



AGA Clinical Practice Update on Screening and Surveillance in Individuals at Increased Risk for Gastric Cancer in the United States: Expert Review

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DESCRIPTION: Gastric cancer (GC) is a leading cause of preventable cancer and mortality in certain US populations. The most impactful way to reduce GC mortality is via primary prevention, namely *Helicobacter pylori* eradication, and secondary prevention, namely endoscopic screening and surveillance of precancerous conditions, such as gastric intestinal metaplasia (GIM). An emerging body of evidence supports the possible impact of these strategies on GC incidence and mortality in identifiable high-risk populations in the United States. Accordingly, the primary objective of this American Gastroenterological Association (AGA) Clinical Practice Update (CPU) Expert Review is to provide best practice advice for primary and secondary prevention of GC in the context of current clinical practice and evidence in the United States. **METHODS:** This CPU Expert Review was commissioned and approved by the AGA Institute CPU Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPU Committee and external peer review through standard procedures of *Gastroenterology*. These best practice advice statements were drawn from a review of the published literature and expert opinion. Because systematic reviews were not performed, these best practice advice statements do not carry formal ratings regarding the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: There are identifiable high-risk groups in the United States who should be considered for GC screening. These include first-generation immigrants from high-incidence GC regions and possibly other non-White racial and ethnic groups, those with a family history of GC in a first-degree relative, and individuals with certain hereditary gastrointestinal polyposis or hereditary cancer syndromes. **BEST PRACTICE ADVICE 2:** Endoscopy is the best test for screening or surveillance in individuals at increased risk for GC. Endoscopy enables direct visualization to endoscopically stage the mucosa and identify areas concerning for neoplasia, as well as enables biopsies for further histologic examination and mucosal staging. Both endoscopic and histologic staging are key for risk stratification and determining whether ongoing surveillance is indicated and at what interval. **BEST PRACTICE ADVICE 3:** High-quality upper endoscopy for the detection of premalignant and malignant gastric lesions should include the use of a high-definition white-light endoscopy system with

image enhancement, gastric mucosal cleansing, and insufflation to achieve optimal mucosal visualization, in addition to adequate visual inspection time, photodocumentation, and use of a systematic biopsy protocol for mucosal staging when appropriate. **BEST PRACTICE ADVICE 4:** *H pylori* eradication is essential and serves as an adjunct to endoscopic screening and surveillance for primary and secondary prevention of GC. Opportunistic screening for *H pylori* infection should be considered in individuals deemed to be at increased risk for GC (refer to Best Practice Advice 1). Screening for *H pylori* infection in adult household members of individuals who test positive for *H pylori* (so-called “familial-based testing”) should also be considered. **BEST PRACTICE ADVICE 5:** In individuals with suspected gastric atrophy with or without intestinal metaplasia, gastric biopsies should be obtained according to a systematic protocol (eg, updated Sydney System) to enable histologic confirmation and staging. A minimum of 5 total biopsies should be obtained, with samples from the antrum/incisura and corpus placed in separately labeled jars (eg, jar 1, “antrum/incisura” and jar 2, “corpus”). Any suspicious areas should be described and biopsied separately. **BEST PRACTICE ADVICE 6:** GIM and dysplasia are endoscopically detectable. However, these findings often go undiagnosed when endoscopists are unfamiliar with the characteristic visual features; accordingly, there is an unmet need for improved training, especially in the United States. Artificial intelligence tools appear promising for the detection of early gastric neoplasia in the adequately visualized stomach, but data are too preliminary to recommend routine use. **BEST PRACTICE ADVICE 7:** Endoscopists should work with their local pathologists to achieve consensus for consistent documentation of histologic risk-stratification parameters when atrophic gastritis with or without metaplasia is diagnosed. At a minimum, the presence or absence of *H pylori* infection, severity of atrophy and/or metaplasia, and histologic subtyping of GIM, if applicable, should be documented to inform clinical decision making. **BEST PRACTICE ADVICE 8:** If the index screening endoscopy performed in an individual at increased risk for GC (refer to Best Practice Advice 1) does not identify atrophy, GIM, or neoplasia, then the decision to continue screening should be based on that individual’s risk factors and preferences. If the individual has a family history of GC or multiple risk factors for GC, then ongoing screening should be considered. The optimal screening intervals in such scenarios are not well defined. **BEST PRACTICE ADVICE 9:** Endoscopists should ensure that all individuals with confirmed gastric atrophy with or without GIM undergo risk stratification.

Individuals with severe atrophic gastritis and/or multifocal or incomplete GIM are likely to benefit from endoscopic surveillance, particularly if they have other risk factors for GC (eg, family history). Endoscopic surveillance should be considered every 3 years; however, intervals are not well defined and shorter intervals may be advisable in those with multiple risk factors, such as severe GIM that is anatomically extensive. **BEST PRACTICE ADVICE 10:** Indefinite and low-grade dysplasia can be difficult to reproducibly identify by endoscopy and accurately diagnose on histopathology. Accordingly, all dysplasia should be confirmed by an experienced gastrointestinal pathologist, and clinicians should refer patients with visible or nonvisible dysplasia to an endoscopist or center with expertise in the diagnosis and management of gastric neoplasia. Individuals with indefinite or low-grade dysplasia who are infected with *H pylori* should be treated and have eradication confirmed, followed by repeat endoscopy and biopsies by an experienced endoscopist, as visual and histologic discernment may improve once inflammation subsides. **BEST PRACTICE ADVICE 11:** Individuals with suspected high-grade dysplasia or early GC should undergo endoscopic submucosal dissection with the goal of en bloc, R0 resection to enable accurate pathologic staging with curative intent. Eradication of active *H pylori* infection is essential, but should not delay endoscopic intervention. Endoscopic submucosal dissection should be performed at a center with endoscopic and pathologic expertise. **BEST PRACTICE ADVICE 12:** Individuals with a history of successfully resected gastric dysplasia or cancer require ongoing endoscopic surveillance. Suggested surveillance intervals exist, but additional data are required to refine surveillance recommendations, particularly in the United States. **BEST PRACTICE ADVICE 13:** Type I gastric carcinoids in individuals with atrophic gastritis are typically indolent, especially if <1 cm. Endoscopists may consider resecting gastric carcinoids <1 cm and should endoscopically resect lesions measuring 1–2 cm. Individuals with type I gastric carcinoids >2 cm should undergo cross-sectional imaging and be referred for surgical resection, given the risk of metastasis. Individuals with type I gastric carcinoids should undergo surveillance, but the intervals are not well defined. **BEST PRACTICE ADVICE 14:** In general, only individuals who are fit for endoscopic or potentially surgical treatment should be screened for GC and continued surveillance of premalignant gastric conditions. If a person is no longer fit for endoscopic or surgical treatment, then screening and surveillance should be stopped. **BEST PRACTICE ADVICE 15:** To achieve health equity, a personalized approach should be taken to assess an individual's risk for GC to determine whether screening and surveillance should be pursued. In conjunction, modifiable risk factors for GC should be distinctly addressed, as most of these risk factors disproportionately impact people at high risk for GC and represent health care disparities.

