Review Article

Screening for gastric cancer in China: Advances, challenges and visions

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Abstract

Gastric cancer (GC) is one of the major cancers in China and all over the world. Most GCs are diagnosed at an advanced stage with unfavorable prognosis. Along with some other countries, China has developed the government-funded national screening programs for GC and other major cancers. GC screening has been shown to effectively decrease the incidence of and mortality from GC in countries adopting nationwide screening programs (Japan and Korea) and in studies based on selected Chinese populations. The screening of GC relies mostly on gastroendoscopy, the accuracy, reliability and safety of which have been indicated by previous studies. However, considering its invasive screening approach, requirements on skilled endoscopists and pathologists, and a high cost, developing noninvasive methods to amend endoscopic screening would be highly needed. Numerous studies have examined biomarkers for GC screening and the combination of biomarkers involving pepsinogen, gastrin, and *Helicobacter pylori* antibodies has been proposed for risk stratification, seeking to narrow down the high-risk populations for further endoscopy. Despite all the achievements of endoscopic screening, evidence on appropriate screening age, intervals for repeated screening, novel biomarkers promoting precision prevention, and health economics need to be accumulated to inform policymakers on endoscopic screening in China. With the guide of *Health China 2030 Planning Outline*, we have golden opportunities to promote prevention and control of GC. In this review, we summarize the characteristics of screening programs in China and other East Asian countries and introduce the past and current approaches and strategies for GC screening, aiming for featuring the latest advances and key challenges, and illustrating future visions of GC screening.

Keywords: Gastric cancer; screening; gastroendoscopy; pepsinogen; gastrin 17; *Helicobacter pylori*

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Introduction

Gastric cancer (GC) remains a critical public health problem worldwide. Globally, GC is the fifth most frequently diagnosed cancer and the fourth leading cause of cancer-related death, responsible for over one million new cases and estimated 769,000 deaths in 2020, with almost half of new cases and deaths occurring in China each year (1). The etiology of GC is still unclear but is known to involve the complex interplay of host and environment, with *Helicobacter pylori* (*H. pylori*) recognized as a major risk factor (2). Its occurrence, particularly of the intestinal type, experiences the multistep evolution of a cascade of

gastric lesions, including superficial gastritis (SG), chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and low-grade intraepithelial neoplasia (LGIN) (3), which is therefore characterized by insidious onset, asymptomatic or minor symptoms at an early stage, resulting in delayed diagnosis and poorer survival for most patients (4,5). Right now, more than 80% of GC patients are diagnosed at an advanced stage in China and the overall 5-year survival rate is only 35.1% (6). The prevention and control of GC poses great challenges to the public health systems.

The beneficial effect of *H. pylori* eradication on GC prevention has been recognized based on several intervention trials (7,8). The Shandong Intervention Trial conducted by our team highlights the long-term effect of *H. pylori* eradication on decreasing GC incidence and mortality and also reports the potential benefits of vitamin supplementation and garlic supplementation for GC (7). Even so, uncertainties persist on the full spectrum of benefits and harms associated with these primary prevention approaches, which require further large-scale studies before the application for large community-based primary prevention. Screening for early detection, early diagnosis and early treatment of GC, known as the secondary prevention has been the mainstay of present endeavor of GC prevention and control in China and all over the world.

While the current GC screening relies primarily on gastroendoscopy, other approaches had been used previously and efforts have also been made to define novel biomarkers for GC detection. Along with some other countries, China has developed the government-funded national screening programs for GC and other major cancers. Since 2012, the screening programs for GC and esophageal cancer have been merged as the national Upper Gastrointestinal Cancer Early Detection (UGCED) program, yielding tremendous achievements for GC prevention (9). However, the past GC screening in China has been restricted to selected areas. There are challenges to extend the coverage of the screening program, prioritize populations at a particularly high risk, and conduct repeated screening for those needed at suitable time intervals. The screening protocol also needs to be refined for the best cost-effectiveness. In this review, we summarize the characteristics of screening programs in China and other East Asian countries and the past and current approaches for GC screening, aiming for featuring the latest advances and key challenges, and illustrating future visions of GC screening.

