a high value on potential reduction in gastric cancer mortality, despite a lack of direct supporting evidence, in the context of an approximate 0.16% annual and an approximate 1.6% ten-year cumulative risk for incident gastric cancer, and who put a low value on the potential risks of repeat surveillance endoscopies may reasonably select to enroll in endoscopic surveillance. Patients with GIM who could be at higher risk

Table 2. Interpretation of the Certainty in Evidence of Effects Using the GRADE Framework

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

for gastric cancer (≥1.6% ten-year risk), who put a high value on potentially reducing gastric cancer mortality despite a lack of direct supporting evidence, and who put a low value on the potential risks of surveillance endoscopies may also reasonably select endoscopic surveillance. Similarly, patients who are at overall increased risk for gastric cancer may also reasonably select endoscopic surveillance. Risk assessment should be individualized. Patients with GIM at higher risk of gastric cancer include those with incomplete (at least partial colonic type) vs complete (small intestinal type) intestinal metaplasia (3.3-fold RR based on low quality of evidence); family history of gastric cancer (4.5-fold RR based on very low quality of evidence); and extensive (involving the gastric body plus either antrum and/or incisura) vs limited GIM (involving the gastric antrum and/or incisura only; 2.1-fold RR based on very low quality of evidence (see Table 2 in Altayar et al,[10]). Although the TR did not find evidence supporting increased risk for gastric cancer among racial/ethnic minorities or immigrants with documented GIM, an overall increased risk for gastric cancer (irrespective of presence/absence of GIM) has been established among these groups, and may be considered as part of decision-making regarding surveillance.[3,14]

There are insufficient data to guide recommendations on the optimal surveillance interval. Based on indirect evidence of cumulative gastric cancer incidence among patients with GIM, repeat upper endoscopy every 3–5 years with careful mucosal visualization and gastric biopsies of the antrum, body, and any concerning lesions could be considered in patients with incidental GIM, if shared decision-making favors surveillance.

Rationale: Based on the comprehensive TR systematic review, there was no direct evidence to inform recommendations for or against endoscopic surveillance after *H pylori* eradication. Specifically, the TR found no randomized controlled trial, cohort study, or case–control study comparing impact of endoscopic surveillance vs no surveillance on gastric cancer risk among patients with GIM. Based on the lack of comparative evidence to support altered gastric cancer incidence or mortality among patients with GIM enrolled in surveillance vs no surveillance, the AGA recommends shared decision-making regarding use of endoscopic surveillance over routine use of surveillance. The TR identified indirect evidence that could inform decision-making on whether to consider endoscopic surveillance in select cases, including prevalence of GIM on routine gastric biopsies; longitudinal risk for incident gastric cancer among individuals with GIM; and factors that may be associated with increased gastric cancer risk among individuals with GIM.

Pooled prevalence of GIM among 897,371 individuals with gastric biopsies was estimated to be 4.8% (95% CI, 4.8%–4.9%).[10] As such, the panel recognizes that any recommendations for surveillance of GIM could impact a significant proportion of individuals undergoing endoscopy with biopsy. A limitation of this meta-analysis is that most of the data were from a single study reporting on prevalence of GIM among gastric biopsies routinely submitted for

Table 3. Interpretation of Strong and Conditional Recommendations Using the GRADE Framework

Implications	Strong recommendation[a]	Conditional recommendation[b]
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision-making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy-makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.

[a]Strong recommendations are indicated by statements that lead with "we recommend."
[b]Conditional recommendations are indicated by statements that lead with "we suggest."