Keywords: Atrophic Gastritis; Gastric Intestinal Metaplasia; Cancer Prevention; Epidemiology; *Helicobacter pylori*; Disparity.

Gastric cancer (GC) remains a leading cause of preventable cancer death worldwide, including in the United States. In the United States, there were an estimated 26,500 new GC cases and 11,130 related deaths in 2023.¹

The 5-year survival rate for GC in the United States is a dismal 32% and reflects the fact that <25% are diagnosed in an early stage, before submucosal invasion when endoscopic or surgical resection is curative.^{1,2} This is in contrast to countries such as Japan and South Korea, where the implementation of programmatic GC screening has directly led to an increase in the proportion of early-stage GC diagnoses, such that now more than 60%–70% of GCs are diagnosed in a curable stage; consequently, survival is now >70% overall and 95%–99% for early-stage GC in these countries.³ Data from the South Korea National Cancer Screening Program demonstrated that in the 10-year interval from the program's inception, the number of endoscopic screening examinations for GC increased 20-fold. During this time, the age-standardized incidence of GC remained stable to slightly increased, whereas overall survival significantly increased and was directly driven by the increased proportion of early-stage GCs.^{2,4} Indeed, a meta-analysis of studies (all from East Asia) comparing GC stage in individuals who underwent GC screening vs those who did not demonstrated that curable early-stage GCs were significantly more common in the screening (73%) vs the no-screening (43%) group.⁵ These data indicate that endoscopic screening is not simply overdiagnosing indolent tumors (ie, lead-time bias), but is instead impacting GC-related mortality.

Noncardia GC in the United States is defined by disparity. There is disparity in incidence and mortality, with a disproportionate burden of nonfatal and fatal GC in racial and ethnic minority groups, early-generation immigrants from countries where GC is endemic, and historically underserved populations.^{2,6–8} There is disparity in the publication of clinical guidance for primary and secondary prevention compared with other preventable gastrointestinal (GI) cancers amenable to endoscopic screening, namely esophageal cancer and colorectal cancer (CRC). There is disparity in public health awareness efforts and interventions for primary (eg, *Helicobacter pylori* eradication) and secondary prevention and early detection of GC. Lastly, there is disparity in research funding, as GC is among the lowest-funded cancers by the National Institutes of Health and National Cancer Institute, which has, in turn, hindered evidence generation regarding optimal approaches to primary and secondary prevention in the United States.⁹

Based on 2020 US Census data, >40% of the US population is non-White. The majority of immigrants to the United States migrate from high-incidence GC nations and retain their elevated GC risk.⁸ By 2065, it is projected that immigrants to the United States and their descendants will account for nearly 90% of the US population growth, with immigrants from Asia

Abbreviations used in this paper: AG, atrophic gastritis; CPU, Clinical Practice Update; CRC, colorectal cancer; EGC, early gastric cancer; EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection; GC, gastric cancer; GI, gastrointestinal; GIM, gastric intestinal metaplasia; gNET, gastric neuroendocrine tumor; GPMC, gastric premalignant condition; HGD, high-grade dysplasia; IEE, image-enhanced endoscopy; IND, indefinite for dysplasia; LGD, low-grade dysplasia; RCT, randomized clinical trial.

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and Latin America dominating this trend and surpassing the non-Hispanic White population.¹⁰ According to Surveillance, Epidemiology, and End Results Program data, the incidence of noncardia GC in the screening-age US population is 2- to >10-fold higher among the 10 most populous non-White racial and ethnic groups compared with the non-Hispanic White population, with Korean Americans ≥ 50 years-old having up to 14.5-fold higher risk. In fact, total GC incidence in Korean Americans (25.9 per 100,000 people) approaches combined colon and rectal cancer incidence in non-Hispanic White Americans (29.8 per 100,000) based on Surveillance, Epidemiology, and End Results Program registry data.^{7,11} GC incidence rates in the United States may even represent underestimates in the absence of programmatic screening because GC typically remains undiagnosed until the advanced stage, when clinical symptoms prompt diagnostic workup.

Considering these epidemiologic data and projected population trends, clinical guidance regarding GC prevention and early detection strategies is needed. There are no established screening guidelines for GC and there is not a large body of evidence informing screening and surveillance practice in the United States, which stands in contrast to esophageal adenocarcinoma and CRC. Accordingly, we acknowledge that the data supporting GC screening in high-risk populations in the United States are limited and clinical guidance is based more so on indirect evidence and expert opinion, rather than rigorous direct evidence. Notably, the lack of strong scientific evidence has not delayed other countries with diverse populations of heterogeneous GC risk (eg, several European countries^{12–15}) from advocating for and implementing risk-based GC screening, and, in parallel, taking action to establish research protocols so that screening strategies can be iteratively refined based on evidence.¹⁵

This Clinical Practice Update (CPU) provides current best practice advice on screening and surveillance in individuals at increased risk for intestinal-type noncardia gastric adenocarcinoma, herein designated “GC,” that is primarily related to chronic *H pylori* infection, but may also encompass autoimmune gastritis. This includes best practice advice for individuals to consider for screening and surveillance, elements comprising a high-quality endoscopic screening and surveillance examination, post-endoscopy management, and considerations for moving the needle to achieve equitable GC outcomes for all individuals residing in the United States. A comprehensive discussion of autoimmune gastritis, gastric intestinal metaplasia (GIM), endoscopic submucosal dissection (ESD) of gastric neoplasia and post-endoscopic resection management are beyond the scope of this CPU and are covered in other CPUs and guidelines.^{16–20} In the United States, cardia GC accounts for a minority of GCs⁷ and has an epidemiologic and risk factor profile that mirrors distal esophageal and gastroesophageal junction adenocarcinoma; for this reason, cardia GC is considered outside the scope of this document.