National screening programs for GC in East Asian countries

GC is particularly prevalent in East Asian countries. Japan and Korea have started nationwide GC screening programs in 1983 and 2002, respectively, leading to increased early detection of GC and declined mortality (10-12). In contrast, the screening program in China is based on selected high-risk areas (*Table 1*).

Japan

At the beginning of the 1960s, Japan started to implement a mass GC screening program with the method of indirect upper gastrointestinal series (UGIS) with barium meal in Miyagi prefecture. In 1983, the program was expanded for all residents aged 40 years and older based on the Health Service Law for the aged. The guidelines were updated in 2018 which suggested GC screening for individuals aged 50 years and older, using endoscopic examination as the screening method. The guidelines also recommended repeated screening at an interval of 2−3 years (14).

Korea

In Korea, within the framework of National Cancer Screening Program (NCSP), GC screening has been provided to the Medicaid participants aged 40 years and older once every two years since 1999 by using either UGIS or endoscopy, which was further expanded to include National Health Insurance (NHI) beneficiaries in 2002 (18). The guideline in 2015 recommended asymptomatic adults from 40 to 74 years for GC screening (15). The screening program has been free of charge for Medicaid participants since the program inception. Participants with family income under the median also do not need to pay any charges since 2005, although others need to pay part of the screening cost (10% co-payment since 2010) (11,18,19). Longitudinal data supported the effect of GC screening on detecting localized GC by using endoscopy or UGIS and reducing the mortality from GC particularly by using endoscopy (20,21). Thereby, upper gastroendoscopy has been recommended for GC screening currently (15).

China

The Chinese government has paid great attention to cancer screening in the last two decades. In 2003, the former Ministry of Health (MoH) (the Current National Health

Table 1 Comparison of GC screening strategies among different countries

Country	Program	Start time	Population	Screening age (year)	Screening methods	Screening intervals	Screening cost	Source
Japan	GC screening	1983	Nationwide	≥40	UGIS	Repeated UGIS within 1 year	Government subsidies, copayment rate is 30% personally	The Japanese Guidelines for GC Screening in 2008 (13)
	GC screening	2018	Nationwide	≥50	Endoscopy	Repeated endoscopy within 2–3 years	Government subsidies, copayment rate is 30% personally	The Japanese Guidelines for GC Screening in 2018 (14)
Korea	National Cancer Screening Program	2002	Nationwide	40–74	Endoscopy	Repeated endoscopy within 2 years	10% test fee for high-income	The Korean Guideline for GC Screening in 2015 (15)
China	Early diagnosis and early treatment program in rural areas (UGCED program since 2012)	2008	Individuals in selected high-risk rural areas	40–69	(1) PG test and endoscopy (2) Endoscopy	(1) Individuals of †PG (–): repeated PG test within 3 years; Individuals of †PG (+) and §endoscopy (–): repeated PG test within 1 year (2) Individuals diagnosed with severe CAG, severe IM and LGIN: repeated endoscopy within 1 year	Free of charge	Technical Plan for Early Diagnosis and Treatment of Cancer (2011) (16)
	UGCED program	2020	Individuals in selected high-risk rural areas	40–69	Endoscopy	Individuals diagnosed with severe CAG, severe IM and LGIN: repeated endoscopy within 3 year	Free of charge	Technical Plan for Screening and Early Diagnosis and Treatment of Upper Gastrointestinal Cancer (Trial Version in 2020) (17)
	The Cancer Screening Program in Urban China (CanSPUC)	2012	High-risk individuals in selected urban cities	45–74	Questionnaire surveys, *H. pylori* serological test, then endoscopy and biopsy for high-risk individuals	Individuals with moderate or severe IM or gastric polyps: repeated endoscopy within 12 months; Individuals with moderate or severe CAG: repeated endoscopy within 6–12 months; Individuals with LGIN: repeated endoscopy within 3–6 months	Free of charge	Technical Plan for CanSPUC (versions 2019 and 2020)

CAG, Chronic atrophic gastritis; GC, gastric cancer; IM, intestinal metaplasia; LGIN, low-grade intraepithelial neoplasia; PG, pepsinogen; UGCED, upper gastrointestinal cancer early detection; UGIS, upper gastrointestinal series; PGR, PG I/PG II ratio; §Endoscopy (–), pathologically diagnosis of normal mucosa or mild lesions including superficial gastritis, mild/moderate CAG, mild/moderate IM; †PG (+)/PG (–), those with serum PG I ≤70 μg/mL and PGR ≤7 are defined as PG-positive (+) and others are PG-negative (–).

