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Review Article

Disparities in Gastric Cancer Screening Worldwide

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Abstract

Gastric cancer is the third most common cause of cancer-related death globally. The highest incidence is encountered in Asia, followed by Europe which has the second highest incidence worldwide. In Europe, gastric cancer is typically diagnosed at an advanced stage, with an estimated five-year survival rate of 24%, compared to 59% in Japan. This disparity is largely attributed to the significant role of screening in Japan. Given the expected rise in absolute numbers of gastric cancer cases, there has been a demand for gastric cancer screening programmes in high-intermediate risk countries, advocated by the International Agency for Research on Cancer, the Science Advice for Policy by European Academies, the European Commission as part of the Europe Beating Cancer Plan, and the Maastricht VI/Florence consensus guidelines. This review article summarizes the current disparities in screening strategies between countries in the East and West and comments on future developments in population-based screening research in this field. The references for this article were identified through PubMed, the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Register of Trials using the search terms "gastric cancer", "stomach cancer", "Helicobacter pylori", and "screening" over the period from 1995 until March 2024. Overall, this review identifies three potential approaches to screening: primary, secondary, and opportunistic. It highlights the lack of a uniform consensus on the best approach to screening, the disparity in the information available in different populations, and upcoming research to address this disparity.

Introduction

Over one million new cases and 770,000 deaths of gastric cancer were estimated in 2020, making it the 6th most common cancer worldwide.[1] While the prevalence has been decreasing, the absolute burden has increased due to the aging population. It is predicted that by 2040, the annual burden of gastric cancer will rise to nearly 2 million new cases and 1.3 million deaths globally.[2] However, not all regions are equally affected; higher incidence rates are encountered in Asia, Latin America, and Central and Eastern Europe (Fig. 1).[3] This discrepancy in incidence is thought to be driven predominantly by environmental risk factors, the most significant of which is *Helicobacter pylori (H. pylori)* infection.[4,5] Other environmental risk factors include smoking, alcohol consumption, high salt intake, ingestion of smoked or cured meat, poor housing sanitation, and exposure to chemicals such as nitrosamines. Regarding genetic causes, familial clustering is observed in approximately 10% of cases, with hereditary mutations accounting for only 1–3% of all gastric cancer cases.[6]

Over 90% of gastric cancers are adenocarcinomas, with the majority being classified as non-cardia tumors. Lauren's histopathologic classification, created in 1960, is the most frequently used histopathological classification system in gastric cancer classification in Europe.[7] It divides gastric cancers into 'intestinal type' and 'diffuse type' based on histopathological findings. The most frequent type is the 'intestinal type' because of its morphological similarity to adenocarcinomas arising in the intestinal tract. It is a slow-growing tumor typically seen in older male patients with severe atrophic gastritis and is strongly associated with intestinal metaplasia caused by persistent *H. pylori* infection. The less common type is diffuse-type gastric cancer, which is more commonly seen in younger age groups and tends to have a more aggressive disease course and poorer outcomes.

