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Where are we with gastric cancer screening in Europe in 2024?

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ABSTRACT

The absolute number of annual cases of gastric cancer in Europe is rising. The Council of the European Union has recommended implementation of gastric cancer screening for countries or regions with a high gastric cancer incidence and death rates. However, as of 2024 no organised gastric cancer screening programme has been launched in Europe.

There are several ways to decrease gastric cancer burden, but the *screen and treat strategy for Helicobacter pylori* (*H. pylori*) seems to be the most appropriate for Europe. It has to be noted that increased use of antibiotics would be associated with this strategy.

Only organised population-based cancer screening is recommended in the European Union, therefore gastric cancer screening also is expected to fulfil the criteria of an organised screening programme. In this respect, several aspects of screening organisation need to be considered before full implementation of gastric cancer prevention in Europe; the age range of the target group, test types, *H. pylori* eradication regimens and surveillance strategies are among them. Currently, ongoing projects (GISTAR, EUROHELICAN, TOGAS and EUCanScreen) are expected to provide the missing evidence. Feedback from the decision-makers and the potential target groups, including vulnerable populations, will be important to planning the programme.

This paper provides an overview of the recent decisions of the European authorities, the progress towards gastric cancer implementation in Europe and expected challenges. Finally, a potential algorithm for gastric cancer screening in Europe is proposed.

INTRODUCTION

Until a few years ago, the need for prevention of gastric cancer has not been prioritised in the Western world, including Europe, because of declining incidence and mortality indicators.

Although the overall incidence and mortality of gastric cancer in age standardised rates per 100 000 population (World population) in the European Union (EU27) is relatively low (6.5 and 4.1, respectively, for both sexes), substantial differences between countries exist. The burden remains the highest in the following among EU27 countries (age standardised rate incidence in men): Latvia (19.0), Lithuania (18.4), Portugal (18.0) and Estonia (17.5).¹ Furthermore, in countries with a relatively low incidence and mortality, the burden is typically higher among vulnerable populations, including immigrants.^{2,3} Globally, there is an approximately 10-fold and 6-fold variability in age-standardised mortality rates in men and women, respectively. In

KEY MESSAGES

- ⇒ Recently, the Council of the European Union has recommended implementation of gastric cancer screening for countries or regions inside countries with a high gastric cancer incidence and death rates.
- ⇒ Several means of primary and secondary prevention are available to decrease the burden of gastric cancer; the screen and treat strategy for *Helicobacter pylori* (*H. pylori*) is the most promising one for Europe.
- ⇒ Only organised cancer screening is recommended to be used in the European Union; this includes clear definition of the intervention, target group and set up of the program; these aspects are not well-defined for gastric cancer screening.
- ⇒ Screen and treat for *H. pylori* is more effective in young age adults, nevertheless compliance in older age groups is expected to be higher.
- ⇒ Currently several ongoing pilot studies in Europe are addressing the missing gaps in the knowledge; further implementation research will be needed. As of 2024, no organised gastric cancer screening programs have been launched in the European Union.
- ⇒ Clear definition of the above aspects is important so that relevant European guidelines can be formulated.

men, the highest mortality rates were observed in Kyrgyzstan, Chile and Latvia.⁴

Furthermore, even in counties in the Western world with a relatively low incidence, the 5-year survival rate from gastric cancer remains poor and is estimated to be 25% across Europe, with the poorest situation in Ireland, UK and East Europe.⁵ This is also demonstrated by the mortality to incidence ratio, which for the EU27 is 0.63.¹ This situation can be explained by diagnosis of the disease at a relatively late stage, therefore, indicating the importance of prevention.

When calculated as an age standardised rate, the incidence and mortality from gastric cancer are typically decreasing across the globe.⁶ A study of recent patterns and trends in cancer mortality in 47 countries based on the WHO mortality database has found that the rates for gastric cancer decreased in all the countries by 0.9–7.2% annually (except for Kyrgyzstan and Denmark), with the most rapid decrease in Korea (7.2%).⁴ This decline is mainly attributable to a decline in non-cardia gastric cancer.⁷



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At the same time, owing to changing patterns of the populations, mainly an ageing population, the absolute number of gastric cancer cases and deaths are expected to increase either globally or in Europe. A population-based modelling study has suggested a 62% rise in the number of cases within a 20-year period if the current trends continue.⁸

According to data from the Global Cancer Observatory (GLOBOCAN, 2022) of the International Agency for Research on Cancer (IARC), in Europe, the number of new gastric cancer cases has been estimated to increase from 136 000 in 2022 to 174 000 in 2050, and gastric cancer-related deaths, from 95 400 to 128 000, respectively.⁹

In late 2013, the global expert group hosted by the IARC stated that the burden of gastric cancer would remain constant in the foreseeable future even with the declining age-standardised incidence unless population-based prevention programmes were implemented following thorough large-scale evaluation activities.^{10 11} Nevertheless, with the exception of some research studies, no significant progress with such large-scale implementation has been made in the previous decade in Europe.