Table 4. AGA Recommendations for Management of Gastric Intestinal Metaplasia

Statement	Strength of recommendation	Quality of evidence
1. In patients with GIM, the AGA recommends testing for *H pylori*, followed by eradication over no testing and eradication	Strong	Moderate
2. In patients with GIM, the AGA suggests against routine use of endoscopic surveillance	Conditional	Very Low
Comments: Patients with GIM at higher risk for gastric cancer who put a high value on potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance.[a]		
Patients with GIM specifically at higher risk of gastric cancer include those with:		
• Incomplete vs complete GIM		
• Extensive vs limited GIM		
• Family history of gastric cancer		
Patients at overall increased risk for gastric cancer include:		
• Racial/ethnic minorities		
• Immigrants from high incidence regions		
3. In patients with GIM, the AGA suggests against routine repeat short-interval endoscopy with biopsies for the purpose of risk stratification	Conditional	Very Low
Comments: Based on shared decision-making, patients with GIM and high-risk stigmata, concerns about completeness of baseline endoscopy, and/or who are at overall increased risk for gastric cancer (racial/ethnic minorities, immigrants from regions with high gastric cancer incidence, or individuals with family history of first-degree relative with gastric cancer) may reasonably elect for repeat endoscopy within 1 year for risk stratification.		

[a]There are insufficient data to guide optimal surveillance interval. Based on indirect evidence regarding cumulative gastric cancer incidence among patients with GIM, repeat upper endoscopy with careful mucosal visualization and gastric biopsies of the antrum and body and any concerning lesions may be considered in 3–5 years among patients with incidentally detected GIM, if shared decision-making favors surveillance.

pathologic review to a single national gastrointestinal pathology service company in the United States.

The 3-, 5-, and 10-year pooled cumulative rates of incident gastric cancer among patients with GIM were estimated to be 0.4% (95% CI, 0.1%–0.8% based on 4 studies); 1.1% (95% CI, 1.0%–1.2% based on 7 studies); and 1.6% (95% CI, 1.5%–1.7% based on 4 studies), respectively.[9] Just 2 of the studies included to estimate cumulative gastric cancer risk were from the United States. For example, among individuals from a large integrated health care plan in Southern California, the cumulative 5-year risk for gastric cancer was estimated to be 0.9% (95% CI, 0.3%–1.6%).[15] The pooled annual rate of progression to gastric cancer among individuals with GIM was estimated to be 0.16% per year. This estimate is lower than the previously reported pooled annual cumulative risk of 0.33% for esophageal adenocarcinoma among patients with non-dysplastic Barrett's esophagus, a condition for which endoscopic surveillance is often routinely recommended.[16] The TR also was able to estimate cumulative rate of progression to dysplasia among individuals with GIM as being 15% at 3 years (95% CI, 13%–17%) and 15% at 5 years (95% CI, 12%–19%), based on 7 total studies with nearly 3000 patients with GIM; all studies contributing data to these estimates were from outside the United States.[9]

The TR also summarized evidence informing differential risk for gastric cancer according to several prespecified potential risk factors for gastric cancer, including race/ethnicity, family history of gastric cancer, smoking, autoimmune gastritis/pernicious anemia, histologic features (incomplete vs complete GIM), extent of GIM (extensive vs limited) and biomarkers (eg, CagA positivity).[10] Assessment of differential risk by race/ethnicity was performed only for North American studies. Meta-analysis of the 3 studies identified showed that among patients with confirmed GIM, cumulative risk for gastric cancer was not statistically significantly different for Hispanics (1.0%; 95% CI, 0.4%–1.7%), Asians (0.3%; 95% CI, 0.1%–0.8%), blacks (0.4%; 95% CI, 0.0%–1.4%), and non-Hispanic whites (0.3%; 95% CI, 0.1%–0.6%) (see Table 2 in Altayar et al,[10]). Although no statistically significant difference across racial/ethnic groups was observed, the wide CIs and varying point estimates (eg, 1.0% for Hispanics vs 0.3% for non-Hispanic whites) do not rule out the possibility of clinically meaningful differences. Thus, while evidence clearly demonstrates that minority populations have overall higher risk for gastric cancer in the United States, current evidence does not support increased risk among racial/ethnic minorities once GIM is established. The TR did not identify higher prevalence of GIM among racial/ethnic minorities, and did not find racial/ethnic minorities with GIM have increased risk for gastric cancer compared to non-Hispanic whites with GIM, but based on the very low quality of evidence available we could not exclude the possibility of increased risk for GIM and progression of GIM among racial/ethnic minorities.

