Clinical Practice Guidelines on the Management of Gastric Cancer and *Helicobacter pylori* in the Philippines

March 2024

Disclaimer and Contact Information

This guideline is for primary care providers, specialists, and allied health professionals treating patients with gastric cancer and *Helicobacter pylori* infection. While the Department of Health (DOH) encourages following this guideline, clinicians should use their clinical judgment and consider patients' values, needs, and preferences. Sound clinical decision-making is crucial, as individual cases may differ in terms of patient history, current physical status, and responses to treatment.

Payors, policymakers, hospital administrators, and employers can use this CPG. However, nonconformance should not be the sole reason for granting or denying financial assistance or insurance claims. The recommendations in this CPG are not strict rules for legal action.

This CPG does not cover the entirety of the management of gastric cancer and *Helicobacter pylori* infection. It focuses on providing recommendations on interventions where variability in clinical practice and some controversies in decision-making exist. The developers acknowledge its limitations, and evidence summaries rely on the best available scientific evidence, which may not fully address certain aspects of interventions or diagnostic tests.

Acknowledgements

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This significant effort was accomplished through the initiative of the Bicol Medical Center's executive and management team, led by its medical director. The Steering Committee supervised the CPG's development, the Technical Working Group conducted the evidence review and proposed draft recommendations, and the Consensus Panel members, representing various healthcare sectors, analyzed scientific evidence while contributing perspectives on feasibility, applicability, and equity for the final recommendations. Special commendation goes to external reviewers for ensuring the guideline's completeness and clarity.

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Participating Societies, Organizations, Agencies, and Institutions

Department of Health (DOH)

Bicol Medical Center

Philippine Society of Digestive Endoscopy (PSDE)

Philippine Alliance of Patient Organizations (PAPO)

Philippine College of Physicians (PCP)

Philippine College of Surgeons (PCS)

Pediatric Infectious Disease Society of the Philippines (PIDSP)

Philippine Pediatric Society (PPS)

Philippine Academy of Family Physicians Inc. (PAFP)

Philippine Society of Gastroenterology (PSG)

Philippine Society for Microbiology and Infectious Diseases (PSMID)

Philippine Society of Medical Oncology (PSMO)

Philippine Society for Pediatric Gastroenterology, Hepatology, and Nutrition (PSPGHAN)

List of Abbreviations

ACG	American College of Gastroenterology
AGREE-II	Appraisal of Guidelines for REsearch & Evaluation-II
AJCC	American Joint Committee on Cancer
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
APC	Argon Plasma Coagulation
ASEAN	Association of Southeast Asian Nations
ASGE	American Society for Gastrointestinal Endoscopy
AUC ROC	area under the curve of the receiver operating characteristic
CA 19-9	cancer antigen 19-9
CAG	Canadian Association of Gastroenterology
CEA	carcinoembryonic antigen
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
COGS	Conference on Guideline Standardization
CP	consensus panel
CPG	clinical practice guidelines
CT	computed-tomography/tomographic scans
DALY	disability-adjusted life year
DOH	Department of Health
ECOG	Eastern Cooperative Oncology Group scale
EGC	early gastric cancer
EGD	esophagogastroduodenoscopy
EHSG	European Helicobacter Study Group
ERE	evidence review experts
ESMO	European Society for Medical Oncology

ESPGHAN	The European Society for Paediatric Gastroenterology Hepatology and Nutrition
ETD	evidence-to-decision
EUS	endoscopic ultrasonography
FDG-PET/CT	F-fluorodeoxyglucose Positron-emitted Tomography/Computed Tomography
FNR	False negative rates
FPR	False positive rates
GBD	Global Burden of Disease
GCa	gastric cancer
GI	gastrointestinal
GIM	gastric intestinal metaplasia
GRADE	Grading of Recommendations Assessment, Development and Evaluation Working Group
HMO	health maintenance organization
HR	hazards ratio
HSP	Hepatology Society of the Philippines
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
JRRE	Joint Committee on Research and Research Education
JSPGHAN	The Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition
KAPs	Knowledge, attitude, and practices/procedures
KM+	Knowledge Management Plus Equity Criteria (DOH)
MDCT	multidetector computed tomography
MDT	multidisciplinary team
MeSH	medical subject headings
NICCA	National Integrated Cancer Control Act
NIH-ICE	National Institutes of Health - Institute of Clinical Epidemiology
NCCN	National Comprehensive Cancer Network

NSPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
NSRI	non-randomized studies of the effects of interventions
OR	odds ratio
PET/AI	positron emission tomography artificial intelligence
PHIC	Philippine Health Insurance Corporation
PICO	population, intervention, control, and outcomes
PPI	proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSDE	Philippine Society of Digestive Endoscopy
PSG	Philippine Society of Gastroenterology
QOL	quality of Life
QUADAS-2	A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies
RCT	randomized control trial
RevMan 5	Review Manager 5 (tool)
RoB	Risk of Bias (Cochrane tool)
RoBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions (Cochrane tool)
RR	risk ratio
RUT	rapid urease test
SAT	stool antigen test
TAE	trans arterial embolisation
TNM system	Tumor-Nodes-Metastasis staging system
UBT	Urea Breath Test
UICC	Union for International Cancer Control
WGO	World Gastroenterology Organization
YLD/s	years lived with a disability/ies
YLL	years of life lost

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[1] *F-fluorodeoxyglucose Positron-emitted Tomography/Computed Tomography (FDG-PET/CT)

Executive Summary

This clinical practice guideline for the Management of Gastric Cancer and *Helicobacter pylori* infection in the Philippines is a collaborative effort between the Department of Health, the National Institutes of Health - Institute of Clinical Epidemiology, Bicol Medical Center, and the Philippine Society of Digestive Endoscopy.

The CPG systematically synthesizes evidence to standardize practices in certain priority topics regarding the screening, diagnosis, management, and surveillance of gastric cancer and *Helicobacter pylori* infection in the country. Equal emphasis is placed on addressing *H. pylori* infection, given its significant role as a major risk factor for the development of gastric cancer.

The guideline development process adhered to the widely accepted Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, including GRADE Adolopment—a systematic process adapting evidence summaries—and the GRADE Evidence to Decision (EtD2) framework. This involved:

1. Identifying critical questions and outcomes
2. Retrieving current evidence
3. Assessing and synthesizing the evidence base
4. Formulating draft recommendations
5. Convening a multi-sectoral stakeholder panel to discuss values, preferences, and assess recommendation strength
6. Planning for dissemination, implementation, impact evaluation, and updates.