More recently, substantial progress has been made in prevention of gastric cancer, as indicated by the official documentation of the European Commission. This progress and challenges to achieve the set goals will be reviewed in this paper.

The rationale

The majority of gastric cancer develops on the background of precancerous lesions—gastric mucosal atrophy, intestinal metaplasia and dysplasia. This is the typical mechanism of intestinal type cancer development described by Pelayo Correa a decade ago.¹² Timely identification of high-risk precancerous lesions with a high risk of progression towards cancer would allow individuals carrying such lesions to be placed under regular surveillance, and upper endoscopies to be performed to identify cancer or even high-risk dysplastic lesions at a curable stage.¹³ Upper endoscopy is required for proper stratification of the lesions at increased risk.

Close to 90% of non-cardia gastric cancers cases are related to *Helicobacter pylori* (*H. pylori*) infection.¹⁴ Globally, this accounts for 770 000 new cases annually, positioning *H. pylori* as the most important infectious cause of cancer in countries with a high and very high Human Development Index.¹⁵ It should be mentioned that *H. pylori* infection is the primary aetiological factor also for diffuse-type gastric cancer, including proximal gastric cancer and a subset of adenocarcinoma of the gastro-oesophageal junction zone.¹⁶

Significant variability in the prevalence of *H. pylori* has been reported within the EU27 countries, ranging from 9.1 in Finland to 69.2% in Estonia⁶; this might, at least partly, explain the differences in the incidence of gastric cancer in these countries.

According to the results of a Cochrane review,¹⁷ based on studies conducted in Asia and Colombia, the number needed to treat to prevent one gastric cancer is 72 and to prevent one gastric cancer-related death is 135. Introducing the *screen and treat* strategy globally would theoretically result in 8.7 million disability-adjusted life-years gained.^{17 18} However, similar estimations cannot be made for the European population since, so far, limited data are available in Caucasian populations.

Although globally the prevalence of *H. pylori* in adults remains high, there has been a substantial decline between the 1990s (52.6%, 95%CI 49.6% to 55.6%) and 2015–2022 (43.9%, 95%CI 42.3% to 45.5%).⁶ This declining trend has not been seen in children and adolescents. During the recent decade,

the prevalence of *H. pylori* infection in the European region has been estimated to be 46.7% (95% CI 40.8% to 52.7%), with a substantial difference between various countries.⁶

Additionally, the prevalence of *H. pylori* varies between different socioeconomic groups within the same country. A significantly higher prevalence has been well-described among first-generation immigrants to the Netherlands.¹⁹ Based on the review conducted by Morais *et al*,²⁰ migrants are particularly at risk of *H. pylori* infection. Most of the studies in the review suggested that the prevalence among migrants is generally similar to, or below, that of their country of origin, but higher than the country of destination. Under the current sociopolitical situation in Europe, migration is expected to increase the prevalence of *H. pylori* in many EU countries, mainly in vulnerable populations. Therefore, inclusion of recent immigrants in cancer screening programmes is of great importance.

Basic principles for cancer screening in Europe

In Europe, only organised, properly governed, population-based and quality-assured screening programmes are recommended.²¹ Recently, an international consensus has been established on 16 essential criteria for an 'organised' cancer screening programme.²² Among others, the following criteria have been included: (a) protocol/guideline should be available, describing target populations, screening intervals, screening tests, referral pathways and management of positive cases; (b) the target population should be identifiable and there should be a system for inviting the eligible individuals for screening; (c) performance indicators should be present and the performance of the system should be evaluated and audited against them; (d) proper governance and quality assurance should be in place. Most of the cancer screening programmes in Europe have followed these recommended criteria for cancer screening programmes until now (breast, cervical, colorectal cancers), yet these criteria are not in place for gastric cancer screening. There are still some gaps in our knowledge of the required indicators before evidence-based protocols or guidelines can be developed for an organised gastric cancer screening programme.

Traditionally, cancer screening has been part of secondary prevention—that is, the search for cancer or precancerous lesions in the target population. In the case of gastric cancer screening, means of either primary or secondary prevention are used and could be combined; this is further elucidated in the following paragraph.

The means for screening to decrease the burden from gastric cancer

Historically, there has been some confusion around the definitions and terminology of gastric cancer screening either in terms of the target group or target lesions. Often screening terminology has been inappropriately used when referring to pretesting of symptomatic individuals to decide whether or not to refer them for upper endoscopy. Depending on the approach, screening could be aimed at different target lesions—that is, screening could be aimed at cancer itself, precancerous lesions or the presence of the main causative risk factor—*H. pylori* infection. Those different target lesions and modalities are demonstrated in figure 1.

Eradication of *H. pylori* infection falls under the primary prevention of gastric cancer, while screening for cancer or precancerous lesions is secondary prevention.²³ Therefore, when discussing gastric cancer screening, we tend not to differentiate between the types of prevention.