Commission) issued the *Outline of Chinese Cancer Program (2004–2010)*. The outline stressed the importance of early detection, early diagnosis, and early treatment in improving cancer prognosis and reducing cancer-specific mortality. In 2004, the Disease Prevention and Control Division of the former MoH and the China Cancer Foundation, also jointly responded by provincial health departments, established national demonstration bases for early diagnosis and early treatment of cancer. In 2005, the Ministry of Finance approved to apply Central Budget Funding Project to the early diagnosis and early treatment of cancer in high-risk areas, which was officially implemented in 2006. The screening program of GC has been launched since 2008 in Linqu County in Shandong province and Zhuanghe County in Liaoning province, two known high-risk rural areas in China (22). Also in 2008, Huai River Basin Cancer Early Diagnosis and Treatment Project was initiated, supported by the Public Health Special Fund. In 2010, Wuwei County in Gansu province was added as a new screening site. Since 2012, the screening program for GC and esophageal cancer has been merged as the national UGCED program, targeting eligible populations of selected high-risk rural areas. By the end of 2018, more than 2.16 million people had undergone upper gastrointestinal (UGI) endoscopy in 194 program sites, reaching a UGI cancer detection rate of 2.05%, with 70% detected at an early stage (23).

While the initial GC screening program targeted residents in selected rural areas, no such screening program was available for urban inhabitants until 2011. In 2012, the Ministry of Finance and the former MoH of China jointly initiated a key national public health program, which is named the Cancer Screening Program in Urban China (CanSPUC). The CanSPUC program was designed to focus on five prevalent cancers, including lung cancer, breast cancer, colorectal cancer, upper gastrointestinal cancers (GC and esophageal cancer), and liver cancer, in urban areas, initially covering nine provinces. The CanSPUC program applied a comprehensive questionnaire-based system to select individuals at high risk of developing GC and other cancers, covering a total of 50,000 urban residents (10,000 for each cancer type) aged 40–69 years in each selected province, with 10,000 of them accepting final cancer screening, which used endoscopy for GC (24).

The current national GC screening programs in China basically follow a modified high-risk population strategy, focusing on individuals aged 40–69 years in selected high-risk areas, and population selection is generally based on cluster sampling in each area. Among the screening methods for GC (as reviewed below in "Screening methods for GC"), *the Technical Plan for Early Diagnosis and Treatment of Cancer* published in 2011 recommended two methods for GC screening. One approach was to test for serum pepsinogen (PG) and do questionnaire surveys for preliminary screening, and individuals with positive serum PG or a personal history of UGI disorders or a family history of GC would be further screened by endoscopy, but this approach was only used before 2012. The other approach was to use gastroendoscopy screening and tissue biopsy directly, the standard approach used in all national programs after 2012. The technical plan suggested that individuals with severe CAG, severe IM, and LGIN be followed up by gastroendoscopy once a year (16). Recently, *Technical Plan for Screening and Early Diagnosis and Treatment of Upper Gastrointestinal Cancer* (*Trial Version in 2020*) suggested that individuals with severe CAG, severe IM and LGIN at a endoscopy screening be followed up by gastroendoscopy at least once within next three years (17). For example, in Linqu County, Shandong province, a rural area with a particularly high GC mortality (25), 3,000 individuals (including individuals receiving the initial or repeated endoscopy) underwent endoscopy screening for GC per year, supported by the national UGCED program.

Screening methods for GC

Imaging examination

UGIS with barium meal (radiographic screening) was used as a screening method for the national GC screening program previously both in Japan and Korea. However, concerns on the radioactivity, lack of biopsy and low sensitivity and specificity of UGIS cannot be addressed, which has generally been replaced by endoscopic screening in the national GC screening programs in East Asian countries. Lee *et al.* reported that higher sensitivity and specificity of endoscopy compared with UGIS (26). Accumulating evidence has also supported GC screening by endoscopy as a more effective approach in reducing GC mortality than UGIS (14,20,21,27-29). Even so, UGIS could still be used as an alternative screening method in areas lacking facilities and trained staffs for endoscopy.