The CPG offers eighteen (18) recommendations and five (5) good practice statements derived from assessing the best available evidence on ten (10) prioritized clinical questions related to screening, diagnosis, management, and surveillance of gastric cancer and *H.pylori* infection.

The recommendations in this CPG will remain valid and will be updated every three years or when new evidence emerges.

Summary of Recommendations

CPG Table 1. Summary of Final Recommendations, 2023 Clinical Practice Guidelines on the Management of Gastric Cancer and Helicobacter pylori in the Philippines.

No.	Recommendations	Strength of Recommendation	Certainty of Evidence
Gastric cancer screening using alarm signs in patients with dyspepsia			
1	Among adults with dyspepsia, we suggest using alarm signs and symptoms* to identify those who may need an upper gastrointestinal endoscopy. **Includes any of the following: unintended weight loss (at least 5% of usual body weight in the preceding 6-12 months), dysphagia or odynophagia, bleeding, anemia, vomiting, abdominal mass, age ≥ 50 years old*	**Weak**	**Very Low** ⊕◯◯◯
Non-invasive tests for diagnosing gastric cancer			
2.1	The gold standard for diagnosing gastric cancer is through biopsy, histopathology obtained through esophagogastroduodenoscopy (EGD) and/or surgery.	**Good practice statement**	
2.2	Among patients with alarm signs and symptoms, we recommend against the use of non-invasive tests in place of biopsy for diagnosing gastric cancer.	**Strong**	**Very Low** ⊕◯◯◯
Conventional CT (computed tomographic) vs. CT + endoscopic ultrasonography/positron emission tomography (EUS/PET) for pre-operative staging of gastric cancer			
3.1	Among patients with gastric cancer, we recommend the use of MDCT for staging gastric cancer prior to surgery.	**Strong**	**Low** ⊕⊕◯◯
3.2	Among patients with early gastric cancer, we suggest the use of EUS as an adjunct to multidetector computed tomography (MDCT) in areas where it is available and technical expertise is present.	**Weak**	**Very Low** ⊕◯◯◯
3.3	Among patients with gastric cancer, we do not recommend the routine use of FDG-PET/CT as an adjunct to MDCT for staging.	**Strong**	**Low** ⊕⊕◯◯
Multidisciplinary team approach for managing patients with gastric cancer			
4	Among patients with gastric cancer, we recommend the use of a multidisciplinary team approach.	**Strong**	**Very Low** ⊕◯◯◯
Non-surgical hemostatic interventions for bleeding			
5.1	Shared decision making for the palliative control of tumor bleeding by endoscopic techniques and/or radiotherapy should be discussed to the patient as deemed necessary.	**Good practice statement**	
5.2	Among patients with unresectable gastric cancer with tumor bleeding, we suggest the use of hemostatic spray powder application or transarterial embolization as bridging therapy for more definitive treatment for tumor bleeding where accessible.	**Weak**	**Very Low** ⊕◯◯◯

No.	Recommendations	Strength of Recommendation	Certainty of Evidence
	Screening for *H. pylori* in asymptomatic general population		
6.1	Among asymptomatic individuals, we suggest against mass screening for *H. pylori.*	**Weak**	**Very Low** ⊕◯◯◯
	Non-invasive tests for *H. pylori* diagnosis		
7.1	Among adults with dyspepsia without alarm signs and symptoms, we recommend the test-and-treat strategy in the non-invasive testing of *H pylori* infection.	**Strong**	**Low** ⊕⊕◯◯
7.2	Among adults with dyspepsia without alarm signs and symptoms, we recommend the use of stool antigen test to diagnose *H. pylori* infection.	**Strong**	**Low** ⊕⊕◯◯
7.3	Among adults with dyspepsia without alarm signs and symptoms, we suggest the use of 13C or 14C Urea Breath test (UBT) to diagnose *H. pylori* infection.	**Weak**	**Low** ⊕⊕◯◯
7.4	Among adults with dyspepsia without alarm signs and symptoms, we suggest against the use of serology to diagnose *H. pylori* infection.	**Weak**	**Low** ⊕⊕◯◯
7.5	Among children with dyspepsia without alarm signs and symptoms, we recommend against non-invasive testing (13C/14C UBT, serology, stool antigen tests) for *H. pylori* infection.	**Strong**	**Low** ⊕⊕◯◯
	Standard triple antibiotic therapy for *H. pylori*		
8.1	Among adults and children with *H. pylori* infection, we suggest using the 14-day concomitant triple therapy containing clarithromycin.	**Weak**	**Very Low** ⊕◯◯◯
8.2	Among adults with *H. pylori* infection, we suggest using alternative regimens*. **14D clarithromycin-based sequential, 14D levofloxacin-based sequential, 10-14D bismuth-containing quadruple, 7D vonoprazan-containing triple therapy*	**Weak**	**Very Low** ⊕◯◯◯
8.3	Among children with *H. pylori* infection, we suggest using alternative regimens*. **14D sequential, bismuth-based quadruple therapy*	**Weak**	**Very Low** ⊕◯◯◯
	Post-treatment surveillance of *H. pylori*		
9.1	In adults and children who completed eradication treatment for *H. pylori* infection, clinicians should consider doing tests of cure using urea breath test or stool antigen test to confirm eradication of *H. pylori*.	**Good practice statement**	
9.2	Biopsy-based testing for cure may be considered only if there are other indications for a repeat EGD.	**Good practice statement**	
9.3	Tests of cure should be done at least 4 weeks after the completion of antibiotic therapy and after proton pump inhibitor (PPI) therapy has been withheld for 1-2 weeks.	**Good practice statement**	

No.	Recommendations	Strength of Recommendation	Certainty of Evidence
	Surveillance for precancerous lesions		
10	Among patients with gastric premalignant conditions, we suggest periodic surveillance using upper gastrointestinal endoscopy. ● **Atrophic gastritis:** within 3 years ● **Gastrointestinal metaplasia:** within 3 years ○ **Dysplasia:** endoscopic resection, if available, or annual surveillance	**Weak**	**Low** ⊕⊕◯◯

Chapter 1. Introduction

BACKGROUND

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer-related deaths worldwide. In the Philippines, it ranks eleventh among cancer-related deaths and thirteenth in incidence.[2]

Common risk factors for gastric cancer include *H.pylori* infection, smoking, alcohol use, a diet high in salt, and genetic predisposition. Global variation in gastric cancer incidence is substantial, influenced by differences in *H. pylori* prevalence, cultural dietary practices, and cancer detection programs. In regions like China, Japan, and South Korea, where *H. pylori* is endemic, population-based and endoscopy-based screening programs, coupled with aggressive measures to eradicate the bacteria, have led to higher rates of early gastric cancer detection and a significant reduction in mortality. Worldwide and in the Philippines, improved sanitation, infection control, and *H. pylori* eradication efforts have contributed to a decline in gastric cancer incidence.