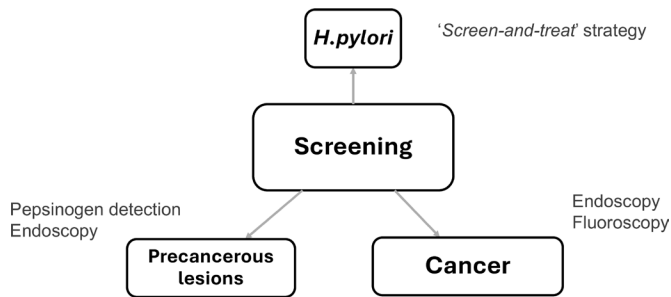


Figure 1 Potential approaches to screening for decreasing the burden of gastric cancer

According to the European Council recommendation, screening is the process of testing for diseases in people in whom no symptoms have been detected.²¹ The presence of *H. pylori* infection is always associated with gastritis, and *H. pylori* gastritis is an infectious disease according to the current guidelines, irrespective of symptoms.^{16 24} Therefore, a *screen and treat* strategy is a screening strategy for *H. pylori* gastritis not for gastric cancer itself. This strategy is very similar to that for cervical cancer screening as the European Commission is recommending testing for human papilloma virus as a primary intervention to prevent cervical cancer.²¹

The appropriate terminology for managing the potential infection should be used as follows:

Screen and treat strategy—searching for *H. pylori* in the general population—that is, screening individuals without symptoms of the disease or previous related medical history (including family history) and treating those who tested positive for the infection.

Test and treat—traditionally has been applied to symptomatic subjects without alarm symptoms and younger than 50 years with the objective of treating those found to be positive for *H. pylori*. However, the term could be used also in case-finding settings (individual level) outside organised screening programmes.

Test and scope—generally applies to symptomatic individuals and involves referral of those with positive *H. pylori* test results for further investigation—that is, upper endoscopy.

Weighing up the benefits and risks of *H. pylori* population-based eradication strategies

Benefits and harms are always present in cancer screening,²⁵ including gastric cancer screening.

A cancer screening strategy is justified if an effect on the target disease mortality has been demonstrated in randomised clinical studies.²⁵ A major study from the Linqu county in China²⁶ will provide important evidence, in addition to benefits documented in the meta-analysis and Cochrane review by Ford and colleagues^{17 18} mentioned earlier. Most of the evidence comes from studies performed in Asian population.

In addition to gastric cancer prevention, other important benefits of *H. pylori* eradication therapies should be noted, such as those related to peptic ulcer disease, dyspepsia, mucosa-associated lymphoid tissue lymphoma, iron deficiency anaemia, idiopathic thrombocytopenic purpura and vitamin 12 deficiency.¹⁶

The following potential harms related to *H. pylori* eradication should be considered: (1) whether the presence of chronic *H. pylori* infection in adults might have any health benefit for humans; (2) whether the potential adverse events related to *H. pylori* eradication do not outweigh the benefits of curing the infection.

Despite a longstanding debate, there does not seem to be any rational justification of benefit for an *H. pylori* infected adult to maintain the infection over years; the Maastricht VI/Florence guideline has positioned *H. pylori* as a gastric pathogen.¹⁶

Since neither vaccine nor antibiotic-free eradication regimens are available, *H. pylori* eradication requires the use of antibiotics. Antibiotic stewardship programmes are expected to reduce antibiotic consumption by considering the expected increase in deaths caused by resistant microorganisms—up to 10 million in 2050.²⁷ There has been an ongoing debate about whether a relatively short (10–14 days) treatment with antibiotics can substantially increase the consumption of antibiotics and/or harm individuals taking them.

Our previous modelling exercise using data from Latvia, a country with high *H. pylori* prevalence and low resistance of this microorganism to clarithromycin, has demonstrated that the use of macrolides would increase substantially if clarithromycin-based triple therapies were prescribed for the general population to prevent gastric cancer.²⁸ This might raise concern from the antibiotic stewardship aspect,²⁹ irrespective of *H. pylori* resistance rates to this antibiotic.

However, much less evidence is available on whether the use of antibiotics for eradication would result in prolonged perturbation of the gut microbiome and the pool of resistant bacteria in the gut. Whereas short-term effects of the treatment regimen for *H. pylori* eradication are well-known, there is limited evidence from randomised studies on the long-term effects of eradication.

An important study of 560 subjects from Taiwan examining these issues has been published by Liou *et al.*³⁰ The authors found no significant alterations in the metabolic parameters 1 year after the eradication compared with baseline. Furthermore, the initial perturbation of the gut microbiome and the antibiotic resistance of faecal microbiota diversity were largely restored to the pretreatment state between 2 months and 1 year after the eradication therapy. Our own data from a randomised controlled clinical trial showed differences in longlasting gut resistome between different eradication regimens based on shotgun sequencing. The results obtained suggested that gut resistome remained increased for at least 6 months after a 14-day eradication regimen containing clarithromycin. A similar result was not observed with amoxicillin/bismuth-containing treatment regimen in the control group.³¹ Therefore, the choice of antibiotic regimen is important and the effects on longlasting resistome should be tested before a particular eradication regimen is recommended for prevention.