Screening and prevention of gastric cancer

The Wilson and Junger criteria

The Wilson and Junger criteria for screening, established in 1968,

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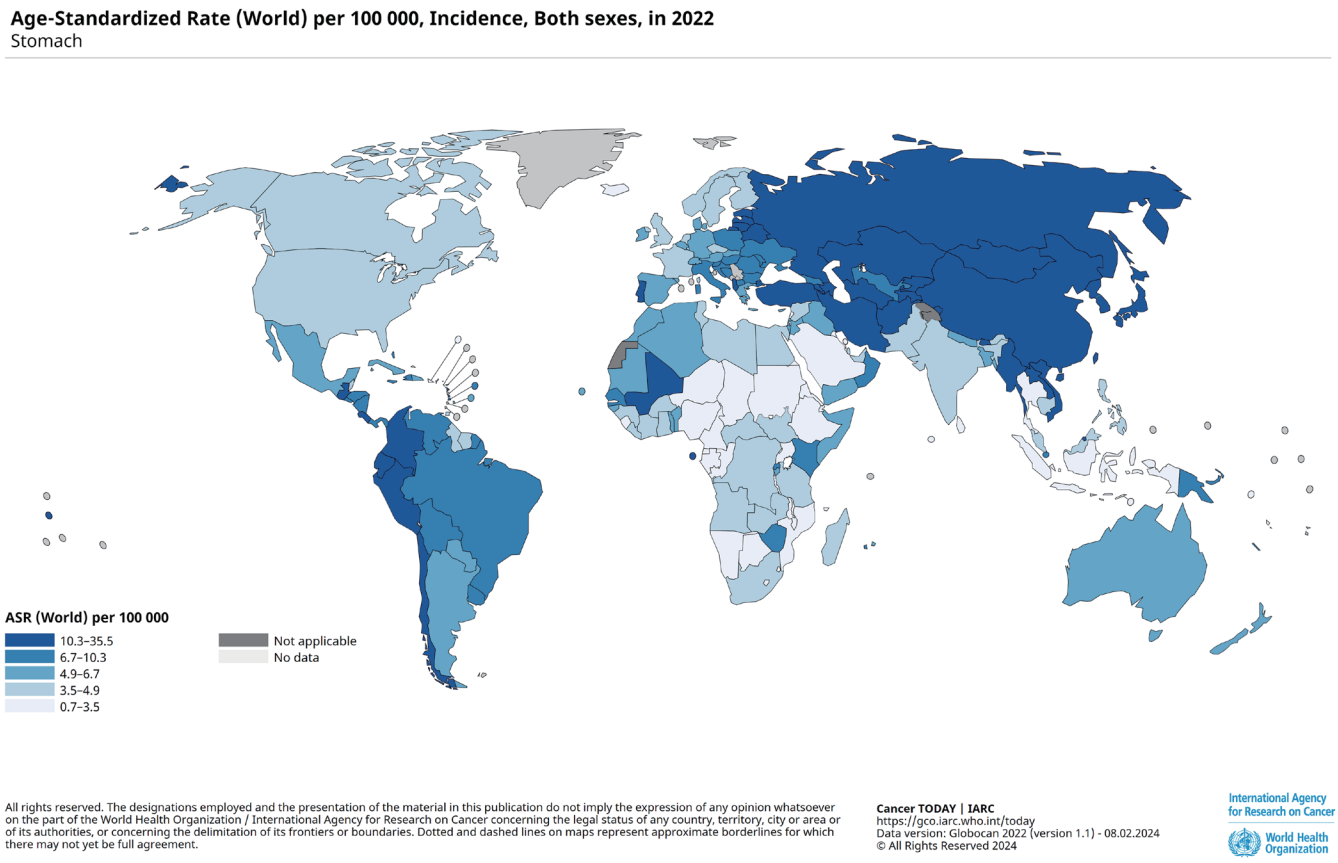

Fig. 1. The incidence of gastric cancer worldwide, GLOBOCAN 2022. License to use Figure 1 granted by the International Agency for Research on Cancer. Cancer TODAY | IARC https://gco.iarc.who.int/today. Data version: Globocan 2022 (version 1.1) - 08.02.2024© Date Accessed March 7, 2024.

outline key requirements for the development of an effective screening programme. These criteria include that the condition being screened for is an important health concern, that it has a recognizable early symptomatic stage, and that we understand the condition's natural course. It also requires the availability of a suitable test that is acceptable to the population and the availability of treatment and facilities for diagnosis and treatment.[8] In the case of gastric cancer, the disease pathway is detailed by the Correa cascade,[9] which describes the progression from normal mucosa through intestinal metaplasia, gastric atrophy, and ultimately, cancer. A significant promoter along this carcinogenic cascade is the presence of *H. pylori*. While *H. pylori* infection is not necessary for cancer development, it significantly promotes progression along this pathway. *H. pylori* can be tested for non-invasively using urea breath testing, stool antigen testing, or serology. Fortunately, effective treatment exists for this pathogen.[10] Notably, in countries with reducing *H. pylori* prevalence, there has been a corresponding reduction in gastric cancer cases (Figs. 2 and 3).[11]