US Populations That Are Considered “High Risk”

Best Practice Advice 1: There are identifiable high-risk groups in the United States who should be

considered for GC screening. These include first-generation immigrants from high-incidence GC regions and possibly other non-White racial and ethnic groups, those with a family history of GC in a first-degree relative, and individuals with certain hereditary GI polypsis or hereditary cancer syndromes.

The success of a standardized program for GC screening relies on accurately identifying which populations in the United States are considered high-risk, as well as the ability to identify high-risk gastric lesions on the endoscopic examination. GC is distinct from CRC in that simple age-based universal screening is not cost-effective for the general US population and would waste limited endoscopic resources, given that endoscopy is the only currently acceptable screening modality. GC risk assessment should be individualized and should consider the person’s age, *H pylori* status, family history of any first-degree relatives with GC, country of origin, immigrant generation, acculturation and ethnic enclave, tobacco exposure, living in places under persistent poverty (defined by the US Department of Agriculture as locations where 20% or more of the residents have lived below the federal poverty level during a 4-decade period), certain hereditary GI polyposis syndromes (eg, familial adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis, MUTYH-associated polyposis, gastric adenocarcinoma, and proximal polyposis of the stomach) and hereditary cancer syndromes (eg, Lynch syndrome, hereditary breast and ovarian cancer syndrome, and Li-Fraumeni syndrome), and potentially dietary factors^{6,21} (Table 1). The risk for GC associated with each of these factors varies and the compounded risk of multiple factors along with their interaction is not defined, further underscoring the importance of personalized risk assessment.

Age is a surrogate measure of cumulative exposure to certain risk factors, particularly *H pylori* infection. Based on data from regions and populations where *H pylori* is endemic, *H pylori* is typically acquired in early childhood from family members. *H pylori* invariably causes gastritis in all individuals. In some individuals, chronic persistent infection after many years (usually 2–3 decades or more) may lead to gastric atrophy with or without metaplasia, with a much smaller percentage progressing to dysplasia and <1%–3% ultimately developing gastric adenocarcinoma. This process, known as the Correa cascade, is slow and characterized by discrete stages that can be assessed endoscopically and histologically, which is why targeted endoscopic screening and surveillance are rational approaches. The ideal age at which to initiate screening in high-risk US populations is not clear. That said, 45 years may be an optimal age as it 1) corresponds to the age for average-risk CRC screening initiation and facilitates the addition of esophagogastroduodenoscopy (EGD) at the time of colonoscopy, which is a cost-effective approach in those who are deemed at high risk for GC and select colonoscopy as their preferred CRC screening modality²²; and 2) mirrors the screening-eligible age in high-risk countries, including South Korea (age ≥ 40 years) and Japan (age 40–50 years).^{3,23} The age of screening initiation should be individualized for those with a first-degree family history of GC

Table 1. Risk Factors That Should Prompt Consideration of a Personalized Approach to Screening for Gastric Cancer in the United States Among Individuals 45 Years and Older

Risk factors
Early-generation immigrants from moderate to high incidence GC regions (defined as GC incidence ≥ 10 –12 per 100,000 people; includes Eastern Europe, Andean Latin America, and East Asia) ^a
Family history of GC in a first-degree relative (to start 10 y earlier than the youngest affected relative)
Non-White racial and ethnic groups with established moderate to high incidence GC ^a
Personal history of chronic <i>Helicobacter pylori</i> infection and at least 1 of the following: • History of regularly smoking tobacco (>20 pack-years) • Chronic consumption of high-salt diet, red meat, processed meats, and foods • Individuals living under persistent poverty in the United States^b
Certain hereditary GI polyposis syndromes and hereditary cancer syndromes

^aResearch efforts should focus on generating evidence to support the development of risk-stratification tools that are independent of race and ethnicity, in line with the goal of moving away from race and ethnicity-based clinical decision making for cancer prevention. Currently, however, country of origin, race, and ethnicity are highly predictive surrogate markers of GC risk, especially when combined with age and other risk factors.

^bDefined as areas where 20% or more of the residents have lived below the federal poverty level during a 4-decade period.

(10 years earlier than the youngest age of diagnosis of the proband family member) and in those with hereditary syndromes associated with GC.

Based on a population-based analysis of the California Cancer Registry of individuals 50 years or older (ie, a screening-eligible age group), non-White individuals had anywhere from a 2-fold up to 14.5-fold higher noncardia gastric adenocarcinoma incidence compared with non-Hispanic White individuals.⁷ Asian, Hispanic, and Black Americans are also 2- to 5-fold more likely to die from GC compared with non-Hispanic White Americans. It is important to emphasize, however, that race and ethnicity are surrogates for underlying risks, including *H pylori* status and social determinants of health. One systematic review and meta-analysis demonstrated that immigrants from countries of high GC incidence and mortality retain this elevated risk upon immigration to a low-incidence region, with up to 5-fold higher incidence and 2-fold higher mortality compared with the native population of the low-incidence host country.⁸ Notably, this risk attenuates with later generations residing in the destination nation, implicating modifiable risk factors, but more precise estimates of this attenuated risk and driving factors are lacking.

According to the International Agency for Research on Cancer, moderate-to-high GC incidence countries/regions are those where GC incidence is 10–12 per 100,000 people or higher.⁸ Therefore, disaggregation of non-Hispanic White Americans, Hispanic Americans, Asian Americans, and Black Americans according to country and region of origin is important for accurate risk stratification and GC mitigation, as disaggregation unearths differential GC risk, modifiable risk factors, and cultural considerations. For example, early-generation immigrants from Eastern Europe are a high-risk group and should be considered for screening, although generally speaking this group would be categorized as “non-Hispanic White” in epidemiologic studies.