Republic Act 11215, commonly referred to as the "National Integrated Cancer Control Act" or NICCA, seeks to establish a cohesive framework for all government activities related to cancer. With the authority granted by the NICCA law, the Department of Health, through the Disease Prevention and Control Bureau, is enhancing its initiatives to combat cancer. The goal is to achieve a 10% reduction in cancer-related mortality across all types of cancer by the year 2035.

As a result of the Clinical Practice Guidelines (CPG) Topic Prioritization for C.Y. 2022 CPG Development, seven topics or areas were identified, which included gastric cancer. Although ranked 13th by cancer site in incidence with a 5-year prevalence of 4.13/100,000 population, it ranked 11th by cancer site in deaths last 2022 based on the recent Globocan report. It may be due to the advanced nature of the illness when seen by physicians since the majority of afflicted patients are asymptomatic at the early stages of the disease.

Despite efforts to reduce its incidence, gastric cancer still imposes a substantial burden due to significant morbidity and mortality. Prognosis is typically poor, as the cancer is often diagnosed at an advanced stage, leaving patients with limited options for palliative approaches aimed at improving survival and enhancing the quality of life, especially for those with locally advanced or metastatic disease. Chronic *Helicobacter pylori* infection is associated with 90% of gastric cancer. Thus, early recognition and treatment of this infection can have a great impact in decreasing gastric cancer related morbidity and mortality.

[2] CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4

OBJECTIVE, SCOPE, TARGET POPULATION, AND TARGET USERS

Objectives

This project aimed to develop evidence-based clinical practice guidelines in the Philippines for gastric cancer and *H. pylori* infection. The primary objective was to provide guidance to healthcare workers in choosing cost-effective interventions. Specifically, the project sought to:

1. Evaluate existing clinical practice guidelines on gastric cancer and *H. pylori*.
2. Prioritize key clinical questions in the management of gastric cancer and *H. pylori* using the GRADE framework, focusing on screening, diagnosis, treatment, monitoring, and prevention of transmission.
3. Summarize evidence on cost-effective interventions through a systematic review, including cost-effectiveness analyses.
4. Generate evidence-based recommendations to promote uniformity of practice.

Scope and Purpose

This guideline aims to sustain progress in controlling gastric cancer in the Philippines by providing recommendations on the diagnosis, treatment, and eradication of *H. pylori*, the predominant risk factor for gastric cancer. Additionally, it aims to minimize practice variation in the diagnosis, staging, and management of gastric cancer.

This CPG addresses clinical issues related to screening, treatment, and eradication of *H. pylori* infection, the primary risk factor for gastric cancer. CPG Table 2 outlines the specific health questions covered in detail by this guideline. Additionally, it will explore topics such as pre-surgical staging for informed treatment decisions, palliative hemostatic control for advanced gastric cancer patients, and surveillance of pre-malignant lesions in the stomach.

The table below outlines the 10 guideline questions intended for discussion in this CPG. Further information on the detailed population, intervention, control, and outcomes (PICO) for each question can be found in the appendix.

CPG Table 2. List of Guideline Questions

#	Topic	Guideline Question	Type
1	Gastric cancer screening using alarm signs in patients with dyspepsia	GQ: Should we use alarm signs and symptoms for the early diagnosis of gastric cancer among patients with dyspepsia? RQ: Among patients with dyspepsia, how accurate are alarm signs and symptoms for the early diagnosis of gastric cancer?	Diagnosis
2	Non-invasive tests for diagnosing gastric cancer	GQ: Should we do non-invasive tests to diagnose gastric cancer? RQ: Among patients with alarm signs and symptoms, how accurate are non-invasive tests (imaging and biochemical tests) compared to biopsy/histopathology in diagnosing gastric cancer?	Diagnosis

3	Conventional CT vs. CT + EUS/PET for pre-operative staging of gastric cancer	GQ: Should we use FDG-PET CT or endoscopic ultrasound (EUS) on top of contrast CT to guide pre-operative staging in patients with gastric cancer? RQ: Among patients diagnosed with gastric cancer, how safe, accurate, and effective is contrast CT alone compared to contrast CT with adjunctive diagnostic modalities (EUS, FDG-PET-CT) in pre-operative staging?	Diagnosis
4	Multidisciplinary team approach for managing patients with gastric cancer	GQ: Should we use a multidisciplinary team approach for patients with gastric cancer? RQ: Among patients with gastric cancer, how effective is a multidisciplinary team approach in improving gastric-cancer related outcomes?	Treatment
5	Non-surgical hemostatic interventions for bleeding	GQ: Should we use non-surgical hemostatic interventions in patients with unresectable gastric cancer with tumoral bleeding? RQ: Among patients with unresectable gastric cancer presenting with tumoral bleeding, how effective are non-surgical hemostatic interventions in improving survival and bleeding control?	Treatment
6	Mass screening for H pylori in asymptomatic general population	GQ: Should we do mass or targeted screening for *H. pylori* infection in asymptomatic individuals? RQ: Among asymptomatic individuals, how safe, accurate, and effective is mass screening compared to targeted screening for detecting *H. pylori* infection and decreasing *H. pylori*-related morbidity and gastric cancer incidence?	Diagnosis
7	Non-invasive tests for H pylori diagnosis	GQ: Should we use non-invasive tests to diagnose active *H. pylori* infection in patients with dyspepsia? RQ: Among patients with dyspepsia, how accurate, safe, and effective are non-invasive tests in diagnosing active H pylori infection?	Diagnosis
8	Standard antibiotic therapy vs. other antibiotic therapy	GQ: Should we use the 14-day triple therapy in patients with *H. pylori* infection? RQ: Among patients with H pylori infection, how effective and safe is 14-day triple therapy compared to novel drug combinations in patients with *H. pylori* infection?	Treatment
9	Post-treatment surveillance for H pylori	GQ: Should we use confirmatory tests to decrease incidence of gastric cancer in patients who completed eradication treatment? RQ: Among patients who completed eradication treatment for *H. pylori*, how effective is confirmatory testing (urea breath test, stool antigen test) compared to no testing in decreasing incidence of gastric cancer, *H. pylori* related morbidity, and drug resistance rates?	Diagnosis, Prognosis
10	Routine surveillance EGD for gastric cancer prevention	GQ: Should we do monitoring and surveillance of precancerous lesions? RQ: Among patients diagnosed with premalignant gastric lesions, how effective is periodic monitoring using EGD in decreasing gastric cancer-related mortality and morbidity?	Diagnosis, Prognosis

**GQ: Guideline Question, RQ: Research Question*

Target Population

This guideline is designed for individuals diagnosed with gastric cancer and for both children and adults infected with *H. pylori* bacteria. Some guideline questions target populations not diagnosed with gastric cancer but with symptoms (Q1, Q2), high-risk individuals (Q10), or the asymptomatic general population (Q6).