Seven studies assessing risk for gastric cancer among patients with GIM based on presence of incomplete (at least

partial areas of colonic type) vs complete (small intestinal type) GIM were identified. Based on meta-analysis, having incomplete vs complete GIM was associated with a 3-fold increased risk for incident gastric cancer on follow-up (RR, 3.33; 95% CI, 1.96–5.64).[9] None of these studies were from the United States. Anecdotally, US pathologists rarely report presence of incomplete vs complete GIM as part of routine GIM diagnosis. This observation raises concerns as to whether the histologic subtype of GIM can be feasibly utilized as part of risk stratification in the United States without a substantial educational initiative for pathologists.

Among patients with GIM, having a family history of a first-degree relative with gastric cancer was associated with 4.5-fold increased risk for incident gastric cancer based on 3 studies (RR, 4.53; 95% CI, 1.33–15.46).[9]

Among patients with GIM who had biopsies obtained from both the gastric antrum/incisura and body, extensive GIM vs limited involvement (ie, including involvement of at least the gastric body vs GIM of the antrum and/or incisura, respectively) was associated with a 2-fold higher pooled RR of incident gastric cancer (RR, 2.07; 95% CI, 0.97–4.42) based on 2 studies.[9] In the United States, the anecdotally reported routine practice of submitting gastric biopsies without specifying the total number of biopsies or separating biopsies taken into separate specimen jars labeled with specific anatomic locations could challenge the ability to use the anatomic extent of GIM for risk stratification unless a shift away from this practice occurs.

Little to no evidence was available to assess the risk for gastric cancer among patients with GIM based on personal history of concurrent smoking, pernicious anemia, autoimmune gastritis, or potential risk biomarkers.

Overall, indirect evidence summarized by the TR suggests GIM is diagnosed commonly (prevalence of 5%) and is associated with a cumulative risk for incident gastric cancer (1.6% at 10 years). Risk for cancer among individuals with GIM may be higher among individuals with incomplete vs complete histology, extensive vs limited GIM, and those with a family history of gastric cancer in a first-degree relative. Taken together, the AGA recommends these factors could be considered as part of the decision on whether to pursue surveillance upper endoscopy among individuals with GIM as part of the shared decision-making process.

Recommendation 3. In patients with GIM, the AGA suggests against routine short-interval repeat endoscopy for the purpose of risk stratification. *Conditional recommendation, very low quality of evidence.*
Comment: Based on shared decision-making, patients with GIM and high-risk stigmata, concerns about completeness of baseline endoscopy, and/or who are at overall increased risk for gastric cancer (racial/ethnic minorities, immigrants from regions with high gastric cancer incidence, or individuals with family history of first-degree relative with gastric cancer) may reasonably elect for repeat endoscopy within 1 year for risk stratification.

Patients with GIM who put a high value on the possible increased risk of gastric cancer associated with extensive GIM, and a low value on the risks associated with repeat endoscopy, could reasonably choose repeat endoscopy to establish the anatomic extent (sometimes referred to as "gastric mapping"), establish histologic subtype of GIM (if local pathologist expertise permits), and exclude prevalent cancer. Patients with GIM and high-risk stigmata (eg, visually detected abnormalities such as nodularity) or concerns about completeness of baseline endoscopy may also elect to undergo endoscopy within 1 year to detect prevalent cancer and/or for gastric biopsies to characterize the anatomic extent and histologic subtype of GIM. Patients with GIM at overall increased risk for gastric cancer (such as Hispanics, Asians, African Americans, and Native Americans/Alaska Natives;[3] immigrants from regions with high gastric cancer incidence[14]; or individuals with family history of first-degree relative with gastric cancer) may elect for repeat endoscopy within 1 year to detect prevalent cancer through targeted biopsies of any visible abnormalities, and to perform untargeted biopsies (at minimum of the antrum and body, submitted in separate specimen jars for pathology)[17] to better define risk for subsequent gastric cancer based on the anatomic extent of GIM and histologic subtype (incomplete vs complete).