GC mortality rates are 43% higher in US counties that fall under persistent poverty designation compared with US counties that do not (for comparison, the differential is 17.7% for CRC mortality and 12.3% for all cancer types combined),²⁴ highlighting the substantial impact of modifiable risk factors for GC, including living environment (eg, exposure to environmental carcinogens), diet, tobacco smoking and exposure to second-hand smoke, access to quality health care, and other social determinants of health. Among immigrant groups, ethnic enclave (level of acculturation) in addition to socioeconomic status impacts GC risk, with individuals in the highest enclave (least acculturation) and lowest neighborhood socioeconomic status having the highest GC risk.²¹ Several meta-analyses consistently found that diets containing high salt, and rich in red and processed meats and foods are associated with increased GC risk, whereas diets with higher intakes of fiber, fresh fruits/vegetables, and lean white meats are associated with a lower risk. Future research should focus on better understanding how the built environment and community and cultural factors interact to influence GC risk and participation in GC prevention and early detection activities, as well as on the implementation of culturally and socially appropriate interventions to target these important modifiable risk factors.

There are insufficient data to inform whether GC screening should be performed solely based on high-risk behavioral determinants (eg, smoking and diet) or living in areas of persistent poverty. Instead, a personalized approach to GC screening should be considered for individuals 45 years or older with multiple behavioral determinants, particularly those with current or former *H pylori* infection (Table 1).

Endoscopy as the Primary Screening Modality for Gastric Cancer

Best Practice Advice 2: Endoscopy is the best test for screening or surveillance in individuals at increased risk for GC. Endoscopy enables direct visualization to endoscopically stage the mucosa and identify areas concerning for neoplasia, as well as enables biopsies for further histologic examination and mucosal staging. Both endoscopic and histologic staging are key for risk stratification and determining whether ongoing surveillance is indicated and at what interval.

Best Practice Advice 3: High-quality upper endoscopy for the detection of premalignant and malignant gastric lesions should include the use of a high-definition white-light endoscopy system with image enhancement, gastric mucosal cleansing, and insufflation to achieve optimal mucosal visualization, in addition to adequate visual inspection time, photodocumentation, and use of a systematic biopsy protocol for mucosal staging when appropriate.

Gastric premalignant conditions (GPMCs, eg, AG, GIM, and dysplasia) and early GC are usually asymptomatic, and endoscopy with histologic confirmation from biopsies is currently the only way to accurately diagnose these conditions in US populations. Dysplasia and early-stage GC will ideally see the same successes in noninvasive screening as CRC; however, until that time, endoscopy is the mainstay for GC screening. The primary purpose of the screening upper endoscopy is to detect gastric neoplasia, ideally in an early stage when curative resection is achievable; and the secondary purpose is to risk-stratify individuals by staging the gastric mucosa through the detection of gastric atrophy and GIM, which is relevant to determining subsequent surveillance strategies (see below).

South Korea and Japan, 2 nations with previously high GC incidence and mortality, as well as sufficient health care resources, adopted population-based screening without the prerequisite of randomized clinical trial (RCT) data to prove the high benefit to negligible harm ratio associated with endoscopic screening. Subsequent long-term data from these screening programs showed undeniable benefit with respect to GC mortality reduction, even without full population adherence to endoscopic screening recommendations. A meta-analysis of 10 observational studies from Asia that comprised 342,013 individuals reported that, compared with no screening, endoscopic screening was associated with a significant 42% reduction in GC mortality (relative risk, 0.58; 95% CI, 0.48–0.70).²⁵ In the United States, current data are indirect and in the form of epidemiologic studies showing high GC incidence and mortality in identifiable high-risk groups in the United States (see Best Practice Advice 1), and cost-effectiveness analyses demonstrating that adding a screening upper endoscopy at the time of colonoscopy performed for CRC screening is cost-effective in Asian, Hispanic, and Black Americans, with ongoing surveillance if GPMCs are diagnosed.^{22,26} Serious harms of nontherapeutic upper endoscopy are very low²⁷ and, therefore, the main considerations are cost, resource utilization, and environmental considerations (“green endoscopy”), which are somewhat mitigated by appropriate risk stratification, combining EGD at the time of CRC screening in those who elect colonoscopy, and ideally the development of low-cost noninvasive screening tests. Ultimately, RCTs evaluating GC screening vs no screening on GC mortality in high-risk US groups should be the goal, although realistically this will require a shift in the funding climate for GC research; regardless, this should not delay current GC prevention and early detection efforts, and this has been the approach in other regions of the world with

mixed populations of heterogeneous GC risk, including Europe.¹⁵

The endoscopic miss rate for early GC is consistently around 10%, and higher among inexperienced endoscopists.²⁸ High-quality upper endoscopy for the detection of premalignant and malignant gastric lesions should include the use of a high-definition white-light endoscopy system with image enhancement (eg, narrow band imaging and linked color imaging), gastric mucosal cleansing and insufflation to achieve complete mucosal visualization, adequate visual inspection time and photodocumentation for endoscopic mucosal staging, and use of a systematic biopsy protocol for histologic staging when appropriate. These metrics are detailed in the AGA CPU on high-quality endoscopy.²⁹ Training, continuing medical education, image libraries, and progressive technological advancements (eg, artificial intelligence) should be prioritized and detection metrics established and adhered to, as low detection rates of gastric premalignant and malignant lesions would surely undermine the success of GC screening in the United States (analogous to low adenoma detection rates compromising the success of screening colonoscopy on CRC mortality).

Opportunistic *H pylori* Screening and Eradication as an Essential Adjunctive Strategy for Gastric Cancer Prevention

Best Practice Advice 4: *H pylori* eradication is essential and serves as an adjunct to endoscopic screening and surveillance for primary and secondary prevention of GC. Opportunistic screening for *H pylori* infection should be considered in individuals deemed to be at increased risk for GC (refer to Best Practice Advice 1). Screening for *H pylori* infection in adult household members of individuals who test positive for *H pylori* (so-called “familial-based testing”) should also be considered.