Intended Users

These guidelines are intended for use by healthcare providers across all levels of care. In the primary care setting, these can offer recommendations for screening, diagnosing, and monitoring gastric cancer and *H. pylori* infection. These can also assist primary care providers in deciding when to refer patients for specialized care. Additionally, specialists can utilize some of the recommendations to optimize the treatment of gastric cancer patients, particularly those requiring pre-surgical staging or managing refractory bleeding in non-surgical cases. Lastly, policymakers can use these recommendations to support the expansion of national programs for gastric cancer and *H. pylori*, as well as in procuring and distributing the health technologies outlined in this CPG.

Chapter 2. CPG Development Methodology

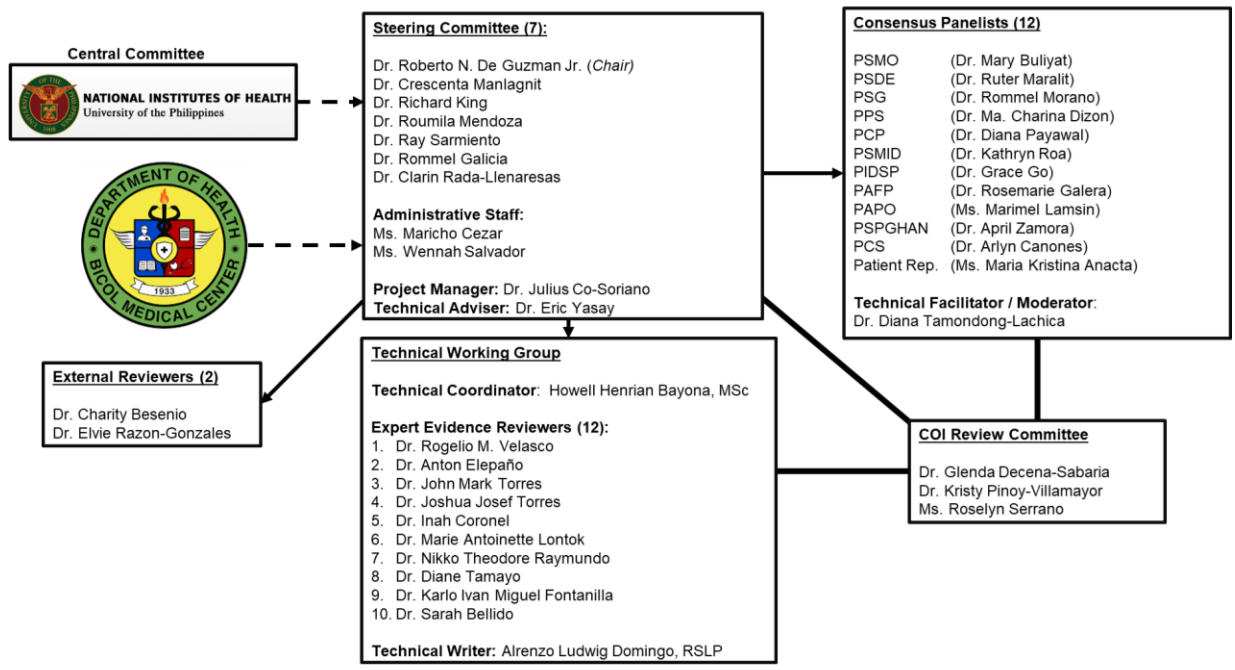
GUIDELINE PREPARATION

Guideline Methodology

This CPG followed the standard methodology described in the 2018 Manual for Clinical Practice Guideline Development by the DOH[3] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for guideline development.[4]

Composition of The CPG Task Force

Bicol Medical Center led the development of this CPG in collaboration with the Philippine Society of Digestive Endoscopy and the University of the Philippines – National Institutes of Health. The CPG Task Force comprised three main working groups: (1) Steering Committee (SC), (2) Technical Working Group (TWG), and (3) Consensus Panel (CP). The organizational chart is depicted in CPG Figure 1.



CPG Figure 1. Organizational Chart for the Composition of the CPG Task Force

The SC comprised 7 members, including experts in different fields, a project manager from Bicol Medical Center, a Technical Adviser for guideline methodology, and support administrative staff, as seen in the table below. The SC identified key guideline areas through consultative meetings with relevant stakeholders. Priority topics focused on interventions or clinical practices with high variation, unclear evidence of efficacy and safety, high interest to patients and healthcare providers, and potential to improve health outcomes and inform policy recommendations.

[3] Department of Health Philippines. 2018. Manual for Clinical Practice Guideline Development.
[4] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6. doi:10.1136/bmj.39489.470347.ad

The SC selected Consensus Panel (CP) members based on their expertise, knowledge, and absence of significant conflicts of interest. The CP comprised 12 representatives from diverse sectors, including medical societies, primary and specialty care physicians, and patient advocates. Members were nominated by their specialty groups, serving as representatives of their respective organizations. To ensure a patient-centric perspective, family members of individuals who had experienced gastric cancer were also included in the panel to represent the views of patients and the broader public.

All members of the CPG Task Force for the Clinical Practice Guidelines for the Management of Gastric Cancer and *Helicobacter pylori* in the Philippines are listed in the table below:

CPG Table 3. Members of the CPG Task Force.