Rationale: The TR found no direct evidence to support the impact of short-interval (<12 months) repeat upper endoscopy among patients with incidental GIM on patient-important outcomes. Specifically, no cohort study or case series of patients with incidentally found GIM systematically subjected to short-interval repeat endoscopy was identified. Thus, there was no direct evidence to inform frequency of detection of higher-risk GIM features or prevalent gastric cancer not appreciated at the initial endoscopy where GIM was diagnosed. Accordingly, based on a lack of data on the yield of short-interval repeat endoscopy and the impact on risk stratification or prevalent cancer detection, the AGA suggests shared decision-making regarding surveillance over routine use of endoscopic surveillance after GIM diagnosis and *H pylori* eradication if present.

The TR did identify indirect evidence that can be used to engage patients with incidentally detected GIM in shared decision-making on whether to consider a short-interval repeat endoscopy. Concern for undetected prevalent cancer could also justify short-interval repeat endoscopy. As mentioned previously, the TR did not identify any studies characterizing the endoscopic miss rate for gastric cancer among patients with GIM. As indirect evidence, the TR estimated the risk for gastric cancer within 1 year of GIM diagnosis, assuming that cancers diagnosed within 1 year of GIM follow-up are more likely to have been missed prevalent cases as opposed to incident cancers. Based on 4 cohort studies, the cumulative incidence of gastric cancer within 1 year of GIM diagnosis was estimated to be 0.5% (95% CI, 0.4%–0.6%),[9] suggesting the overall risk of missed cancer is low. Nonetheless, the AGA recognizes that individuals with any concerns for quality or completeness of the baseline endoscopy, and/or assessment of visually detected abnormalities, may reasonably elect to undergo a short-interval repeat upper endoscopy to exclude prevalent cancer.

As reported previously, the TR found evidence suggesting a 3-fold increased risk for incident gastric cancer among individuals with incomplete (at least partial colonic type) vs complete (small intestinal type) GIM, and a 2-fold increased risk for cancer among individuals with extensive vs limited GIM. Because GIM is often diagnosed based on an unspecified number of "random" biopsies submitted in a single pathology jar in clinical practice, the ability to confidently rule out the presence of incomplete GIM and extensive GIM could be limited. Accordingly, patients and providers who put a high value on these factors for determining the need for subsequent longitudinal endoscopic surveillance, may reasonably elect to undergo a short-interval repeat upper endoscopy to assess anatomic extent and histologic characteristics of GIM.

In the United States, racial/ethnic minorities have a much higher risk for incident and fatal gastric cancer than non-Hispanic whites.[3] While the TR did not identify substantially different rates of incident gastric cancer among individuals with previously established GIM across racial/ethnic groups, the AGA recognizes that groups with overall increased risk for gastric cancer may also reasonably elect for a short-interval repeat endoscopy for gastric biopsies to characterize anatomic extent and histologic subtype of GIM (if a decision favoring surveillance has not yet been made) and to exclude prevalent cancer.

Discussion

GIM is often detected as part of routine endoscopy, frequently when the original indication for the endoscopy was not screening for gastric cancer. As such, when GIM is detected as part of routine endoscopy, questions arise regarding whether *H pylori* should be identified and treated, whether endoscopic surveillance is indicated, whether an area with more advanced histology may not have been identified, and whether short-interval repeat endoscopy is needed for more precise risk stratification and/or to rule out prevalent gastric cancer. Based on an extensive TR of evidence to support management of patients with incident GIM, the AGA has made recommendations for management and surveillance (Table 4). Based on moderate-quality evidence, the AGA recommends testing for *H pylori* and eradication among individuals with GIM. Based on a very low quality of evidence, mainly due to a lack of studies specifically addressing clinical impact of short-interval repeat endoscopy and longitudinal endoscopic surveillance, the AGA suggests against routine short-interval repeat endoscopy and longitudinal surveillance.