Screening mechanisms

Three potential screening strategies have been suggested to target gastric cancer: primary prevention, secondary prevention, and opportunistic screening. A primary preventive strategy focuses on screening individuals for this carcinogenic bacteria before the development of preneoplastic lesions and treating it where present; this is known as a 'screen and treat' strategy.[12] A substantial body of evidence supports this approach, at reducing the risk of gastric cancer mortality and incidence. However, debate exists around the optimal age to begin screening. Recent studies have suggested the potential role of screening school-aged children, while others argue that infection in childhood rarely causes complications such as peptic ulcer disease.[13–15] A recent meta-analysis of randomized controlled trials using this 'screen and treat' approach in adult populations estimated the number needed to treat to prevent one case of gastric cancer as 72 and one cancer-related death as 135.[16] A significant body of observational data in Asia also supports this approach. The most notable of these is the Matsu Islands study. In this study, 7,000 adults over the age of 30 were screened and treated for *H. pylori*. Compared to the historical period from 1995 to 2003, there was a 53% reduction in gastric cancer incidence and a 23% reduction in mortality.[17] While limited, observational population data exists in a European population to support this approach. A systematic review conducted by Doorakkers *et al*.[18] on the Swedish database provided data associating *H. pylori* eradication with a reduction in gastric cancer in a Western population. The most significant benefit was observed when *H. pylori* infection was treated earlier, with a reported standardized incidence ratio over 5–7 years of 0.87.[19]

Secondary preventive strategies involve screening those in a high-risk age cohort when a pre-neoplastic or early neoplastic lesion has already occurred and endoscopically treating these before progression. Research on secondary prevention has primarily focused on endoscopic screening, the role of X-rays as part of an upper gastrointestinal series (UGIS), and serological markers. While both endoscopic screening and UGIS have limitations, me-

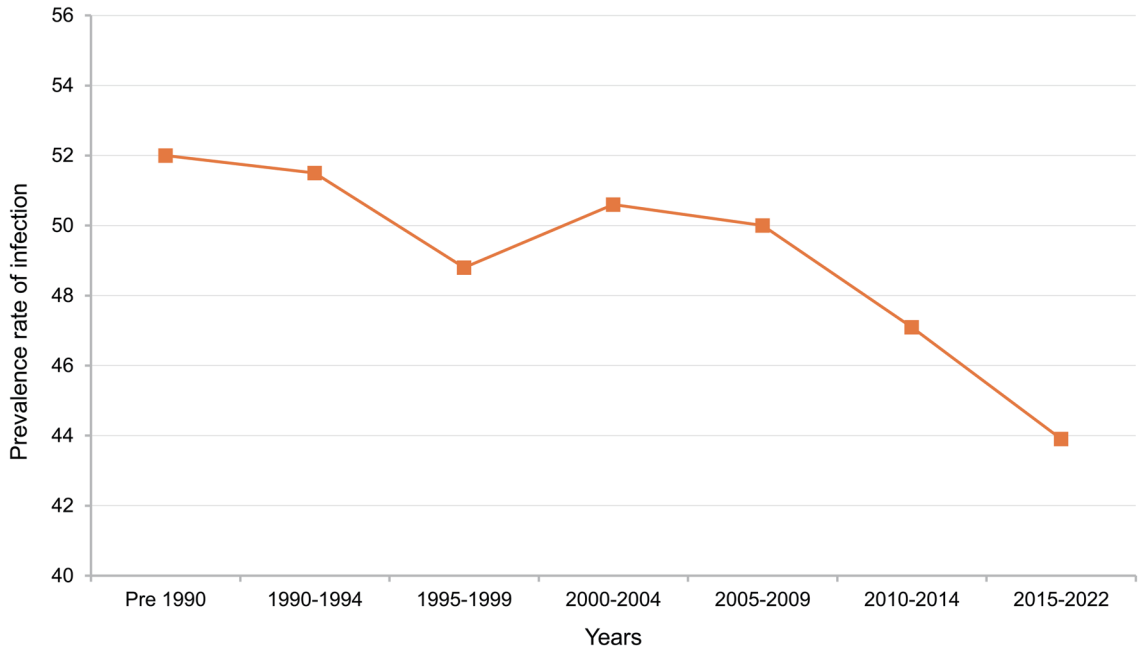

Fig. 2. The declining global prevalence of *Helicobacter pylori* infection.