H pylori is the most common infectious carcinogen worldwide and is responsible for 90% of the global GC burden.³⁰ Non-US RCTs consistently demonstrate that *H pylori* eradication is associated with significantly reduced GC incidence and mortality, with a meta-analysis of these RCTs reporting a significant 46% (relative risk, 0.54; 95% CI, 0.40–0.72; number needed to treat = 72) and 39% (relative risk, 0.61; 95% CI, 0.40–0.92; number needed to treat = 135) respective reduction in GC incidence and mortality among those with vs without *H pylori* eradication therapy.³¹ Corresponding US data consist of 2 recent observational studies, 1 from a nationwide Veterans Affairs cohort and a second from a diverse Northern California population, both demonstrating that patients with successful *H pylori* eradication had substantially reduced risk of GC compared with those with persistent infection.^{32,33} *H pylori* eradication also lowers the risk of metachronous GC in patients with resected gastric neoplasia.³¹

These compelling data, coupled with the fact that the vast majority of people infected with *H pylori* are

asymptomatic and unaware of their *H pylori* status, form the basis for opportunistic screening for *H pylori* infection via nonserologic testing as a GC prevention strategy. All adults diagnosed with *H pylori* infection warrant eradication treatment, irrespective of symptoms, barring contraindications or limited life expectancy. Successful eradication should be confirmed in all people at least 4 weeks after the treatment course.³⁴ Universal *H pylori* screening in asymptomatic adults has not proven to be a cost-effective strategy in the United States. Instead, opportunistic screening for active *H pylori* infection should be considered in individuals deemed to be at increased risk for GC (refer to Best Practice Advice 1). Screening adult household members of individuals who test positive for *H pylori* (so-called “familial-based testing”) should also be considered. A meta-analysis of 12 RCTs (9 from China, 2 from Turkey, 1 from England) demonstrated that the eradication success rate of the whole-family test and treatment group was 3-fold higher (odds ratio, 2.93; 95% CI, 1.68–5.13) than the single-patient treatment group, with a 70% lower recurrence rate (odds ratio, 0.3; 95% CI, 0.19–0.48).³⁵ The optimal age for *H pylori* screening for the purpose of primary GC prevention in high-risk populations is not established for the diverse US population.³⁶ The greatest benefit of *H pylori* eradication is before the development of gastric precancerous changes. A non-US RCT with nearly 27 years of endoscopic follow-up found that *H pylori* eradication in individuals without gastric precancer at baseline was associated with a significant 63% reduction in GC risk vs a 43% reduction when considering individuals overall irrespective of histology.³⁷ Based on these data, the Taipei Global Consensus on screening and eradicating *H pylori* for GC prevention suggests screening for *H pylori* between ages 20 and 40 years.³⁸

Opportunistic *H pylori* screening and subsequent eradication treatment is essential, but should be considered an adjunctive measure to endoscopic screening because *H pylori* eradication does not suffice as a stand-alone population GC prevention strategy. This is distinctly because individuals with histologic changes related to *H pylori*, particularly if more advanced, remain at risk for neoplastic progression even once *H pylori* is eradicated and, therefore, should still be considered for endoscopic screening and surveillance.

Methods to Improve the Detection of Gastric Premalignant Conditions and Early Gastric Cancer

Best Practice Advice 5: In individuals with suspected gastric atrophy with or without intestinal metaplasia, gastric biopsies should be obtained according to a systematic protocol (eg, updated Sydney System) to enable histologic confirmation and staging. A minimum of 5 total biopsies should be obtained, with samples from the antrum/incisura and corpus placed in separately labeled jars (eg, jar 1, “antrum/incisura” and jar 2, “corpus”). Any suspicious areas should be described and biopsied separately.

Best Practice Advice 6: GIM and dysplasia are endoscopically detectable. However, these findings often go undiagnosed when endoscopists are unfamiliar with the characteristic visual features; accordingly, there is an unmet need for improved training, especially in the United States. Artificial intelligence tools appear promising for the detection of early gastric neoplasia in the adequately visualized stomach, but data are too preliminary to recommend routine use.

The risk of GC associated with AG and GIM varies according to several established risk factors, including age, concomitant *H pylori* infection, anatomic extent and distribution of AG/GIM, histologic severity of AG/GIM, GIM subtype (eg, complete vs incomplete), family history of GC, smoking, diet, and other factors. Non-White race, ethnicity, and immigration from a high GC incidence country are risk factors for GPMC and GC, but are not established risk factors for GPMC malignant progression.^{39,40} GIM can be accurately detected on high-definition white light endoscopy when image-enhancing technologies that are routinely available (eg, narrow band imaging and linked color imaging) are used concomitantly, with sensitivity and specificity of narrow band imaging and linked color imaging without magnification exceeding 85%–90% for GIM. The use of upper endoscopy for a global endoscopic risk assessment is already practiced outside the United States,⁴¹ particularly in the East, where biopsies in the absence of a concern for advanced gastric neoplasia are not part of routine practice.

Until US endoscopists achieve more reliable detection rates for GPMCs, individuals with suspected gastric atrophy with or without metaplasia should have gastric biopsies obtained according to a systematic protocol (eg, updated Sydney System) to enable histologic confirmation and staging. A minimum of 5 total biopsies should be obtained, with samples from the antrum/incisura and corpus placed in separately labeled jars (ie, a minimum of 2 separate jars).⁴² Any suspicious areas should be described and biopsied separately.

Endoscopic Management According to Findings on the Index Screening Examination

Best Practice Advice 7: Endoscopists should work with their local pathologists to achieve consensus for consistent documentation of histologic risk-stratification parameters when atrophic gastritis (AG) with or without metaplasia is diagnosed. At a minimum, the presence or absence of *H pylori* infection, severity of atrophy and/or metaplasia, and histologic subtyping of GIM, if applicable, should be documented to inform clinical decision making.

Best Practice Advice 8: If the index screening endoscopy performed in an individual at increased risk for GC (refer to Best Practice Advice 1) does not identify atrophy, GIM, or neoplasia, then the decision to continue screening should be based on that individual’s risk factors and preferences. If the individual has a family

history of GC or multiple risk factors for GC, then ongoing screening should be considered. The optimal screening intervals in such scenarios are not well defined.