NAME	AFFILIATION/S	AREA/S OF EXPERTISE
Steering Committee (SC)		
De Guzman, Roberto Jr. *(chair)*	Our Lady of Lourdes Hospital	Adult Gastroenterology
Galicia, Rommel	Bicol Medical Center	Surgical Oncology
King, Rich Ericson C.	Philippine General Hospital	Medical Oncology, Clinical Epidemiology
Manlagñit, Maria Crescenta	Bicol Medical Center	Internal Medicine, Gastroenterology
Mendoza, Roumilla F.	West Visayas State University West Visayas State University Medical Center	Pediatric Gastroenterology
Rada-Llenares, Clarin M.	Bicol Medical Center Universidad de Sta. Isabel - Health Services	Internal Medicine / Geriatrics
Sarmiento, Ray I.	Rizal Medical Center, St. Luke's Medical Center-BGC, Asian Hospital & Medical Center	General Surgery - Surgical Endoscopy, Upper GI Surgery & Advanced Minimally Invasive Surgery
Soriano, Julius C. *(Project manager)*	Bicol Medical Center	Adult Gastroenterology Advance Therapeutic Endoscopy
Technical Adviser		
Yasay, Eric B.	UP College of Medicine Philippine General Hospital	Gastroenterology, Therapeutic Endoscopy, Clinical Epidemiology
Technical Coordinator		
Bayona, Howell Henrian G.	Graduate School of Health Sciences, Fujita Health University	Clinical Epidemiology, Deglutology
Technical Writer		
Domingo, Alrenzo Ludwig B.	Communicare Therapy Center	Speech-Language Pathology
Technical Facilitator/Consensus Panel Meeting Moderator		
Tamondong-Lachica, Diana R.	UP College of Medicine - Philippine General Hospital	Internal Medicine

NAME	AFFILIATION/S	AREA/S OF EXPERTISE
Evidence Review Experts (ERE)		
Bellido, Sarah Jean	St. Luke's Medical Center QC	Internal Medicine - Gastroenterology Clinical Epidemiology
Coronel, Inah Jane	Mary Mediatrix Medical Center	Internal Medicine - Gastroenterology
Elepaño, Anton	Nuffield Department of Primary Care Health Sciences, University of Oxford	Internal Medicine, Digital Health
Fontanilla, Karlo Ivan Miguel	Holy Mother of Mercy Hospital Corazon Locsin Montelibano Memorial Hospital	Gastroenterology
Lontok, Marie Antoinette	St. Luke's Medical Center BGC St Luke's Medical Center QC Asian Hospital and Medical Center	Gastroenterology Clinical Epidemiology
Raymundo, Nikko Theodore	N/A	Gastroenterology
Tamayo, Diane	Philippine Pharmacists Association (PPhA)	Pharmacovigilance
Torres, John Mark K.	Skyline Hospital and Medical Center ACE San Jose del Monte Medical Center North Caloocan Doctors' Hospital	Internal Medicine - Gastroenterology
Torres, Joshua Josef R.	Los Banos Doctors Hospital and Medical Center HealthServ Los Banos Medical Center Calamba Medical Center St. John the Baptist Medical Center	Gastroenterology
Velasco, Rogelio	Philippine Heart Center Lung Center of the Philippines	Medical Oncology Clinical Epidemiology
Consensus Panelists (CP)		
Anacta, Maria Kristina (Patient representative)	N/A	Information Technology (Patient Representative)
Buliyat, Mary Gay (Philippine Society of Medical Oncology)	Baguio General Hospital and Medical Center Region 2 Trauma and Medical Center	Medical Oncology
Cañones, Arlyn (Philippine College of Surgeons)	Rizal Medical Center	General Surgery/Surgical Endoscopy
Dizon, Ma. Charina (Philippine Pediatric Society)	St. Luke's Medical Center BGC Cardinal Santos Medical Center Rizal Medical Center	General Pediatrics Pediatric Gastroenterology and Nutrition
Galera, Rosemarie I. (Philippine Academy of Family Physicians)	Baguio General Hospital and Medical Center	Family Medicine

NAME	AFFILIATION/S	AREA/S OF EXPERTISE
Go, Grace Devota G. (Pediatric Infectious Disease Society of the Philippines)	San Lazaro Hospital Jose R. Reyes Memorial Medical Center Mary Chiles General Hospital De Los Santos Medical Center	Pediatric Infectious Diseases
Lamsin, Marimel (Patient representative)	Philippine Alliance of Patient Organizations (PAPO)	Patient Advocacy
Maralit, Ruter M. (Philippine Society of Gastroenterology)	Philippine General Hospital Asian Hospital and Medical Center	Internal Medicine - Gastroenterology
Padua-Zamora, April (Philippine Society for Pediatric Gastroenterology, Hepatology, & Nutrition)	Philippine General Hospital	Pediatric Gastroenterology
Payawal, Diana A. (Philippine College of Physicians)	Philippine College of Physicians Cardinal Santos Medical Center	Internal Medicine, Gastroenterology
Roa, Kathryn Uy (Philippine Society of Microbiology and Infectious Diseases)	Davao Doctors Hospital	Infectious Diseases, Public Health
Romano, Rommel (Philippine Society of Digestive Endoscopy)	University of Santo Tomas Hospital	Gastroenterology
External Reviewers		
Besenio, Charity	Bicol Medical Center	Family Medicine
Razon-Gonzales, Elvie	West Visayas State University Medical Center, Medicus Medical Center, Iloilo Mission Hospital, Iloilo Doctors' Hospital	Internal Medicine, Gastroenterology, Clinical Epidemiology
Project Support Staff		
Cezar, Maricho	Bicol Medical Center	Training Specialist IV
Salvador, Wennah	Bicol Medical Center	Administrative Officer I
COI Committee		
Decena-Sabaria, Glenda	Bicol Medical Center Universidad de Sta. Isabel - Health Services NICC Doctors Hospital Bicol Access Health Centrum St. John Hospital Dr. Nilo Roa Hospital	Pediatrician
Pinoy-Villamayor, Kristy	Bicol Medical Center Universidad de Sta. Isabel - Health Services	Adult and Child Allergy, Asthma, and Immunology
Serrano, Roselyn	Bicol Medical Center	Nurse

Data was gathered from the pilot sites through demonstration reports, performance updates, or interim reports submitted to the Department of Health (DOH). This aimed to identify current program implementation practices requiring evidence review and guidance. Brainstorming sessions with project managers and the DOH were held to develop key research questions that addressed limitations in the applicability of existing recommendations as well as areas that require additional guidance and supporting evidence. The SC summarized and prioritized questions arising from these activities, as well as those nominated by program managers, using an online form. Subsequently, the SC finalized the scope and the list of questions, forwarding them to the EREs for initiation of evidence synthesis.

The Department of Health funded this CPG. It is important to note that the final recommendations from *en banc* meetings were independent of any influence from the funding agency. To ensure transparency, competing interests of each member in the guideline development group (including the Steering Committee, Consensus Panel, and Technical Working Group) were thoroughly documented at the beginning of the CPG development process.