Electronic endoscopy

Electronic endoscopy with pathological diagnosis of biopsy is the golden criteria for diagnosis of GC and is currently the most acceptable method for GC screening in screening

programs all over the world. White light endoscopy, chromoendoscopy, digital chromoendoscopy, narrow-band imaging, magnifying endoscopy are among the most commonly used electronic endoscopy technologies (30).

Previous studies on Korean and Japanese national programs have reported the beneficial effect of endoscopic screening on GC prevention by early detection and treatment of asymptomatic early-stage GC (21,31). Studies have also reported the effectiveness of endoscopic screening on upper gastrointestinal cancers based on selected high-risk rural areas of esophageal cancer in China (9,32). A case-control study based on Linzhou, Henan province, a recognized high-risk area for esophageal cancer (33), reported a 28% reduction in risk of GC mortality by endoscopic screening [odds ratio (OR)=0.72, 95% confidence interval (95% CI): 0.54–0.97] (32). Combining the data from six high-risk areas for esophageal cancer, a multicenter population-based cohort study was conducted in China, which revealed significantly decreased incidence [relative risk (RR)=0.66, 95% CI: 0.59–0.73] and mortality from non-cardia GC (RR=0.38, 95% CI: 0.33–0.45) and also significantly decreased mortality from cardia GC (RR=0.58, 95% CI: 0.49–0.68) associated with one-time endoscopic screening (9). Further studies are also warranted to confirm the effectiveness based on populations from high-risk areas of GC directly. In addition, whether repeated screening would further strengthen the beneficial effect and the association magnitude is still unknown.

Although endoscopy may lead to bleeding and participants may have other concerns on safety, adverse effects are generally tolerable (7,34). Despite so, the invasive nature of endoscopic examination and the related epigastric discomfort under non-sedated situations have lowered the compliance for attending. The successful conduct of endoscopic screening also requires a large team of experienced endoscopists and pathologists and the availability of gastroscopes, which has precluded the possibility of conducting nationwide screening for GC in China with such huge population.

Magnetically controlled capsule endoscopy (MCE)

In addition to electronic endoscopy, capsule endoscopy was first introduced in 2000, which represents a noninvasive, recipient-friendly alternative method of digestive tract examination without significant discomfort (35,36). The use of capsules maneuvered with a simple external magnetic field or a more sophisticated magnetic guidance system, called MCE, has been shown as an accurate and reliable approach for gastric examination in several studies (37-43). For example, Zou *et al.* showed a kappa value of 0.77 (P<0.001) for the overall agreement between the diagnostic accuracy of MCE and that of standard gastroendoscopy for gastric diseases (42). Two prospective studies in Germany and in China showed consistent findings (37,43). These findings supported the accuracy of MCE similar to standard gastroscopy and suggested MCE as a promising alternative to gastroendoscopy with the advantages of noninvasive screening, no anesthesia required, and no major epigastric discomfort, which can be accepted by the population easily (44). However, there were concerns that the stomach may not be a good target organ for passive capsule endoscopy because of the large size of the gastric cavity (45), even with the use of MCE. We also cannot take biopsies or perform endoscopic treatment by MCE (46). In addition, MCE is also much more expensive than conventional gastroendoscopy (38,47). All these disadvantages restrict the potential use of MCE for mass GC screening.

Exploration of biomarkers and their combinations assisting GC screening

Numerous studies have sought to explore biomarkers that can be applied for GC screening. Several traditional serum biomarkers have been investigated for a long time, such as PG, gastrin-17 (G-17) and *H. pylori* antibodies, but none of any single biomarker was proved to have sufficient sensitivity and specificity for GC screening. A series of studies have been conducted taking advantage of novel technologies and have examined the potential application of the combination of serum biomarkers, expecting to identify high-risk populations for further diagnostic endoscopy, and to stratify subjects' risk of developing GC and thus to guide targeted screening and precision prevention (48,49). However, evidence needs to be accumulated before any combination of biomarkers can be used for mass GC screening in the real-world setting.