Recognizing that the lack of evidence could put some patients at risk for adverse outcomes pending the generation of new, rigorous evidence, we investigated evidence that could help guide shared decision-making between patients and providers on whether to elect to undergo longitudinal surveillance or short-interval repeat endoscopy. Because we found incomplete (vs complete) GIM and extensive vs limited (involving the antum/incisura only) GIM were associated with increased risk for incident gastric cancer among patients with GIM, patients and providers may reasonably elect to undergo short-interval upper endoscopy to characterize presence/absence of these features, or commit to longitudinal surveillance if these features are known to be present. Similarly, because we found evidence supporting increased risk for gastric cancer among patients with GIM and a first-degree relative with gastric cancer, patients with GIM and a family history could reasonably elect for longitudinal endoscopic surveillance. Identifying the best management strategies for racial/ethnic minorities with GIM remains a challenge. The TR found, based on limited evidence, no statistically significant variation across racial/ethnic groups in cumulative gastric cancer risk among individuals with GIM. As noted previously, the wide CIs and varying point estimates for rate of incident gastric cancer (eg, 1.0% for Hispanics vs 0.3% for non-Hispanic whites) do not rule out the possibility of clinically meaningful differences. The overall higher risk for gastric cancer among racial/ethnic minorities in the United States, and for individuals in high-incidence regions, is well established. Further, data on variation in risk by racial/ethnic groups came from just 3 studies, and those studies did not account for whether minorities were from the United States or foreign-born, or the duration of their residence in countries with high gastric cancer incidence. New immigrants from high-incidence geographic areas (such as East Asia or South America) have higher risk of gastric cancer, likely due to shared risk factors, such as *H pylori* infection and other exposures.[14] Recognizing the uncertainty in risk, racial/ethnic minorities with GIM may reasonably elect to undergo short-interval repeat endoscopy to characterize anatomic extent of GIM, histologic subtype of GIM, exclude prevalent cancer, and/or to undergo longitudinal surveillance endoscopy until new evidence is generated. A suggested algorithm for management of patients with GIM is provided in a Clinical Decision Support Tool.

What Do Other Guidelines Say?

Compared to the AGA guidelines, the recommendations from other professional societies in the United States and Europe specific to patients with GIM within the scope of AGA recommendations are generally similar. The American Society of Gastrointestinal Endoscopy (ASGE) 2015 guidelines state: "We suggest surveillance endoscopy for patients with GIM who are at increased risk for gastric cancer due to ethnic background or family history. Optimal surveillance intervals have not been extensively studied and should be individualized."[18] ASGE guidelines also suggest surveillance may be suspended when 2 consecutive endoscopies are negative for dysplasia, and recommend eradication of *H pylori* if identified. Thus, ASGE guidelines are consistent with the AGA's recommendation against routine surveillance, and similar to our suggestion that surveillance may be considered based on shared decision-making between patients and providers for

patients with family history of gastric cancer or increased background risk for gastric cancer; duration of surveillance was not within the scope of the current AGA guideline. Further, the AGA recommendations to test and eradicate *H pylori* complement and extend the ASGE recommendation to eradicate *H pylori* if identified.