Best Practice Advice 9: Endoscopists should ensure that all individuals with confirmed gastric atrophy with or without GIM undergo risk stratification. Individuals with severe AG and/or multifocal/incomplete GIM are likely to benefit from endoscopic surveillance, particularly if they have other risk factors for GC (eg, family history). Endoscopic surveillance should be considered every 3 years; however, intervals are not well defined and shorter intervals may be advisable in those with multiple risk factors, such as severe GIM that is anatomically extensive.

Best Practice Advice 10: Indefinite and low-grade dysplasia (LGD) can be difficult to reproducibly identify by endoscopy and accurately diagnose on histopathology. Accordingly, all dysplasia should be confirmed by an experienced GI pathologist, and clinicians should refer patients with visible or nonvisible dysplasia to an endoscopist or center with expertise in the diagnosis and management of gastric neoplasia. Individuals with indefinite or LGD who are infected with *H pylori* should be treated and have eradication confirmed, followed by repeat endoscopy and biopsies by an experienced endoscopist, as visual and histologic discernment may improve once inflammation subsides.

Best Practice Advice 11: Individuals with suspected high-grade dysplasia (HGD) or early GC should undergo ESD with the goal of en bloc, R0 resection to enable accurate pathologic staging with curative intent. Eradication of active *H pylori* infection is essential but should not delay endoscopic intervention. ESD should be performed at a center with endoscopic and pathologic expertise.

The findings on the index screening endoscopy should determine subsequent management (Figure 1). All individuals confirmed to have active *H pylori* should be treated and eradication confirmed.

Normal (No Premalignant or Malignant Findings)

If the index screening EGD performed in an individual at increased risk for GC does not identify GPMCs or GC, the decision to continue endoscopic screening should be based on individual risk factors, in addition to patient preference. A Markov model simulating endoscopic gastric screening in US individuals starting at age 50 years at the time of screening colonoscopy with ongoing biennial stand-alone screening EGD when the gastric mucosa was normal was not cost-effective; however, this simulation model only considered age, race, ethnicity, and endoscopic or histologic findings and did not consider other individual-level risk factors, such as first-degree family history of GC.²² In individuals with an established or suspected hereditary syndrome associated with increased GC risk, endoscopic surveillance should continue at regular intervals determined according to the syndrome. If the individual has a family history of GC and/or persistent *H pylori* infection

despite attempts at eradication, then ongoing screening should be considered. The optimal screening intervals in such scenarios are not well defined, but endoscopy every 3–5 years should be considered. Notably, although biennial EGD is a suggested population-based screening strategy in South Korea and Japan, irrespective of a normal index screening examination, this strategy is being re-evaluated in the context of the birth cohort-related decline in *H pylori* prevalence and decline in GC incidence and mortality due in large part to national *H pylori* screen-and-eradicate campaigns and endoscopic GC screening; instead, a risk-stratified approach is now being discussed.⁴⁴

Atrophic Gastritis and Gastric Intestinal Metaplasia Without Dysplasia

Endoscopists should ensure that all individuals with confirmed AG with or without metaplasia undergo risk stratification. Endoscopists should work with their local pathologists to achieve consensus for consistent documentation of histologic risk-stratification parameters when AG with or without metaplasia is diagnosed. At a minimum, the presence or absence of *H pylori* infection, the severity of AG and/or GIM, and the histologic subtype of GIM, if applicable, should be documented in order to inform clinical decision making.^{16,20}

Individuals with histologically confirmed moderate to severe AG with or without GIM of the antrum or corpus, incomplete- or mixed-type GIM (vs complete-type only), or corpus-extended GIM (defined as involvement of the corpus in addition to antrum and/or incisura) identified on the index examination are likely to benefit from endoscopic surveillance, particularly if they have other risk factors for GC. Endoscopic surveillance should be considered every 3 years, but evidence-based intervals are not well defined; shorter intervals may be advisable in those with multiple risk factors or severe corpus-extended GIM, given that studies have found a substantially higher risk of progression in these cases, often within 2 years of the previous endoscopy.⁴⁵ A full discussion of AG and GIM surveillance is beyond the scope of this CPU and is covered in both US^{16,17} and corresponding international clinical guidance documents.²⁰ Although histologic risk-stratification parameters (eg, GIM subtype, severity, and extent) are among the strongest determinants to inform clinical decision making on the need for ongoing surveillance and at what interval, these parameters are inconsistently reported on US pathology reports. Coordinated efforts between pathologists and gastroenterologists are needed to improve the consistency of reporting.

Dysplasia and/or Early Gastric Cancer

Dysplasia, particularly indefinite for dysplasia (IND) and low-grade dysplasia (LGD), is subject to interobserver variability and all biopsies concerning for dysplasia should be confirmed by an experienced GI pathologist. One study reported that approximately 40% of IND may be reclassified—either as negative for dysplasia or upstaged to LGD and even HGD—on re-review by an experienced GI

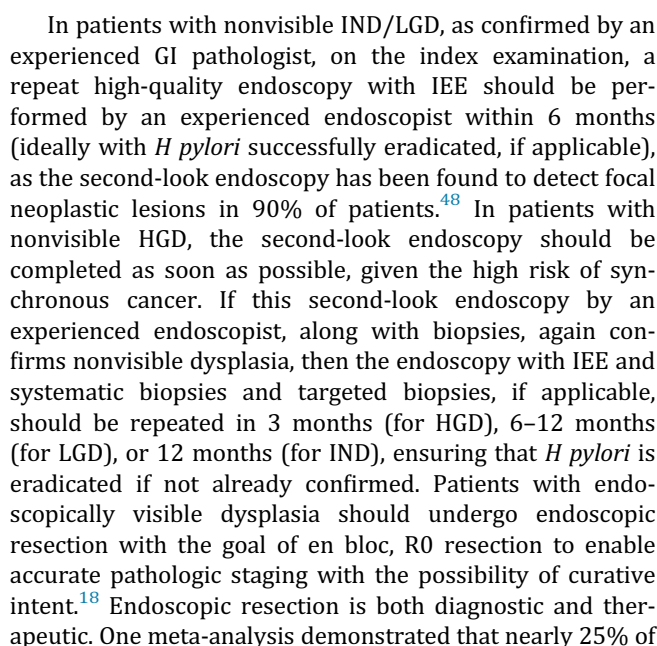


Figure 1. Clinical pathway suggested for the care of individuals in the United States who have undergone a high-quality EGD to screen for GC or who have endoscopic or histologic findings of AG, GIM, or neoplasia. *This clinical pathway does not apply to individuals at risk for hereditary diffuse GC. **Typically ESD; in select scenarios, such as lesions <1 cm or confirmed IND histology, en bloc endoscopic mucosal resection can be considered. Algorithm design adapted with permission from Pimentel-Nunes et al.⁴³