Exploration of GC biomarkers

PG

PG is a precursor of pepsin, which can be divided into PG I and PG II according to its biochemical and immunological activity characteristics. PG I is secreted mainly by the chief and mucus neck cells in the fundic mucosa (50), while PG II is also secreted by cells in the pyloric glands and the proximal duodenal mucosa besides these cells (51). Studies have shown an association between the concentration of serum PG and gastric mucosal lesions, proposing PG as a potential biomarker for CAG (52-56). A meta-analysis of

42 studies reported a pooled sensitivity of 0.77 and specificity of 0.73 for the performance of PG in defining atrophy when both criteria of a serum PG I level of 70 μg/mL or lower and a PG I/PG II ratio (PGR) of 3 or lower are simultaneously fulfilled (56). In addition to the unideal sensitivity and specificity, the concentration of PG may be influenced by *H. pylori* infection, regions, smoking, alcohol intake, and many other factors (57-59), and various cutoffs of PG were defined (52,54,56). For example, previous guidelines used different optimal cutoff values in China. *The Technical Plan for Early Diagnosis and Treatment of Cancer in 2011* recommended a cutoff value of PG I ≤70 μg/mL and PGR≤7 for GC screening. However, the Chinese Experts Consensus in 2018 suggested to use PG I ≤70 μg/mL and PGR≤3 as cutoff values for early GC screening (60).

G-17

Gastrin was the first discovered gastrointestinal peptide hormone. It is predominantly produced by gastric antral G cells. Gastrin stimulates the parietal cells to secrete gastric acid, promoting the growth and differentiation of the normal gastric mucosal epithelial cells, accelerating mucosal tissue repair, and participating in the inflammatory reaction of gastric mucosae (61-63). The level of serum G-17 depends on intragastric acidity and the number of G cells in the gastric antrum and normally increases after food stimulation, and also may be affected by regions, diets, lifestyle habits, and *H. pylori* infection (64,65). G-17 level can indicate the atrophy or function of gastric antrum mucosa. A hospital-based study showed that serum G-17 levels were higher among cases of corpus-predominant gastritis than among cases of antral-predominant gastritis (P<0.05), which suggested an increase in G-17 level might indicate the location of gastritis (65). Several studies have assessed the performance of G-17 as a potential biomarker. For example, a study with 4,064 participants in China indicated that G-17 levels significantly increased from the progression of normal stomach mucosa to malignancy (66). However, the accuracy, particularly the sensitivity, of G-17 as a biomarker has been unsatisfactory. A meta-analysis showed that G-17 only had 48% in sensitivity and 79% in specificity for predicting CAG (67). In general, G-17 is not recommended as a single biomarker to screen GC (68).

H. pylori antibodies

H. pylori is well recognized as a class I carcinogen for GC (69). *H. pylori* infection can be detected by invasive (e.g., histology, rapid urease test, culture, and so on) and non-invasive (e.g., urea breath test, stool antigen test, and serology test) methods. Urea breathing test is the most widely used non-invasive test, whereas serology is useful in screening and epidemiological studies (70,71). Serological tests based on the detection of anti-*H. pylori* IgG antibodies are useful for evaluation of *H. pylori* infection status. In addition, *H. pylori* virulence factors such as CagA, VacA and others have been identified as potential biomarkers for GC development. Pan *et al.* found that individuals of gastric lesions with antibodies for either CagA and GroEL were more likely to progress to GC (72). In a latest study, individuals that were detected seropositive for two new virulence factors, Omp and HP0305, were more likely to have severe CAG or even severer precancerous gastric lesions (OR=7.43, 95% CI: 5.59−9.88) compared with seronegative individuals for both (73). However, serological tests cannot distinguish active infection from past *H. pylori* infection. Urea breath test could be an effective complementary test for individuals with positive *H. pylori* antibodies who cannot determine whether there is an active infection (74).

Other biomarkers

Other serum biomarkers, such as carcinoembryonic antigen (CEA), the carbohydrate antigens (CA)-199, CA-724, CA-125, and α-fetoprotein (AFP) also have been proposed as GC biomarkers but all had low sensitivity and specificity. Efforts have also been made to examine single nucleotide polymorphisms, somatic mutations, DNA methylations, microRNAs and long non-coding RNAs as possible markers. In recent years, the development of molecular biology and next-generation sequencing (NGS) and omics technologies, such as genomics, methylome, metabonomics, and proteomics, have opened new avenues for examining novel promising biomarkers for GC screening (75,76).