Certain other aspects should be considered when designing a population-based *H. pylori* *screen and treat* programme and will be discussed below.

Organisational aspects of a gastric cancer screening programme

Proper *governance* and quality assurance are critical aspects of a cancer screening programme.³² Monitoring of outcomes, which entails the linkage to cancer registries, is an important aspect for measuring effectiveness of the programme.²⁵ An important consideration is attributing *H. pylori* eradication to cancer incidence and mortality. The timeframe between these events can be decades.

Definition of the *target age group* is an important factor of an organised screening programme. Eradication is most effective before precancerous lesions have developed since in the latter case the patient might have passed the so-called point-of-no-return and cancer could be developing even in the absence of the

infection. At the same time, eradication might be effective also after the age of 50.³³ Another important factor for considering intervention in early adulthood is the fact that transmission to offspring would be prevented; this is justified by the evidence on typical *H. pylori* transmission from the mother to child.³⁴ At the same time, effective recruitment and retention of young adults to studies and health interventions is a challenge,³⁵ and it could be expected that participation rates of this age group would be lower than in the age group used in screening interventions for other cancers. These aspects are addressed in the studies discussed below.

An effective *invitation strategy* is a prerequisite for a successful screening programme.²⁵ The target group for gastric cancer prevention might differ from the traditional target groups for other types of cancer screening—for example, men aged less than 50 years are not routinely invited for other cancer screening programmes. Some EU countries, like Slovenia and Croatia, are operating preventive programmes (health check-ups) for young adults in their 30s. This could potentially be combined with gastric cancer prevention. Yet, in this case attendance at the screening programme for gastric cancer would be dependent on participation in existing preventive programmes.

As recommended by the Council of the European Union, decisions on implementation of an *H. pylori* *screen and treat* strategy might depend on the gastric cancer incidence and death rates.²¹ Furthermore, the prevalence of *H. pylori* infection and the risk of gastric cancer are higher in *vulnerable populations*, including lower socioeconomic groups³⁶ and immigrants.²⁰ Engaging these populations in screening requires tailored invitation strategies. In countries that have a low gastric cancer burden and do not plan population-based screening programmes, vulnerable populations might still need to be included in screening using tailored approaches.

Aspects related to non-invasive testing in screening settings

Non-invasive test to be used for detection of H. pylori. The optimal approach for non-invasive *H. pylori* assessment would be the ¹³C-urea breath test (UBT)¹⁶; however, the cost of the test could be a limiting factor. A locally validated monoclonal stool antigen test (SAT) could be an alternative, with slightly lower accuracy.³⁷ In terms of the cost-effectiveness, use of *H. pylori* IgG antigen detection in serum would be an option if a positive result is confirmed by another test, such as UBT.¹⁶ The limitations of these approaches are summarised in [table 1](#).

Non-invasive testing for *precancerous gastric lesions* is an attractive approach and has been considered in a number of guidelines. The Maastricht VI/Florence guideline states that gastric functional serology (pepsinogens I–II and gastrin levels), anti-intrinsic factor and antiparietal cell autoantibodies might provide clinically valuable information on the likelihood of gastric mucosal atrophy, including aetiology.¹⁶ The use of serology for gastritis as an ancillary approach is further endorsed by the RE.GA.IN consensus, even though pepsinogen testing has 59% sensitivity for atrophic gastritis.³⁷ In the GISTAR pilot study the sensitivity of pepsinogens for atrophic gastritis ranged from 18.4% to 31.1% depending on the test and cut-off point, whereas specificity was acceptable.³⁸ Our study in patients with gastric cancer indicated decreased level of pepsinogens only in 32.4% of the patients,³⁹ so the majority of patients had normal pepsinogen levels and would not be identified based on pepsinogen testing alone. Another important aspect is that the results obtained with different methods differ in absolute values, although they are strongly

correlated, therefore, both cut-off values and the method of testing should be considered when setting diagnostic thresholds.⁴⁰ In summary, although pepsinogens are the best studied non-invasive markers for atrophic gastritis and gastric cancer, relatively low sensitivity for the target lesions has to be considered if pepsinogens are to be used in prevention programmes.

A number of non-invasive *cancer biomarkers* have been suggested, but at present the available evidence is insufficiently strong to recommend their use in screening settings,⁴¹ and therefore their potential use for screening is not detailed here.

The principal aspects to be considered when designing a gastric cancer prevention programme by screening and eradicating *H. pylori* are summarised in [table 1](#).