ta-analysis supports the role of endoscopic screening over UGIS.[20] UGIS carries concerns over radioactivity, lack of biopsy capability, and low sensitivity and specificity compared to endoscopy, potentially resulting in lost opportunities to treat early-stage cancers endoscopically. Endoscopy, while both a screening and diagnostic test, is costly, comes with a small risk of significant complications, and requires considerable training to perform at a high quality. Despite these factors, UGIS has largely been replaced by endoscopic screening in national gastric cancer screening programmes in East Asian countries. However, in areas lacking facilities and trained endoscopy staff, UGIS can still be considered based on the patient's clinical situation.[21]

Research has been ongoing on the role of serological markers as a potential screening mechanism for decades.[22,23] *H. pylori* antibodies, pepsinogen I & II levels, gastrin-17, and anti-parietal cell antibodies have been studied for their potential role as a prescreening tool to determine who requires a gastroscopy. Support currently exists for the potential use of pepsinogen and *H. pylori* antibodies as a screening mechanism from the Kyoto Global Consensus; however, limitations exist in their application across popu-

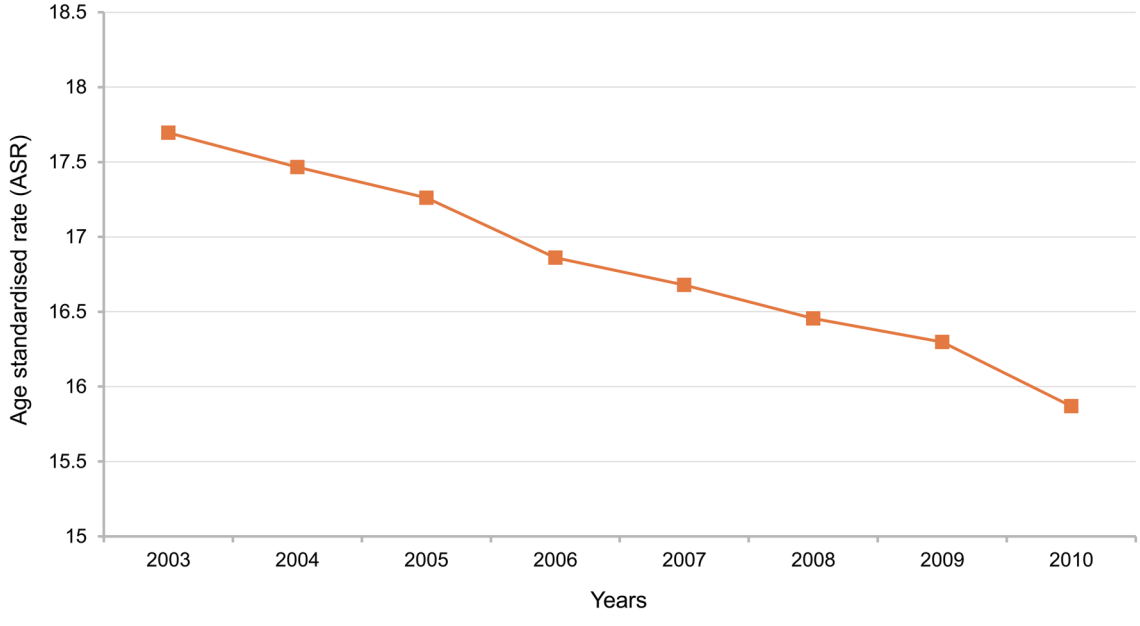

Fig. 3. The declining age standardized rate (ASR) of gastric cancer.