Exploration of combination of serum biomarkers

ABC method: Combination assay of *H. pylori* antibodies and serum PG

The combination assay of *H. pylori* antibodies and serum PG, called the ABC method, was recommended as a method to screen GC and stratify high-risk populations in Japan. Following this method, individuals are tested for serum anti-*H. pylori* IgG antibody titers and the PG I and II levels. Those with the serum PG I ≤70 μg/L and PGR≤3

are defined as PG-positive (+) and others are PG-negative (−). Those with a serum *H. pylori* antibody titer of >10 U/mL are defined as *H. pylori* (+), and others are *H. pylori* (−) (77,78). Individuals can then be classified into group A [*H. pylori* (−) and PG (−)], group B [*H. pylori* (+) and PG (−)], group C [*H. pylori* (+) and PG (+)], or group D [*H. pylori* (−) and PG (+)]. Studies indicated gradually higher risk of GC by the order of group A–D, and the risk was especially increased in groups C and D (79-82). According to ABC method, groups C and D individuals would be defined as high-risk populations for GC requiring endoscopy screening then. However, researchers further observed heterogeneity of group A, as this group might also include *H. pylori*-eradicated individuals, which may be at a relatively high risk of GC compared with *H. pylori* uninfected and endoscopy examination would be needed for them as well (83-85). Therefore, ABC method may have led to false-negative population stratification for those in group A. Even so, considering the continuously decreased *H. pylori* infection rate and decreased incidence of GC in Japan, the false-negative rate may be decreased and ABC method would still hold clinical significance at least in the near future (86).

New ABC method: Combination assay of serum PG and G-17

As above mentioned, the limitation of ABC method on the possible false negative report for group A (the low-risk group) has been reported (83-85). A new ABC method was proposed to combine the assay of serum PG and G-17, recommended by the International Symposium on early GC screening in 2015 (87). Those with the serum PG I≤70 μg/L and PGR≤7 are defined as PG (+) and others are PG (−). Those with G-17≤1 pmol/L or G-17≥15 pmol/L are defined as G-17 (+) and others are G-17 (−). Individuals can be classified into group A [G-17 (−) and PG (−)], group B [G-17 (+) and PG (−)], group C [G-17 (−) and PG (+)], or group D [G-17 (+) and PG (+)]. The risk of non-cardia GC increased corresponding with decreasing quintiles of PGR and increasing quintiles of serum G-17 (88). Compared with ABC method, the new ABC method was proved to be more effective in detecting individuals at a high risk for GC (89). A recent study in China showed that combining PG and G-17 levels with endoscopy could be a promising approach to screen for early-stage GC (90).

Combination of anti-*H. pylori* IgG antibody, PG and G-17

The combination of PG, G-17, and anti-*H. pylori* antibodies serological assays appears to be a reliable tool for the diagnosis of CAG and may be used for screening high-risk populations for GC among those with CAG (91). A multi-phase study in northern China showed that low PG I level, low PGR, and both low (<0.5 pmol/L) and high (>4.7 pmol/L) G-17 levels were associated with a higher risk of developing GC. The combination of PG, G-17, and anti-*H. pylori* IgG antibodies improved the prediction ability beyond traditional risk factors (age, sex, smoking, family history of GC, and upper gastrointestinal symptoms) for identifying precancerous lesions at enrollment (area under the curve from 0.58 to 0.81, P<0.001), which were then associated with an elevated risk of GC during the follow-up (48).

New GC screening scoring system: China's Early Gastric Cancer Screening Process Expert Consensus

A new GC scoring system was raised in China's Early Gastric Cancer Screening Process Expert Consensus in 2018 (60), including 5 variables of age, gender, *H. pylori* antibodies, PGR and G-17. Following this scoring system, each individual is assigned a score based on these variables with a total score of 0−23. Subjects could then be divided into low (0−11 scores); medium (12−16 scores) and high-risk group (17−23 scores). A nationwide multicenter study in China indicated that 70.8% of GCs and 70.3% of early GCs were detected among individuals with medium and high risk, and the required endoscopy would be reduced by 66.7% of individuals (49). Comparing with the ABC and new ABC methods, Ni *et al.* reported that the new scoring system had a better predictive value for early GC (92).