All members of the CPG Task Force disclosed potential financial or intellectual conflicts of interest (COI) from the four (4) years preceding their involvement in the project. The COI declarations underwent review by an Oversight Committee, which classified the COI status of each member. The Oversight Committee then recommended to the Steering Committee the extent of participation allowed for each member. Details regarding the results of the COI assessments may be found in CPG Appendix 1. The decisions of the COI Oversight Committee were categorized as follows:

- **Acceptable** – Individuals with no intellectual or financial conflicts of interest were allowed full participation.
- **Manageable A** – Individuals with intellectual conflicts of interest could vote but were required to declare their intellectual conflicts (e.g., affiliations, positions, authorship) during en banc meetings.
- **Manageable B** – Individuals with some intellectual and financial conflicts of interest could NOT vote but were allowed to contribute their expertise to the group. Examples included panelists from government agencies involved in program implementation and those from the agency funding the guidelines. The specific management terms, as decided by the Oversight Committee, were modified to address specific clinical questions
- **Disqualified** – Individuals with serious financial and intellectual conflicts of interest that could compromise objectivity and independence in decision-making were disqualified from participation.

EVIDENCE SYNTHESIS

Search Methods and Strategies

High-quality systematic reviews with recent updates comprised the studies appraised for each evidence summary. An updated search, using the review's last search date, was conducted to identify potential new articles for inclusion in evidence synthesis for reviews published over two years ago.

A universal search strategy for gastric cancer and *H. Pylori* and related concepts were used. Depending on the clinical questions, concepts and search terms were derived and jointly finalized by the Steering Committee and the evidence review experts (ERE).

Comprehensive searches for all ten guideline questions spanned from March to August 2023. For each guideline question, a systematic review of the evidence was conducted. Details of the search strategy, including search terms used, electronic databases, and dates of search were described in the appendix of

each evidence summary. For information sources, at least two of the following databases and trial registries were searched: MEDLINE, Cochrane CENTRAL Database, clinicaltrials.gov, EU Clinical Trials Register, Chinese Clinical Trial Registry, and/or the International Clinical Trials Registry Platform (ICTRP). Literature searches were date and language unrestricted, and all search strategies were documented and reviewed by at least 2 EREs and the Technical Coordinator to ensure that the search was comprehensive, reproducible, and free from biases.

Note that the cost estimates of the interventions and tests were based primarily on either publicly available data from government/private hospital websites, key informant interviews from content experts and personal communication/knowledge of the evidence reviewers.

Inclusion and Exclusion Criteria

Relevant inclusion and exclusion criteria were applied to screen titles, abstracts, and full-text articles resulting from the search. Specific characteristics for the target population, study design, comparisons, interventions, tests, outcomes, and applicable subgroups were defined for each guideline question. To minimize selection bias in the screening process, at least two evidence review experts (EREs) were involved in screening for eligible articles. In cases of discrepancies, a third reviewer (the Technical Coordinator) was consulted, and final decisions regarding article inclusion/exclusion were reached through consensus. The search, retrieval, and appraisal process results were documented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Study Quality Assessment

Each included article was evaluated for bias by at least two evidence review experts (EREs) using appropriate risk of bias tools based on the study type. The Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was employed for diagnostic studies, Cochrane Risk of Bias (RoB) for therapy studies using Randomized Controlled Trial (RCT) designs, Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) for non-randomized studies of interventions, Newcastle Ottawa Scale for prognostic studies with case-control or cohort designs, and A MeaSurement Tool to Assess systematic Reviews - 2 (AMSTAR-2) for systematic reviews. EREs then extracted relevant data about each study, including PICO characteristics, effect estimates, methodological limitations, etc., providing detailed descriptions in the appendix.

Rating the Overall Quality/Certainty of the Evidence

The certainty of evidence for each outcome across studies was rated as VERY LOW, LOW, MODERATE, HIGH following the GRADE approach.

CPG Table 4. Certainty of Evidence Ratings

Certainty	Definition and Implications	Randomized Trials	Observational Studies
HIGH ⊕⊕⊕⊕	The group is very confident that the true effect lies close to that of the estimate of the effect (Further research is very unlikely to change confidence in the effect estimate)	No serious flaws in study quality	Extremely strong association and no major threats to validity
MODERATE ⊕⊕⊕◯	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that is substantially different. (Further research is likely to have an important impact)	Serious flaws in design or execution; quasi-experimental design	Strong consistent association and no plausible confounders
LOW ⊕⊕◯◯	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. (Further research is very likely to have an important impact)	Very serious flaws in design or execution	No serious flaws in study quality
VERY LOW ⊕◯◯◯	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. (The estimate of the effect is very uncertain)	Very serious flaws and at least one other serious threat to validity	Serious flaws in design and execution

An initial high rating was assigned to randomized controlled trials (RCTs), while observational studies were rated low. This initial rating for RCTs has been subject to downgrade based on factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. Observational studies, on the other hand, have received upgraded certainty of evidence when a large effect, dose-response relationship, and/or a significant effect despite confounding effects were observed. These assessments were reflected in a GRADE Evidence Profile and a Summary of Findings table, prepared using the GRADEpro GDT online tool. The individual GRADE Evidence Profiles and Summary of Findings tables for each of the 10 guideline questions may be found in the attached Appendix document.

Data Extraction and Evidence Retrieval

After proper appraisal and data extraction, meta-analysis was conducted to generate overall effect estimates for each outcome. In cases where studies could not be combined to calculate an overall effect estimate, a narrative synthesis was instead performed along with a tabulated summary of results.

The evidence review experts (ERE) then compiled an evidence summary detailing the benefits and harms associated with the intervention or test. The summary also included relevant information on the burden/priority of the problem, resource requirements, feasibility, implementation concerns, research gaps, and cost-effectiveness studies.

EVIDENCE TO DECISION

Formulation of the Recommendations

Approach

The recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method.[5] Panelists first assessed the overall quality of evidence, and then determined the direction and strength of the recommendations.

Finalizing guideline recommendations

The GRADE Evidence-to-Decision (ETD) frameworks facilitated the transition from evidence to recommendations. The ERE created online surveys for each guideline question, which the consensus panel (CP) used to review information and provide an overall quality rating. This rating was considered the lowest certainty rating among critical outcomes, and the CP completed ETD forms.

En banc meetings, conducted via the Zoom video conferencing platform, involved all CP members. These meetings (a total of seven) discussed evidence summaries, addressed queries, and voted on final recommendations and their strength. Six meetings focused on evidence summaries and outcomes, while one served as a practice session to familiarize participants with the discussion process. Meeting dates and main agenda are detailed below.