Brief insight into the global programmes

We have reviewed gastric cancer programmes, including two population-based gastric cancer screening programmes running in Asia—Japan and Korea elsewhere.²³

In Asia, screening for early gastric cancer as the target lesion is the leading approach. Briefly, *Japan* has added upper endoscopy to the initial fluoroscopic (upper gastrointestinal series) investigation for screening.⁴² The lower age of screening has been increased from 40 to 50 years.⁴³ *H. pylori* eradication is reimbursed in Japan if a diagnosis of chronic gastritis is obtained and therefore, endoscopy is required.⁴⁴ In *Korea*, the National Cancer Screening Programme offers either upper endoscopy or upper gastrointestinal series for gastric cancer screening; individuals aged 40 years and older are eligible for screening, which is performed every 2 years.^{45–47} Gastric cancer screening in Korea has been shown to be cost-effective and significantly improving prognosis.⁴⁸

Bhutan became the first country to implement a nationwide population-level gastric cancer screening programme using the *screen and treat* approach for *H. pylori*.⁴⁹ The National Health Flagship Programme (2018–2023) involved population-level screening for three cancers: gastric, cervical and breast. The three key strategic actions for the programme were as follows: (i) mass eradication of *H. pylori* infection (target age group 18–75 years), (ii) early gastric cancer endoscopic screening and treatment (target age group 40–75 years) and (iii) an enhanced advocacy and awareness programme.

SAT was used as the primary test to screen for *H. pylori*, whereas upper endoscopy was reserved for high-risk groups and symptomatic patients. The programme succeeded in very high coverage of target population with SAT 90.2%.⁴⁹

Now also in the recommendations of the European Commission

Until recently, European countries have been following the 2003 Council of the European Union Recommendation on Cancer Screening,⁵⁰ including breast, cervical and colorectal cancer screenings. In late 2022, the Council issued a new recommendation, ‘Council recommendation on strengthening prevention through early detection: a new EU approach on cancer screening replacing Council Recommendation 2003/878/EC’.²¹ In addition to the previously recommended screening programmes, three new programmes have been recommended—that is, for lung, prostate and gastric cancers. The details of how each of the programmes has to be implemented, have still to be elaborated.

Specifically for gastric cancer, the recommendation states as follows: ‘*Screen and treat* strategies for *Helicobacter pylori*, including implementation studies, should be considered in those countries or regions inside countries with high gastric

Table 1 Principal aspects to be considered with a *screen and treat* programme for *H. pylori*

No	Intervention	Options	Advantages	Limitations	Notes/solutions
1	Age group	Option 1. Adults in their 30s or under the age of 30 years	<i>H. pylori</i> gastritis would be cured before the development of precancerous lesions. Transmission to an offspring would be prevented	Lower participation rates could be anticipated.	Screening should be offered only in adulthood, preferably at younger ages. Modelling could provide the benefit of using therapy before childbirth since longitudinal data are not available
		Option 2. ≥50 years	Higher participation rates are expected. The programme for gastric cancer may be combined with screening for other cancers	A proportion of population might have passed the point-of-no-return	The programme would allow to combine screening for gastric cancer with colorectal cancer screening
2	Choice of a non-invasive test for screening	Option 1. UBT	This is a preferred test. It is indicative for the current infection only	Cost. Use of proton pump inhibitors (PPI) and antibiotics should be avoided for proper sensitivity.	
		Option 2. Serology – anti <i>H. pylori</i> IgG followed by UBT in the case of a positive serology	It could be cost-saving in low <i>H. pylori</i> prevalence areas	Screening facilities will need to be attended twice, which is expected to decrease the compliance	False-positivity is expected in subjects with past infection. False-negativity of serology is not expected, although has been observed in some studies. Locally validated tests should be used to address false-negativity
		Option 3. Monoclonal SAT	As an UBT alternative, it is indicative for the current infection only	Use of various test types may result in different accuracy. Antibiotic and PPI use should be avoided for proper sensitivity	Locally validated tests should be used. UBT may still be considered for confirming a positive result
3	<i>H. pylori</i> resistance to antibiotics	Option 1. Choosing a treatment regimen less dependent on <i>H. pylori</i> resistance	Higher success rates	Cost. Availability in many EU countries could be an issue	New alternatives requiring fewer antibiotics may become available in the near future
		Option 2. Tailoring the treatment regimen towards <i>H. pylori</i> resistance in an individual patient (molecular stool analysis)	Individualised treatment options could be chosen aiming at higher success rates	Cost. Complexity of the programme. Variability in test and laboratory performance (in particular for DNA extraction) So far, insufficient evidence	This approach might have limited benefit if an effective therapy regimen with less resistome induction potential was used in the programme as a routine. Testing for clarithromycin resistance might not be rational if this antibiotic will not be used in the programme for other reasons
4	Potential induction of resistome	Choosing a treatment regimen with less effect on resistome	Less effect on gut and other resistome. Shorter course of treatment (10 instead of 14 days)	Cost. Availability in many EU countries could be an issue	New treatment regimens should desirably be evaluated for their long-time effects on gut resistome
5	Testing for the success of eradication	UBT or SAT to be used to test for the success of the treatment in screening settings	The option to provide a second-line eradication therapy if the initial one has failed	Cost. Additional workload and expected decrease in compliance	This is recommended as routine in clinical settings
6	Repeated testing	Repeated testing for the presence of <i>H. pylori</i> if the initial test was negative or following successful eradication	Could potentially reveal subjects infected later during lifetime as well as those with reinfection or recrudescence	In high-risk areas <i>H. pylori</i> infection is preliminary acquired early at life. The likelihood of the reinfection is relatively low	Could potentially provide an option to combine strategies in early adulthood and at the risk age for cancer screening (see also figure 2)