dysplastic lesions with LGD on biopsies were up-staged after complete endoscopic resection—17% to HGD and 7% to carcinoma.⁴⁹ Lesions with confirmed or suspected HGD, lesions that are depressed, ulcerated, and/or ≥ 20 mm should be resected using ESD as opposed to endoscopic mucosal resection, as these lesions are more likely to harbor carcinoma. Before endoscopic resection, patients should be counseled that additional treatment, including surgery, may be indicated if cancer is diagnosed, and this would depend on the cancer grade and stage, along with patient-level factors and preferences.

Gastric ESD is a novel technique that was invented and then continually innovated in Japan and then Korea as the direct consequence of successful programmatic GC screening programs in these countries. The number of advanced endoscopists with proficiency in performing gastric ESD and achieving high R0 and low complication rates has been increasing in the United States in the past several years and gastric ESD is becoming more of an established practice.⁵⁰ A necessary component of successful programmatic GC screening in the United States among high-risk groups is ensuring the quality and consistency of training in the detection of gastric lesions among all general gastroenterologists and proficiency of gastric ESD among advanced endoscopists.

Surveillance After Gastric Neoplasia Resection

Best Practice Advice 12: Individuals with a history of successfully resected gastric dysplasia or cancer require ongoing endoscopic surveillance. Suggested surveillance intervals exist, but additional data are required to refine surveillance recommendations, particularly in the United States.

All patients with resected gastric neoplasia should have ongoing surveillance endoscopy. Suggested surveillance intervals exist and depend on the lesion histology and whether R0 resection was achieved.¹⁹ Additional data are required to refine surveillance recommendations, particularly in the United States.¹⁹ Endoscopic surveillance should be continued indefinitely in patients with previously resected HGD or GC, unless the patient's health status or preference indicates otherwise, given that the risk of metachronous and recurrent gastric neoplasia remains elevated after curative resection, even several years post resection.⁵¹ Readers should refer to 2 recently published AGA CPUs for more detailed best practice guidance on ESD¹⁸ and post-resection surveillance of gastric neoplasia, which also applies to patients after partial gastrectomy for gastric neoplasia.¹⁹

Management of Type I Gastric Carcinoid and Neuroendocrine Tumor

Best Practice Advice 13: Type I gastric carcinoids in individuals with AG are typically indolent, especially if <1 cm. Endoscopists may consider resecting gastric carcinoids <1 cm and should endoscopically resect

lesions measuring 1–2 cm. Individuals with type I gastric carcinoids >2 cm should undergo cross-sectional imaging and be referred for surgical resection, given the risk of metastasis. Individuals with type I gastric carcinoids should undergo surveillance, but the intervals are not well defined.

The serum gastrin level (elevated vs normal), histology of the surrounding gastric mucosa (atrophic vs non-atrophic), anatomic location, and focality (multifocal vs singular) are essential for determining the type of gastric carcinoid (ie, type I, type II, or type III), which is essential to determining management and prognosis. Type I gastric neuroendocrine tumors (gNETs) account for 70%–80% of all gNETs. Fortunately, these are typically small (<1 cm) benign tumors that are indolent with low mitotic and Ki67 proliferation indices. These develop in the setting of gastric (corpus) atrophy due to chronic *H pylori* infection, autoimmune gastritis, or an overlap of these conditions, as the result of physiologic hypergastrinemia due to parietal cell loss–mediated achlorhydria. Endoscopists may consider resecting small type I gNETs (<1 cm). Lesions measuring 1–2 cm should be endoscopically resected by an endoscopist with experience in resection of gastric lesions. Endoscopic ultrasound should be considered for patients with larger type I gNETs to assess depth of tumor invasion or local metastasis to guide management. Patients with type I gNETs >2 cm or those with unfavorable histology (eg, World Health Organization grade II or higher) are at risk of metastasis, and should undergo endoscopic ultrasound and cross-sectional imaging, and should be discussed in a multidisciplinary tumor board consisting of an advanced endoscopist, surgical oncologist, and experienced pathologist. Surgical resection should be performed in medically appropriate patients with gNETs >2 cm, invasion past the submucosa, and/or lymph node metastasis. The management of type II gNETs, which develop from gastrinoma-mediated hypergastrinemia (Zollinger-Ellison syndrome), and type III gNETs, which are sporadic and more often associated with malignant behavior, is beyond the scope of this CPU.

De-escalation of Endoscopic Gastric Cancer Screening and Surveillance

Best Practice Advice 14: In general, only individuals who are fit for endoscopic or potentially surgical treatment should be screened for GC and continued surveillance of premalignant gastric conditions. If a person is no longer fit for endoscopic or surgical treatment, then screening and surveillance should be stopped.

Only individuals who are fit for endoscopic or potentially surgical treatment should be screened for early GC and surveilled for premalignant gastric conditions. There is no strict age or comorbidity threshold at which to consider de-escalation of screening and surveillance, and this consideration should balance patient life expectancy, perceived benefit of ongoing screening and surveillance, risk of complications, and personal preferences. Generally speaking,

once a person is no longer fit for endoscopic or surgical treatment, then screening and surveillance should be stopped.

Implementation and Sustainability

Best Practice Advice 15: To achieve health equity, a personalized approach should be taken to assess an individual's risk for GC to determine whether screening and surveillance should be pursued. In conjunction, modifiable risk factors for GC should be distinctly addressed, as most of these risk factors disproportionately impact people at high risk for GC and represent health care disparities.