Table 1. A summary of existing screening strategies by country or region

Region	National screening programme available	Methods of screening
Japan	Yes	Endoscopic screening every 2–3 years from age 50
Korea	Yes	Endoscopic screening every two years for those aged 40–75
Mainland China	Targeted population screening: Individuals in selected high-risk rural areas; High-risk individuals in urban cities	Endoscopy from age 40–69
Europe	No	
North America	No	

lations.[24] Four key models have been proposed using these markers, including the ABC, ABCD, five-markers study, and the seven variables study. All scoring systems incorporate serology, with the more recent seven variables study also including recognized gastric cancer risk factors. The ABC and ABCD methods measure serum pepsinogen I, II, I/II ratio, and *H. pylori* antibody status.[25,26] The five-markers and seven variables methods measure *H. pylori* antibody status, pepsinogen I & II levels, gastrin-17 levels, and antiparietal cell antibodies. The seven variables method also assesses exposure to nitroso compounds such as pickled and fried food.[27,28] Out of these scoring systems, the seven variables method suggests a better discriminative ability to identify patients with gastric cancer than the other methods.[29] However, it is important to note differences in baseline risk in these study groups and variations in reproducibility of results in different populations. In Europe, a retrospective review by Gašenko *et al*.[30] found a poor correlation between changes in pepsinogen and gastrin-17 levels and gastric cancer, suggesting these serological markers have an uncertain application in a Caucasian population. Despite this, in countries where these markers are validated in the population being screened, they could potentially be used to select those who require gastroscopy, allowing for a 'work smart' approach to screening.

Vaccination against H. pylori

Research into the development of a vaccine against *H. pylori* has been ongoing for decades. While a significant body of knowledge about the bacteria has been developed, only one vaccine has reached a phase III clinical trial.[31] *H. pylori* possesses several strategies to survive hostile gastric environments and modify the host immune response to ensure its survival. As a result, no vaccine has successfully induced long-term protection against *H. pylori,* which is important since most infections occur in childhood.[32,33] Consequently, a vaccination strategy to reduce gastric cancer rates is not currently feasible.

Recommendations on gastric cancer screening from different societies

There has been a growing focus on adopting an evidence-based approach to gastric cancer screening. The 8th report from the International Agency for Research on Cancer Working Group strongly recommended that all nations incorporate gastric cancer into national cancer control programmes.[34] Their suggestion emphasized the importance of evaluating *H. pylori* prevalence and the potential effectiveness of prevention strategies tailored to each country.

The 2015 Kyoto Global Consensus Report on *H. pylori* gastritis further supported the importance of treatment, highlighting that eradicating *H. pylori* significantly diminishes the risk of developing gastric cancer.[24] This sentiment was echoed by the Taipei global consensus in 2020.[5]

The Maastricht/Florence VI guidelines propose incorporating gastric cancer screening in countries reporting an intermediate-high incidence of gastric cancer. They also support the role of mechanisms such as *H. pylori* screening in lower-incidence countries; however, they note that it may impact cost-effectiveness.[35] The Science Advice for Policy by European Academies network recommends implementing population-based screening and treatment programmes for *H. pylori* in regions with intermediate to high gastric cancer incidence.[36] Lastly, the European Commission identified gastric cancer as a target for an upcoming screening programme as part of the Europe Beating Cancer Plan.[37]

This collective body of recommendations from international organizations and academic reports underscores the global consensus on gastric cancer as a significant problem and the importance of evidence-based strategies for its screening and prevention. Notably, screening for gastric cancer is not a new concept, and certain countries have been screening for decades. This is explored further below and summarized in Table 1.