Continued

Table 1 Continued

No	Intervention	Options	Advantages	Limitations	Notes/solutions
7	Combining gastric cancer screening with colorectal cancer screening	Option 1. Upper endoscopy combined with screening colonoscopy	It is expected to reveal a proportion of patients with precancerous lesions in need of further surveillance	Upper endoscopy is not recommended for screening in the EU. Generally, FIT not colonoscopy is recommended for colorectal cancer screening in the EU. If only FIT-positive cases undergo gastric cancer screening, the major part of the population will not be screened	This strategy is not going to meet the criteria of organised cancer screening in Europe, but could be used on a case-finding basis for early diagnosis
		Option 2. Monoclonal SAT combined with FIT	This could be offered within an organised screening programme. Tests could be delivered and collected by mail (or alternative modes) and performed at home	No randomised studies are available in the EU. No implementation studies have been performed in the EU thus far	Implementation studies are planned in the EU during the upcoming years. Evidence is available from Asia

FIT, faecal immunochemical testing; PPI, proton pump inhibitor; SAT, *H. pylori* stool antigen test; UBT, ¹³C-urea breath test.

cancer incidence and death rates. Screening should also address strategies for identification and surveillance of patients with precancerous stomach lesions unrelated to *Helicobacter pylori* infections.' There is a minor inconsistency with formulation of this recommendation. Since most high-risk precancerous lesions are related to *H. pylori*, screening 'strategies for identification and surveillance' would target patients with precancerous lesions irrespective of the presence or absence of the infection.

This Council recommendation has been subject to a thorough scientific review conducted by SAPEA (Science Advice for Policy by European Academies) on the request of the Scientific Advice Mechanism of the European Commission and followed by extensive consultations with the member states of the EU. In March 2022, two documents were published: SAPEA Evidence Review Report No. 10 'Cancer Screening in the European Union'⁵¹ and Scientific Opinion No. 12 by the Group of Chief Scientific Advisors 'Cancer screening in the European Union'.⁵²

The SAPEA experts have identified that there is insufficient evidence to recommend endoscopic screening for gastric cancer in Europe, but the *screen and treat* strategy for reducing *H. pylori* infection provides an opportunity to prevent gastric cancer in EU member countries with intermediate to high gastric cancer incidence.⁵¹ The report of the Scientific Advice Mechanism endorses the statement by emphasising the importance of the population-based *screen and treat* approach for *H. pylori* as the only strategy that could be recommended in regions with intermediate to high gastric cancer incidence. Additionally, the report emphasises the importance of following available guideline recommendations for endoscopy referrals in groups at risk to maximise the opportunities for earlier diagnosis.⁵²

Ongoing activities in Europe

Several gastric cancer prevention initiatives are currently ongoing in Europe.

A multicentric randomised study of *H. pylori* eradication and pepsinogen testing for prevention of gastric cancer mortality (GISTAR study) has been recruiting individuals aged 40–64 years at the time of enrolment from an average-risk population. Recruitment for GISTAR has been ongoing since 2013.⁵³ The intervention group is offered *H. pylori* testing and eradication therapy, if found to be positive. Additionally, pepsinogen levels

are measured in plasma, and upper endoscopy recommended if the pepsinogen levels are found to be low. The general study was preceded by a pilot to test the study procedures and adjust them as needed.⁵⁴ Altogether 11 223 participants have been randomised in 11 consecutively operated recruitment centres in regional cities of Latvia up until 2023. Permanent follow-up is performed; currently, the study group is involved in follow-up to be performed within the EUROHELICAN and TOGAS projects.

EUROHELICAN (Accelerating Gastric Cancer Reduction in Europe through *Helicobacter pylori* Eradication) is one of two ongoing projects supported by the EU4HEALTH programme of the EU. The recruitment of individuals aged 30–33 years is ongoing for *H. pylori* screen and treat strategy in Slovenia with the objective to reach 2000 recruited subjects and evaluate feasibility of this approach in young age individuals. In Latvia, the potential adverse effects will be evaluated in 2000 subjects initially recruited into GISTAR. Finally, EUROHELICAN will support an international working group to be hosted by IARC aiming to establish a set of minimum standards for evaluation of the impact of the strategy for worldwide implementation of population based search for *H. pylori*. The results are expected to be applicable to areas of Europe and other parts of the world with a high prevalence of *H. pylori* and burden of gastric cancer. The working group meeting will be held in 2025 and work on the report is already ongoing.