The European Society of Gastrointestinal Endoscopy (ESGE) recently published guidelines for management of epithelial precancerous conditions and lesions in the stomach, including GIM.[19] ESGE recommendations were based on updating the literature search for key questions of interest since their 2012 guidelines,[20] rating available evidence using a GRADE framework, and achieving consensus statements using a Delphi process. ESGE recommends consideration of *H pylori* eradication in patients with GIM, similar to the AGA's outright recommendation to test and eradicate *H pylori* for this group. With regard to endoscopic surveillance, ESGE highlighted increased risk associated with GIM at a single anatomic location (GIM of limited extent), but, with respect to having GIM at a single anatomic location alone, judged that the "increased risk does not justify surveillance in most cases, particularly if a high quality endoscopy with biopsies has excluded advanced stages of atrophic gastritis," citing this as a strong recommendation based on moderate-quality evidence. ESGE did recommend that surveillance 3 years from baseline could be considered for individuals with GIM at a single location but with family history of gastric cancer, incomplete GIM, persistent *H pylori* gastritis, citing this as a weak recommendation based on low-quality evidence. ESGE made a strong recommendation based on low-quality evidence in favor of surveillance endoscopy every 3 years among individuals with severe gastric atrophy or GIM in both the antrum and body, and/or (OLGA) Operative Link on Gastritis Assessment/OLGIM (Operative Link on Gastritis Assessment based on Intestinal Metaplasia) stage III/IV. ESGE also suggested that those with a family history plus these findings might consider even more intense 1- to 2-year surveillance endoscopy, citing this as a weak recommendation based on low-quality evidence. Taken together, ESGE and AGA recommendations are consistent in not recommending routine surveillance for patients with GIM in the absence of increased extent (antrum and body), family history of gastric cancer, and incomplete GIM. While AGA recommends shared decision-making to discuss pros and cons of surveillance in patients with risk factors, such as increased extent, family history, and incomplete GIM, ESGE explicitly recommends surveillance for individuals with increased extent and, similar to AGA, recommends consideration of surveillance for those with family history of gastric cancer and incomplete GIM. If surveillance is planned, whereas AGA recommends consideration of a 3- to 5-year interval for surveillance, ESGE recommends 3 years, with consideration for more intense surveillance in the setting of extensive GIM plus a family history of gastric cancer. ESGE did not explicitly make a recommendation for or against short-interval repeat endoscopy for characterizing extent of GIM or presence of GIM if not done at baseline, although all of its recommendations imply knowledge of biopsy findings from at least the antrum and body of the stomach.

Future Research Needs and Evidence Gaps

Our recommendations highlight several areas of uncertainty ripe for future research. Key evidence gaps include a lack of observational studies and randomized trials on impact of surveillance vs no surveillance on outcomes, such as early detection and prevention of gastric cancer. More data are needed to understand the importance of extensive vs limited (antral/incisura only) GIM on risk for gastric cancer. The yield of systematically repeating baseline endoscopy to characterize the anatomic extent and histologic subtype of GIM (eg, short-interval endoscopy with gastric mapping) requires study. Studies on the yield of repeat baseline endoscopy for patients with GIM detected on routine endoscopy should pay specific attention to the number of additional individuals identified as potentially at increased risk for progression to cancer based on findings at the repeat examination to clarify whether repeat examinations might change decisions on surveillance. Our TR suggests the most robust evidence base for a risk factor linked to gastric cancer among individuals with GIM is presence of incomplete vs complete metaplasia. As such, studies should investigate the potential benefit of implementing routine characterization of incomplete vs complete intestinal metaplasia by pathologists, particularly in the United States. Additional natural history studies are required, such as investigation of differences based on race, ethnicity, or country of origin, and whether risk of GIM detected as part of routine endoscopy differs from patients who are engaged in a specific screening program for gastric cancer. Additionally, there have been conflicting reports with respect to whether GIM continues to progress after *H pylori* eradication. Although some studies observed improvement or reversal of GIM after *H pylori* eradication,[21–23] others suggested that GIM may persist or continue to progress (ie, "a point of no return") after *H pylori* treatment.[24,25] The optimal protocol for obtaining gastric biopsies to increase the yield of GIM detection in clinical practice remains to be determined. Prior studies using the OLGA and OLGIM classifications have shown benefits in identifying patients with more extensive disease and at increased risk for disease progression, but adopting these systems in daily clinical practice may be challenging.[26,27] Using image-enhanced technologies (or virtual chromoendoscopy, such as narrow band imaging) to perform targeted gastric biopsy has been reported to improve detection of GIM.[28,29] Application of these techniques in routine practice and whether it translates to improved outcomes warrant further investigation. In addition, biomarkers such as pepsinogen (I and II) levels are commonly used in Asian countries for gastric cancer risk-stratification but have not been well studied in the United States.[30–32] Such studies may generate useful information in selecting patients with increased risk for gastric cancer who may benefit most from screening and