Screening strategies in high and intermediate-incidence countries and regions

Japan

Japan pioneered its inaugural gastric cancer screening initiative in the 1960s, and since then, screening initiatives have had a substantial influence on reducing mortality associated with gastric cancer. The 5-year survival rate in Japan stands at 59%, a stark contrast to Europe's lower rate of only 24%.[38] In 1983, the gastric cancer screening programme was expanded for all residents aged 40 years and older, involving an indirect UGIS using a barium meal. In 2018, the guidelines were updated to recommend biannual gastric cancer screening (using endoscopy) for individuals aged 50 and above.[39]

Korea

The Korean National Cancer Screening Programme for gastric cancer was launched in 2002, and the Korean National Guideline for gastric cancer screening was published in 2015. They currently recommend screening individuals aged 40–75 through endoscopy every two years.[40] They do not recommend screening those aged 75–84 due to insufficient evidence to assess the benefits and risks of screening in this age group and actively advise against screening adults over 85. While endoscopy is recommended as the screening test of choice, the guidelines allow for clinician judgment and patient preference, should they deem UGIS more appropriate in individual cases.

Mainland China

There is currently no nationwide screening programme in China; opportunistic screening with endoscopy is the primary method of early gastric cancer detection and prevention. Since 2005, two organized screening programmes for gastric cancer have been implemented in high-risk areas: the Cancer Screening Programme in Urban China and the Cancer Screening Programme in Rural Areas. These programmes focused on high-risk individuals in rural and urban areas.[21] High-risk individuals, as defined by the Chinese national guidelines, aged 40 years or above, were invited for upper gastrointestinal screening. Those with severe atrophic gastritis, intestinal metaplasia, and low-grade intestinal metaplasia at endoscopy were offered follow-up gastroscopy at least once within three years. By the end of 2018, more than 2 million rural people had undergone endoscopy, with a cancer detection rate of 2%, of which 70% were detected at an early stage.

Chinese Taiwan

Taiwan has no documented population-based screening strategy; however, several proposed methods to reduce gastric cancer incidence have been investigated. The most notable are the Matsu Island studies, detailed above and the Changhua County study.[17,41] The Changhua County study combined the national colorectal cancer screening strategy with screening for *H. pylori.* In this randomized controlled trial, stool samples were tested for fecal immunochemical testing and *H. pylori* in the intervention group, and those who tested positive were treated. This resulted in a 9% lower gastric cancer mortality rate in the intervention arm.

Europe

There is currently no population-based screening programme available in Europe despite it having the second highest incidence in the world after Asia. The current European guidelines, Management of Epithelial Precancerous Conditions and Lesions in the Stomach II, suggest opportunistic screening in those already identified as having premalignant lesions.[42] They do not make recommendations on screening the general population.

In comparison, the Maastricht VI/Florence consensus guidelines, published on behalf of the European Helicobacter and Microbiota Study Group, state that a population-based *H. pylori* 'screen and treat' programme is cost-effective in populations with an intermediate or high incidence of gastric cancer and that screening modalities for gastric cancer prevention (non-invasive or endoscopic) combined with colorectal cancer screening are a potential opportunity for screening.[35] The appetite for such recommendations has grown in response to the EU's Beating Cancer Plan.

Low-incidence countries and prevention studies

The United Kingdom (UK)

The UK lacks a standardized national screening programme for gastric cancer. Screening is currently based on recommendations by the British Society of Gastroenterology, which advises endoscopic screening for those over the age of 50 with risk factors for gastric cancer. These risk factors include pernicious anemia, a first-degree relative with a family history of gastric cancer, and other risk factors such as smoking and male gender.[43]

North America

No national gastric cancer screening programme is endorsed in North America. Furthermore, there is limited support for opportunistic screening in the guidelines from the American Gastroenterology Association. Currently, the support for endoscopic surveillance of intestinal metaplasia is debated and is generally only suggested for those at high risk of gastric cancer.[34] However, data does support the positive effect of *H. pylori* eradication on risk reduction for non-cardia gastric cancer eight years after treatment in a North American population.[44] Riquelme *et al*.[45] proposed measures for the Americas that could be used to control gastric cancer. These measures include promoting improvements in population-based cancer registry data to capture the burden of gastric cancer, supporting the development and dissemination of standards aimed at promoting quality endoscopy, enabling the training of healthcare workers specialized in gastric cancer, creating a *H. pylori* database to ensure optimal testing, follow-up and monitoring for resistance, ensuring endoscopic surveillance of patients with high-risk intestinal metaplasia, establishing quality research, and promoting population-based measures to reduce the incidence of gastric cancer such as strengthening smoking regulations, creating strategies to reduce salt intake, and promoting health literacy in the community.[45]