The TOGAS project (Towards Gastric Cancer Screening Implementation in the European Union) has been designed to provide knowledge of the missing evidence needed for recommending appropriate implementation of gastric cancer screening across the EU. This includes evaluation of the effectiveness of various strategies for prevention of gastric cancer mortality in EU countries with various burdens of gastric cancer and prevalence of *H. pylori* infection. The project will extend knowledge from the TOGAS project and inform the decision-makers of cancer screening organisations. The TOGAS results will aid policy makers to incorporate gastric cancer screening into their healthcare priorities while balancing its effectiveness, feasibility and acceptability and long-term potential adverse effects.

The studies initiated within EUROHELICAN will be extended to new sites and additional patient cohorts. Such extension will assure greater validity of the results obtained. *H. pylori* screen

and treat strategy will be evaluated in 6000 young individuals (aged 30–35 years) in seven centres of six countries (Croatia, Ireland, Latvia, Poland, Romania and Slovenia). Analysis of potential adverse events (eg, gastro-oesophageal reflux disease and metabolic disease) will be evaluated in a standardised way 5–10 years following eradication in 3000 subjects from the GISTAR cohort. An additional study will evaluate the presence of stomach precancerous lesions in individuals aged >50 years undergoing colonoscopy within a colorectal cancer screening programme. This is expected to provide valuable information on the proportion of patients with advanced stomach lesions within this age group.

In addition to the research studies, other important activities are being performed within TOGAS. Among them are cost-effectiveness modelling, collection of feedback from the decision-makers and potential screenees, including those representing vulnerable populations, as well as communication activities with screening experts in all the EU member states.

Further extension of the ongoing activities is also expected. European Joint Action *EUCanScreen* (Joint Action on the New EU Cancer Screening Scheme Implementation) has been launched in 2024. Gastric cancer screening will be part of *EUCanScreen* together with many other cancer screening initiatives. A feasibility study of SAT, in combination with faecal immunochemical screening (FIT)-based colorectal cancer screening and activities related to harmonisation of data on gastric cancer prevention, is planned within *EUCanScreen*. The feasibility study will involve the group of patients who are eligible for colorectal cancer screening—that is, those over the age of 50.

Therefore, the screen and treat approach for *H. pylori* in the general population will be piloted either in a young age group—that is, those aged 30–35 years (EUROHELICAN and TOGAS), or in individuals aged >50 years (*EUCanScreen*).

Finally, cost-effectiveness modelling that is also been planned in *EUCanScreen* is expected to provide additional information on the most appropriate gastric cancer prevention modality.

Could gastric cancer screening be combined with colorectal cancer screening?

According to the Maastricht VI/Florence guideline, screening modalities for gastric cancer prevention (non-invasive or endoscopic) could be combined with colorectal cancer screening; yet, agreement on such a combination was relatively low—81%.¹⁶ This agreement rate is based on the results of a few small pilot studies investigating feasibility of stomach examination at the age when subjects are invited for colorectal cancer screening.^{55 56} More data are to come from the ongoing TOGAS project (discussed above).

The benefits of such an approach include potentially better participation and adherence rates than in a younger age group; some evidence from other screening programmes⁵⁷ could support such a combination. The proportion of individuals with a positive *H. pylori* result would be expected to be higher than in the younger group in view of the infection acquisition possibilities later during a lifetime.

Nevertheless, two major limitations of combining screening for gastric and colorectal cancers have to be considered: (1) a subfraction of individuals might have passed the *point-of-no-return* and therefore, it might be too late for them to undergo *H. pylori* eradication for cancer prevention (discussed above); estimating the subfraction might be difficult; (2) organisational aspects of the programme might pose challenges. A brief insight into different options is provided below (see also table 1):

Screening for stomach lesions at the time of screening colonoscopy. With a few exceptions (being accepted by the European Council Recommendations) colonoscopy is not the primary screening tool for colorectal cancer screening in the EU. Therefore, this approach in population-based settings, even from a theoretical viewpoint, could be feasible only in a few EU countries or within opportunistic programmes, but not as a population-based approach across Europe. If only those individuals who test positive with FIT are to be evaluated (invasively or non-invasively) for stomach conditions (including *H. pylori*), a very small subfraction of population will undergo gastric cancer