- Meeting 1: 16 August 2023 - Questions 1 and 2
- Meeting 2: 30 August 2023 - Question 3
- Meeting 3: 6 September 2023 - Questions 7 and 9
- Meeting 4: 22 September 2023 - Questions 4 and 10
- Meeting 5: 4 October 2023 - Question 6
- Meeting 6: 25 October 2023 - Questions 5 and 8

A standardized language was used to indicate the direction and strength of each recommendation (e.g., '*suggest*' for weak recommendations, '*recommend*' for strong recommendations). Key discussion points raised during the meetings were noted and summarized in the CPG manuscript to ensure transparency and reproducibility. The Consensus Panel evaluated the direction and strength of the recommendation using the GRADE Approach based on the following criteria:

1) overall quality of evidence,
2) balance between benefits and harms,
3) values and preferences of patients,
4) economic impact and burden on patients,
5) cost and resource use, and
6) feasibility and acceptability of the intervention or test
7) other considerations that may arise during the discussion.

[5] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6. doi:10.1136/bmj.39489.470347.ad

Panelists voted on whether to recommend interventions based on their assessment of their positive and negative effects for all outcomes deemed "critical." A strong recommendation was made when the panel was confident that the benefits outweigh the drawbacks, or vice versa. A weak recommendation was issued when uncertainties existed due to insufficient evidence, imprecise estimates, limited applicability, or high costs. Standardized language ("We suggest" for weak recommendations, "We recommend" for strong ones) was used to convey the direction and strength of each recommendation.

The en banc meetings were moderated by a skilled facilitator/ moderator. Each member recorded his/her vote. A consensus was reached when there was more than 75% agreement among the members both for the direction and strength of recommendations. If a consensus was not reached, each member was allowed to discuss their votes and ideas on the topic, after which, another round of voting was done. The process was allowed to be repeated up to three times until a consensus was reached. Any issues left unsettled after the en banc meeting were finalized through a modified Delphi activity. If a consensus recommendation was still unattained despite these efforts, the issue was declared as undecided and stated as such in the final CPG manuscript.

Equity was incorporated in each step of the process following the Knowledge Management Plus (KM+) Equity Criteria described in the DOH Manual for Clinical Practice Guideline Development.

External Review

Two external reviewers have independently evaluated the validity, clarity, applicability, and usefulness of this CPG using the AGREE tool (CPG Appendix 2). Both external reviewers rated the CPG as high quality with strong recommendations to endorse the CPG in the appropriate context. The Department of Health (DOH) has also assessed this CPG through its National Practice Guidelines Program with results of this appraisal being vital in the finalization of this document, addressing concerns on the clarity of presentation, applicability to stakeholders, target population and end-users, and implementation.

Editorial Independence

The final manuscript of the CPG was composed by a technical writer after summarizing the discussions during the consensus meetings. The CPG was written following the AGREE-II tool to ensure that it follows best practice standards for CPG development. This draft was then sent to all members of the CPG Task Force for their review. Revisions were made until a final version was approved.

Chapter 3. Recommendation and Evidence Summaries

GUIDELINE QUESTION 1:

Should we use alarm signs and symptoms for the early diagnosis of gastric cancer among patients with dyspepsia?

RESEARCH QUESTION: Among patients with dyspepsia, how accurate are alarm signs and symptoms for the early diagnosis of gastric cancer?

Among adults with dyspepsia, we **SUGGEST using alarm signs and symptoms*** to identify those who may need an upper gastrointestinal endoscopy.

Certainty of Evidence: **Very Low** ⊕◯◯◯
Strength of Recommendation: **Weak**

*Includes any of the following: unintended weight loss (*at least 5% of usual body weight in the preceding 6-12 months*), dysphagia or odynophagia, bleeding, anemia, vomiting, abdominal mass, age ≥ 50 years

CONSIDERATIONS

The panel recommends using alarm signs and symptoms for gastric cancer testing, emphasizing their benefits over risks, despite some chance of false positives. They suggest a cut-off age of ≥50, supported by local data showing higher gastric cancer incidence in this age group. However, screening isn't cost-effective for children and adolescents due to low prevalence, with only 45 cases reported from 2006-2023. The potential for higher false positives in this age group leads to a weak recommendation for those with ≥3 alarm signs. The review focuses on direct medical costs, likely underestimating actual expenses. Considering endoscopy availability and patient preference, using alarm symptoms as a guide for referrals is advisable.

KEY FINDINGS

This review looked at 11 studies to see how well using certain signs and symptoms can help find gastric cancer. However, there's no direct evidence showing whether this approach reduces deaths, complications, or improves outcomes related to gastric cancer. The signs and symptoms were moderately good at detecting gastric cancer, with about 75% accuracy for sensitivity and 70% for specificity. Endoscopy, the procedure used to check for cancer, had some side effects like a sore throat or nausea. Overall, the evidence certainty is very low due to potential biases and inconsistencies, making the findings less certain.

BACKGROUND

In 2020, 3,381 cases of gastric cancer (3.1 per 100,000 population) were recorded in the Philippines and 2,860 deaths noted.[1] According to the American Society for Gastrointestinal Endoscopy (ASGE) guidelines, endoscopy for dyspepsia is recommended among patients with alarm features (i.e. family history of upper gastrointestinal malignancy in a first-degree relative, unintended weight loss, GI bleeding or iron deficiency anemia, dysphagia, odynophagia, persistent vomiting, abnormal imaging suggesting organic disease) or among those older than 50 years old.[2] Despite the high prevalence of gastric cancer in the Asia-Pacific

regions, no local data exists on whether the use of alarm signs can aid in the early detection of gastric cancer.

REVIEW METHODS

A comprehensive literature review was conducted to determine the diagnostic accuracy of alarm signs and symptoms for the early diagnosis of gastric cancer among patients with dyspepsia. Databases used include MEDLINE, Google Scholar, and Cochrane Library. In addition, authors of retrieved articles were contacted for relevant data. A combination of keywords and free text search terms related to the following concepts were used: stomach neoplasms, diagnosis, alarm, symptoms, warning signs, dyspepsia. The full search strategy and yield are detailed in the Appendix Q1.1. Studies conducted until May 14, 2023 were included in the analysis. `

We included studies that: (1) used prospective or retrospective cohort or cross-sectional study designs, (2) reported on the diagnostic accuracy of alarm signs and symptoms for gastric cancer diagnosis, (3) used endoscopy as reference standard with or without histopathology confirmation, and (4) involved patients of any age with dyspepsia. A positive index test result was defined as the presence of any alarm sign or symptom elicited through interview or questionnaire or as indicated in the study. A *de novo* meta-analysis was conducted using Meta-Disc 2.0 to obtain pooled diagnostic accuracy estimates.