Future research developments in screening

Upcoming population-based screening

Research funded by the European Union is underway as part of the Eurohelican and the Towards Gastric Cancer Screening Implementation in the European Union (TOGAS) studies to determine the feasibility of a screening programme in member states. The Eurohelican research, based in Slovenia, seeks to evaluate the feasibility and cost-effectiveness of a primary preventive strategy towards gastric cancer.[46] The Towards Gastric Cancer Screening Implementation in the European Union trial is being run in 14 European countries with varying prevalence rates. The aim is to compare the feasibility and cost-effectiveness of primary and secondary preventive strategies amongst member states.[47] Two longitudinal studies evaluating the impact of screening in a European population are also underway. The *Helicobacter Pylori* Screening Study, a longitudinal study based in the UK that will conclude in 2024, aims to determine the potential impact of screening and treating *H. pylori* on gastric cancer risk over ten years in a low-incidence country.[48] The GISTAR study in Latvia will examine this effect in a high-incidence European country; it is due for completion in 2035.[49] These studies hold promise in offering valuable insights into the effectiveness of *H. pylori* screening and treatment strategies in an adult population in the context of low-intermediate and intermediate-high-risk European populations. In doing so, these studies will guide European member states in implementing local policies.

Other vital studies due for completion include the Linqu County study in China and the *Helicobacter Pylori* Eradication for Gastric Cancer Prevention in the General Population study from Korea.[36,50] These will provide data on the impact of *H. pylori* eradication on gastric cancer incidence. The clinical study by Gallardo *et al*.[51] in Chile, in which 14-18-year-olds are screened for *H. pylori*, will also provide data on the acceptability of this approach in a young adult cohort.

Requirement for the development of key performance indicators

Finally, future screening programmes will need to consider potential key performance indicators for gastric cancer screening, taking into account the mode of screening, cost of screening, and

diagnostic yield. In the case where a 'screen and treat' approach is adopted, consideration should be given to creating local registries that would allow for the audit of treatment compliance and effectiveness. If endoscopic screening is adopted, defining the minimum standards and markers of a 'quality screening endoscopy' will be required.

Conclusion

While the incidence of gastric cancer is falling, the absolute burden is rising, and it is estimated that there will be over a million cases by 2040. Despite the call for screening programmes, disparities still exist in the availability of gastric cancer screening. While national screening programmes have been created in high-incidence countries such as Japan and Korea, this contrasts with other high-incidence regions, such as Eastern Europe, where no national screening programme exists. This disparity is further exacerbated by the limited research available in Europe evaluating the feasibility of screening. Research is expected in the medium term that will aim to address this disparity.

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Conflict of interest

Dr. Deane reports receipt of research funding from an EU4 Health grant GA number: 101101252, support for attending meetings from Takeda, Richen, Jansen, Abbvie, future receipt of equipment from Richen and the role of committee membership of young United European Gastroenterology. Dr. Kelly reports receipt of previous research grants from Abbvie, consulting fees from Takeda & Abbvie, lecture fees from Abbvie, Johnson & Johnson, participation on an advisory board for Pfizer, Takeda and Galapagos and leadership roles as a board member of the Irish Society of Gastroenterology and council member of the Irish Hospital Consultants Association. Professor O'Morain reports receipt of a an EU4 Health grant, GA number: 101101252, participation on an advisory board for DMC Alvotech & Pfizer and the role of National Clinical lead of Gastroenterology, Health Services Executive.

Author contributions

Drafting of the manuscript (CD); critical revision of the manuscript for important intellectual content (COM, OK). All authors have made a significant contribution to this study and have approved the final manuscript.

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