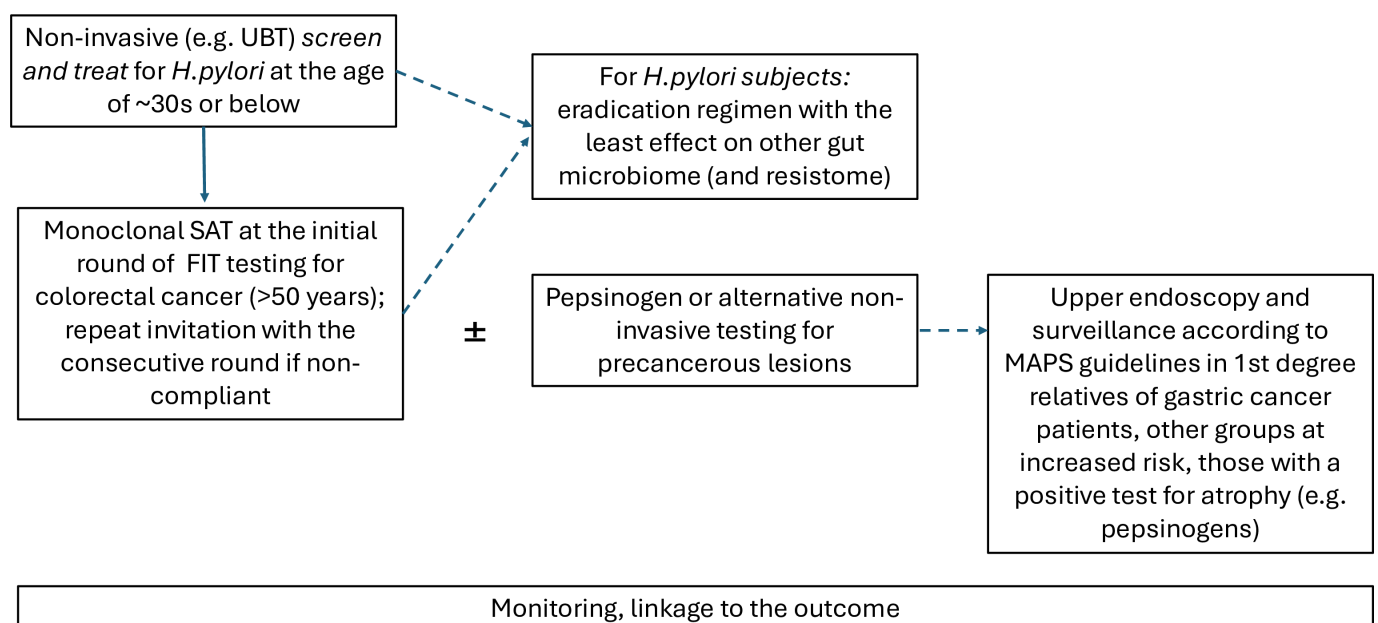


Figure 2 Proposed algorithm for gastric cancer screening in Europe. FIT, faecal immunochemical testing; MAPS, management of epithelial precancerous conditions and lesions in the stomach; SAT, stool antigen test; UBT, ¹³C-urea breath test.

screening, which is not compliant with an organised screening programme. Furthermore, gastric cancer endoscopic screening in Europe has not been supported by the SAPEA expert group.⁵¹

Screening for *H. pylori* and/or precancerous lesions at the time of FIT screening for colorectal cancer. In most efficient programmes, FIT is delivered to the participants, and samples are collected by an indirect contact (mail-delivered, pharmacy-delivered). Therefore, from an organisational viewpoint, stool testing for *H. pylori* antigen could be the preferred approach for this target group since the test-system delivery and collection could be handled in a way similar to FIT.

Use of serology testing would require a participant to attend the screening facilities on several occasions: initially, for blood sampling, thereafter, for UBT following a positive serology result in cases where *H. pylori* serology is used, and for treatment prescriptions. This is expected to decrease the participation rates. This downside has to be considered if examination of non-invasive gastric precancerous lesions (eg, using pepsinogens) is included in the programme.

Ideally, SAT could be combined with FIT within one single test-system. In the future, molecular stool testing simultaneously for the presence of *H. pylori* and its resistance to antibiotics could be an option,⁵⁸ if the benefits outweigh the costs.

Studies to test the feasibility of such an approach are being planned within the EUCanScreen project, but promising results from Asia have become available. In Taiwan, a study conducted in a large general population cohort aged 50–69 years demonstrated the feasibility of combining SAT with FIT, and, additionally there was higher participation in the group who were offered combined testing for either gastric or colorectal pathology than when combined with colorectal cancer screening alone.⁵⁹

The potentially optimal scenario for gastric cancer screening in Europe

There are considerable limitations for each of the above-described gastric cancer screening and prevention scenarios for Europe. It is possible that new screening methods will enter clinical practice and overcome the current limitations; volatile markers in breath for either cancer or high-risk precancerous lesions, improved markers or set of markers for atrophy, and new molecular markers, including multitarget cancer tests, could be among them.

However, at present, there is a clear need to implement gastric cancer prevention with the existing tools. Thus, we suggest the following algorithm (figure 2).

The ongoing and planned studies will provide additional information on the rationale of particular paths in this algorithm. Modelling of various scenarios would allow identification of the most effective and cost-effective set-up. Nevertheless, further implementation research would be required to assure proper results of such screening programmes in various countries. EU level and national investments will be required to conduct such implementation research. Furthermore, we live in a time when personalised cancer screening is becoming part of prevention and early diagnosis. This could have a particular importance for gastric cancer screening to identify patients expected to progress towards cancer and avoid unnecessary treatments. However, for the time being, we are obliged to effectively use the available tools.

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