surveillance endoscopy. Studies are also required to place the effectiveness and cost-effectiveness of GIM management within the larger context of gastric prevention that may include screening for *H pylori* and screening endoscopy.

Several limitations should be considered when interpreting these recommendations. The recommendations were based on a paucity of evidence. In particular, the strength of recommendations was conditional for our recommendations on surveillance endoscopy, and the overall quality of evidence to support these recommendations was judged to be very low. Thus, it is highly possible that new studies addressing current evidence gaps may markedly impact future recommendations regarding the management of individuals with GIM.

In conclusion, the AGA recommends patients with GIM be tested and treated for *H pylori* to reduce risk for gastric cancer. In light of current evidence gaps, the AGA suggests against routine use of short-interval repeat endoscopy with biopsies for the purpose of risk stratification and routine endoscopic surveillance, but encourages patients and physicians to participate in shared decision-making regarding potential pros and cons of these strategies in light of current evidence gaps. The AGA recognizes that new evidence may emerge in the future that might more strongly support short-interval repeat endoscopy with biopsies for risk stratification, and/or endoscopic surveillance for gastric cancer risk reduction.

Plans for Updating This Guideline

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. This document will be updated when major new research is published. The need for update will be determined no later than in 2022.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
3. Gupta S, Tao L, Murphy JD, et al. Race/ethnicity-, socioeconomic status-, and anatomic subsite-specific risks for gastric cancer. Gastroenterology 2019;156:59–62.e4.
4. Plummer M, Franceschi S, Vignat J, et al. Global burden of gastric cancer attributable to *Helicobacter pylori*. Int J Cancer 2014;136:487–490.
5. Correa P. Gastric cancer: overview. Gastroenterol Clin North Am 2013;42:211–217.
6. Hamashima C, Shibuya D, Yamazaki H, et al. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol 2008;38:259–267.
7. Zhang X, Li M, Chen S, et al. Endoscopic screening in asian countries is associated with reduced gastric cancer mortality: a meta-analysis and systematic review. Gastroenterology 2018;155:347–354.e9.
8. Vance RB Jr, Kubiliun N, Dunbar KB. How do we manage gastric intestinal metaplasia? A survey of clinical practice trends for gastrointestinal endoscopists in the United States. Dig Dis Sci 2016;61:1870–1878.
9. Gawron AJ, Shah SC, Altayar O, et al. AGA technical review on gastric intestinal metaplasia—natural history and clinical outcomes. Gastroenterology 2020; 158:705–731.
10. Altayar O, Davitkov P, Shah SC, et al. AGA technical review on gastric intestinal metaplasia—epidemiology and risk factors. Gastroenterology 2020;158:732–744.
11. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
12. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press, 2011.
13. El-Serag HB, Kao JY, Kanwal F, et al. Houston Consensus Conference on testing for *Helicobacter pylori* infection in the United States. Clin Gastroenterol Hepatol 2018;16:992–1002.e6.
14. Pabla BS, Shah SC, Corral JE, et al. Increasing incidence and mortality of gastric cancer in immigrant populations from high to low regions of incidence: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019 May 30 [Epub ahead of print].
15. Reddy KM, Chang JI, Shi JM, et al. Risk of gastric cancer among patients with intestinal metaplasia of the stomach in a US integrated health care system. Clin Gastroenterol Hepatol 2016;14:1420–1425.
16. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut 2012;61:970–976.
17. Yang YX, Brill J, Krishnan P, et al. American Gastroenterological Association Institute guideline on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions. Gastroenterology 2015;149:1082–1087.
18. Evans JA, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc 2015;82:1–8.
19. Pimentel-Nunes P, Libanio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019;51:365–388.
20. Dinis-Ribeiro M, Areia M, de Vries AC, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology

(ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy 2012;44:74–94.
21. Kong YJ, Yi HG, Dai JC, et al. Histological changes of gastric mucosa after *Helicobacter pylori* eradication: a systematic review and meta-analysis. World J Gastroenterol 2014;20:5903–5911.
22. Leung WK, Lin SR, Ching JY, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. Gut 2004;53:1244–1249.
23. Hwang YJ, Kim N, Lee HS, et al. Reversibility of atrophic gastritis and intestinal metaplasia after *Helicobacter pylori* eradication—a prospective study for up to 10 years. Aliment Pharmacol Ther 2018;47:380–390.
24. Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004; 291:187–194.
25. Lahner E, Bordi C, Cattaruzza MS, et al. Long-term follow-up in atrophic body gastritis patients: atrophy and intestinal metaplasia are persistent lesions irrespective of *Helicobacter pylori* infection. Aliment Pharmacol Ther 2005;22:471–481.
26. Rugge M, Meggio A, Pennelli G, et al. Gastritis staging in clinical practice: the OLGA staging system. Gut 2007; 56:631–636.
27. Capelle LG, de Vries AC, Haringsma J, et al. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. Gastrointest Endosc 2010;71:1150–1158.
28. Pimentel-Nunes P, Dinis-Ribeiro M, Soares JB, et al. A multicenter validation of an endoscopic classification with narrow band imaging for gastric precancerous and cancerous lesions. Endoscopy 2012;44:236–246.
29. Buxbaum JL, Hormozdi D, Dinis-Ribeiro M, et al. Narrow-band imaging vs white light vs mapping biopsy for gastric intestinal metaplasia: a prospective blinded trial. Gastrointest Endosc 2017;86:857–865.
30. Mukoubayashi C, Yanaoka K, Ohata H, et al. Serum pepsinogen and gastric cancer screening. Intern Med 2007;46:261–266.
31. Cho JHJS, Kim HG, Jin SY, Park S. The serum pepsinogen levels for risk assessment of gastric neoplasms: new proposal from a case-control study in Korea. Medicine (Baltimore) 2017;96(29):e7603.
32. Huang YK, Yu JC, Kang WM, et al. Significance of serum pepsinogens as a biomarker for gastric cancer and atrophic gastritis screening: a systematic review and meta-analysis. PLoS One 2015;10:e0142080.

Correspondence
Address correspondence to: Chair, Clinical Guidelines Committee, American Gastroenterological Association National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: clinicalpractice@gastro.org.

Acknowledgments
The authors would like to thank the outstanding efforts of the AGA Gastric Intestinal Metaplasia Technical Review team, without whom this guideline could not have been written: Andrew J. Gawron, MD, PhD, MS; Shailja C. Shah, MD, MPH; Osama Altayar, MD; Perica Davitkov, MD; Douglas Morgan, MD, MPH; Kevin Turner, DO; Reem A. Mustafa, MD, MPH, PhD.

This document presents the official recommendations of the American Gastroenterological Association (AGA) Institute on the management of incidentally detected gastric intestinal metaplasia. The guideline was developed by the AGA's Clinical Practice Guideline Committee and approved by the AGA Governing Board.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported in part by the National Cancer Institute (NCI) of the National Institutes of Health (NIH) under Award Numbers R37 CA222866; 1UG3CA233314-01A1; and DK120515; and the Department of Veterans Affairs under Award Number I01 HX001574.