Challenges for GC screening

Age of GC screening population

The recommended age of GC screening has been diverse in different countries. GC screening program is recommended for population aged 50 years and over according to Japan's national screening program. Similarly, the British Society of Gastroenterology guidelines (93) suggested that endoscopy screening be considered in individuals aged 50 years and older with multiple risk factors for gastric adenocarcinoma (male, smokers, and pernicious anemia). In Korea, GC screening is conducted for populations aged 40−74 years. In China, all screening programs currently are conducted for populations aged 40−69 years. Numerous studies have sought to examine the

suitable starting and stopping ages for GC screening, reporting differed findings. A study in Japan based on the nationwide data showed the endoscopic screening program would be cost-effective when implemented for populations aged 50–75 years (94). A nationwide study in Singapore revealed that GC screening was cost-effective among Chinese men aged 50–70 years (95). In China, a study found that GC endoscopic screening was beneficial for individuals aged 50–59 years but not for those aged 40–49 years and those aged 60 years or older (32). However, in contrast to the Japanese and Singaporean studies mentioned above (94,95), this study is only conducted based on one-center (Linxian of Henan province), with a limited sample size. The suitable starting and stopping age of GC screening needs to be defined based on large-scale prospective studies, also accounting for the availability of resources and cost-effectiveness.

Screening intervals

The time interval for repeated screening is also a controversial issue. The national program in Japan recommended repeated GC screening every 2–3 years. In Korea, an interval of 2 years is recommended. British Society of Gastroenterology (93) has recommended that endoscopic follow-up should be taken every 3 years for individuals with severe CAG or IM and within one-year interval for LGIN, the same as the management of epithelial precancerous conditions and lesions in the stomach (MAPS II) guideline (96). In China, the National Health Commission recommended that individuals diagnosed with severe CAG, severe IM and LGIN at an endoscopy screening should be followed up by gastroendoscopy at least once within next three years in principle, and HGIN should be treated clinically. However, the official guidelines on screening intervals in China basically follow a "one-fit-all approach". Several studies in Japan and Korea revealed that 2–3 years may be the appropriate intervals for repeated GC screening (20,97-100). However, high-quality prospective research is required on the optimal follow-up interval of endoscopic screening in China. We need to further explore the progression rate of precancerous gastric lesions and to elucidate the mean sojourn time of gastric mucosal lesions, also taking into consideration of the perspective of health economics. In this way, we can make a systematic cost-benefit evaluation and clarify the optimal follow-up interval of endoscopic screening, promoting optimizing the program on repeating screening and avoiding "over screening".

Health economic evaluation of GC screening

With limited health resources, the evaluation of health economics is always critical for policy making of endoscopic screening. A study in Korea found that the GC screened group had significantly lower medical care expenses and showed a significantly better prognosis of GC than the unscreened group (101). A systematic review of economic evaluation in China suggested GC and colorectal cancer as the most-effective targeted cancers for screening in the general population (102). However, studies on the health economic evaluation of endoscopic screening for GC in China have been sparse. The evidence from well-designed studies on health economics should be incorporated before any policies and official guidelines on area selection for GC screening, the screening starting and stopping ages, and screening intervals can be made, so that health resources can be allocated more reasonably, maximizing the social and economic benefits of GC screening.

Precision screening

At present, the concept of precision medicine has been deeply rooted. The concept of precision prevention requires that we precisely identify high-risk exposure phenotypes and concentrate high-risk population subgroups, transiting to individualized prevention mode of GC in the future. To realize this goal, the development of accurate, reliable, highly integrated biomarkers is needed, also fulfilling cost-effective principles, in line with China's basic national conditions as a developing country.

Conclusions

With the guide of *Health China 2030 Planning Outline* and *National Medium and Long-term Plan on Prevention and Control of Noncommunicable Diseases* (*2017–2025*), it is our mission to promote prevention and control of GC. In China, the last decade has witnessed great advances in the national screening programs for GC in both rural and urban areas. The challenges we confront require us to keep conducting high-quality research on GC screening and searching for novel biomarkers. The implementation of precision prevention would help promote the performance of GC screening system and expand the coverage of

screening, leading to significantly improved GC prevention and control in China.

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Footnote

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