GC epitomizes racial and ethnic disparity in cancer at all levels, from epidemiology, stage at diagnosis, post-diagnosis management, and stage-specific and overall survival. Adhering to clinical practice guidance that is rational and supported by the best available evidence is the first step to achieving health equity in GC prevention and early detection. A personalized approach should be taken to assess an individual's risk for GC to determine whether screening and surveillance should be pursued. In conjunction, modifiable risk factors for GC should be distinctly addressed, as most of these risk factors disproportionately impact people at high risk for GC and represent health care disparities (eg, *H pylori* infection, persistent living in poverty, tobacco use, diets high in salt and processed foods and lacking in fresh produce, barriers to accessing and paying for high-quality health care).

To ensure the success of GC screening in the United States and the actualization of GC mortality reduction, 3 foundational elements must be upheld and sustained equally (Figure 2): the first is preprocedural, the second is intraprocedural, and the third is postprocedural. The preprocedural foundation encompasses consistently and appropriately identifying and referring eligible high-risk individuals for endoscopic screening and removing

system-level and patient-level barriers to screening participation, including ensuring equitable access to endoscopy and ensuring that GC screening procedures are covered by insurance through stakeholder engagement. We can expect that the same barriers to screening participation that undermine colorectal and other screenable cancer prevention programs will undermine GC screening programs and may plausibly be more pronounced, considering that GC disproportionately impacts historically underserved groups where language, education, economic, transportation, and cultural barriers are overrepresented. The intraprocedural foundation relies on ensuring endoscopists are performing high-quality upper endoscopic examinations, are appropriately detecting and risk-stratifying GPMCs and early GC and ensuring that high-quality gastric ESD becomes increasingly accessible. The postprocedural foundation relies on equitable access to post-endoscopic management, including surveillance, equitable access to oncologic services if needed, and working to correct the disparate outcomes in GC morbidity and mortality, including stage-specific survival.

Finally, a recent analysis demonstrated that GC ranked lowest (19th) in terms of National Cancer Institute funding-to-lethality ratio.⁹ Amplification of research funding for primary and secondary GC prevention in the United States is needed to ensure clinical practice is being driven by the best-quality evidence, to correct disparities, to improve outcomes, and to ensure the sustainability of GC screening moving forward with iterative modifications made to clinical practice guidance according to the contemporary evidence and resource climate. Current high-priority evidence gaps include identifying precise, cost-effective biomarkers, particularly noninvasive biomarkers, for individualized risk stratification to reduce the burden of endoscopy, to ensure environmental sustainability of programmatic GC screening, and to move away from race and ethnicity-based recommendations; enhanced endoscopic technologies (eg, artificial

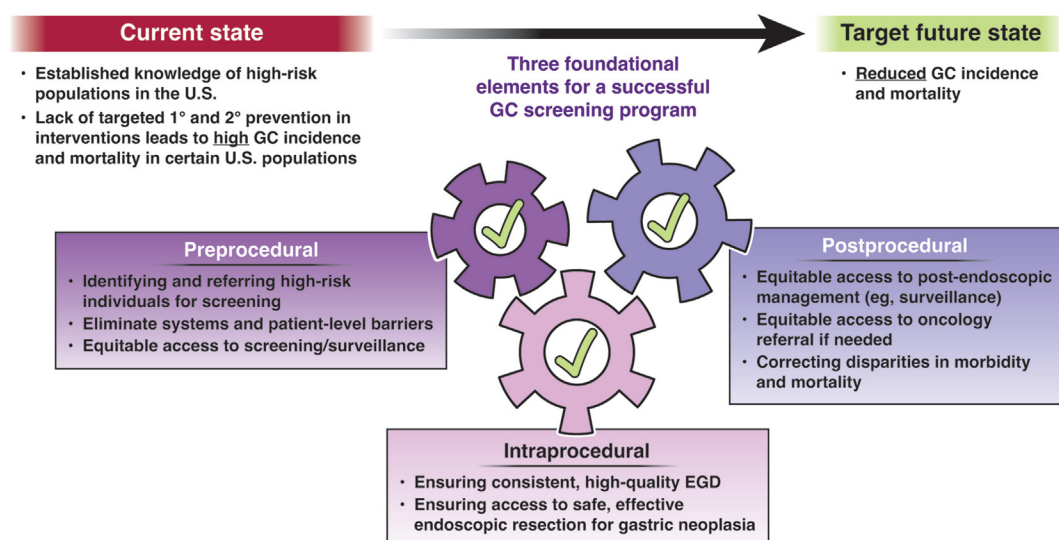


Figure 2. Preprocedural, intraprocedural, and postprocedural pillars that are needed to secure the foundation for effective programmatic GC screening in the United States.

intelligence) to aid in detecting and resecting gastric lesions; and evidence-based interventions to improve screening uptake (eg, culturally and linguistically aligned patient navigators).

Supplementary Material

Note: To access Supplementary References 26–51 accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2024.11.001>.

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Author Contributions

Shailja C. Shah: writing the first draft. Shailja C. Shah, Andrew Y. Wang, Michael B. Wallace, Joo Ha Hwang: critical revisions for manuscript content and presentation. All authors approved the content of this manuscript in full before submission. All authors contributed to drafting and revising the Best Practice Advice statements.

Conflicts of interest

The authors disclose the following: Shailja C. Shah is a consultant for RedHill Biopharma, Phathom Pharmaceuticals, and third-party consulting firms GLG and Guidepoint; is an unpaid advisory board member for Ilico Genetics, Inc;

and has previously received personal income/remuneration from Medscape LIVE. Andrew Y. Wang owns publicly traded stock in GE HealthCare Technologies and Pfizer. Michael B. Wallace is a consultant for Cosmo/Aries Pharmaceuticals, Verily Life Sciences, LLC, Boston Scientific, Endiatix, InterVenn Biosciences, AlphaMed UAE, Fujifilm, and ClearNote. Joo Ha Hwang is a consultant for Olympus, Medtronic, Boston Scientific, Fujifilm, and Micro-Tech; and also receives research grant support from AI Medical.

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