SUMMARY OF THE EVIDENCE

Evidence Considered

No studies were identified that directly compared the effectiveness of screening using alarm signs and symptoms versus no screening in lowering gastric cancer-related deaths or complications. The guideline recommendation is based on evidence from 11 observational prospective cohort studies. These studies, involving a total of 133,054 patients presenting with dyspepsia who underwent endoscopy, assessed the sensitivity and specificity of alarm signs and symptoms (either individual or combined) for detecting gastric cancer. (Appendix Q1.2).[4-14] The benchmark for diagnosis was upper gastrointestinal endoscopy, either with or without confirmation through examining tissue samples (histopathological confirmation). Out of the studies, seven reported cases of gastric cancer, while five reported other malignancies in the upper gastrointestinal (GI) tract. According to Hsu et al., most of the gastric cancer cases were in an advanced stage (18 out of 23 cases). Similarly, as per Melleny et al., all six cases of other upper GI malignancies were also in an advanced stage.[10]

The studies looked at various signs that might indicate a problem, including losing weight (in 11 studies), difficulty swallowing (in 10 studies), black or bloody stools, vomiting, or bleeding in the digestive tract (in 10 studies), low levels of red blood cells (anemia) (in 9 studies), and a few others like a family history of stomach-related cancers, swollen lymph nodes, older age, and so on.

Efficacy Outcomes

Diagnostic accuracy of any alarm sign

The use of any alarm sign or symptom in screening for gastric cancer had a fair sensitivity, specificity, and diagnostic odds ratio, and weakly positive and weakly negative likelihood ratios (Table Q1.1).

Table Q1.1. Overall diagnostic accuracy of alarm signs and symptoms compared to histopathology for the diagnosis of gastric cancer.

Outcomes	No. of studies (participants)	Effect estimate (11 studies)	95% CI	CERTAINTY OF EVIDENCE
Sensitivity	11 (n=133,054)	**74.9%**	53.1 to 88.7%	**Very low** ⊕○○○
Specificity	11 (n=133,054)	**70.2%**	51.9 to 83.7%	**Very low** ⊕○○○
False positive rate (FPR)	11 (n=133,054)	**29.8%**	16.3 to 48.1%	**Very low** ⊕○○○
False negative rate (FNR)	11 (n=133,054)	**25.1%**	11.3 to 46.9%	**Very low** ⊕○○○
Diagnostic odds ratio (DOR)	11 (n=133,054)	**7.02**	3.93 to 12.54	**Very low** ⊕○○○
Positive likelihood ratio (LR+)	11 (n=133,054)	**2.51**	1.72 to 3.68	**Very low** ⊕○○○
Negative likelihood ratio (LR-)	11 (n=133,054)	**0.36**	0.21 to 0.62	**Very low** ⊕○○○

Diagnostic accuracy of individual alarm signs and symptoms

The sensitivities of dysphagia, weight loss, and pain ranged between 25% to 49% while the specificity ranged between 75% to 96%. Table Q1.2 summarizes the sensitivity, specificity, diagnostic odd's ratio, positive likelihood ratio, negative likelihood ratio, and the false positive rate of specific alarm signs and symptoms reported in three meta-analyses.

Table Q1.2. Diagnostic accuracy of each individual alarm sign and symptom compared to histopathology for diagnosing gastric cancer.

Alarm sign or symptom	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Dysphagia	**40%** (36 to 43%)[a] **32%** (17 to 52%)[b] **39.2%** (23.1 to 66.5%)[c]	**92%** (81 to 97%)[b] **85%** (78 to 92%)[c]	4.32 (2.46 to 7.58)[b]	0.73 (0.60 to 0.89)[b]
Weight loss	**41%** (37 to 44%)[a] **25%** (12 to 0.43%)[b] **49%** (37 to 65%)[c]	**96%** (88 to 98%)[b] **84%** (81 to 87%)[c]	5.46 (3.47 to 8.60)[b]	0.79 (0.68 to 0.92)[b]
Anemia	**9%** (6 to 11%)[a] **12%** (8 to 19%)[b] **12.9%** (8.4 to 19.7%)[c]	**97%** (94 to 99%)[b] **95%** (92 to 97%)[c]	4.32 (2.64 to 7.08)[b]	0.90 (0.86 to 0.94)[b]
Bleeding	**11%** (8 to 13%)[a]			

Nausea/vomiting	**21%** (18 to 25%)[a] **17%** (5 to 46%)[b]	**84%** (60 to 94%)[b]	1.07 (0.52 to 2.19)[b]	0.99 (0.85 to 1.15)[b]
Pain	**41%** (24 to 62%)[b]	**75%** (51 to 89%)[b]	1.64 (1.20 to 2.24)[b]	0.78 (0.71 to 0.87)[b]

a. Fransen et al. 2004[15] - based on 17 case studies and 9 cohort studies
b. Astin et al.[16] - based on 14 studies that excluded those from Asian countries
c. Vakil et al.[17] - based on 15 studies

Impact of number of alarm signs and age

Combining three or more alarm signs and symptoms improved the diagnostic accuracy (sensitivity 48.4 to 97.1%, specificity 73.3 to 79.8%). Table Q1.3 summarizes the sensitivity, specificity, diagnostic odd's ratio, positive likelihood ratio, negative likelihood ratio, and the false positive rate of combined alarm signs and symptoms based on two studies.

A study by de Jong et al. suggests that to detect nearly 80% of stomach malignancies during upper endoscopy, a cutoff age of 50 and above is recommended. This conclusion is based on Asian studies involving people with dyspepsia and no alarming signs or symptoms. According to the Institute for Health Metrics and Evaluation, stomach cancer rates in the Philippines are 2.21 per 100,000 (15-49 years) and 16.65 per 100,000 (50-69 years) based on Global Burden of Disease data.(Appendix Q1.7)

Table Q1.3. Diagnostic accuracy of more than one alarm sign based on two studies.

Number of alarm signs or symptoms	Sensitivity	Specificity	PLR	NLR
1 alarm sign[a]	50%	84.1%	3.14	0.59
2 alarm sign[a]	50%	87.5%	4	0.57
≥ 3 alarm signs[a]	97.1%	79.8%	4.81	0.04
Dysphagia, bleeding, weight loss and vomiting[b]	51.6%	73.3%	1.93	0.66
Dysphagia, bleeding and weight loss[b]	48.4%	79.6%	2.37	0.65
Age > 50 years[b]	74.2%	47%	1.4	0.55
Age > 50 OR dysphagia, bleeding, weight loss and vomiting[b]	83.9%	34.5%	1.28	0.47
Age > 50 OR dysphagia, bleeding, weight loss[b]	83.9%	37.9%	1.35	0.42

NOTE:
a. Akinci et al.[14] - includes anemia, dysphagia, weight loss, anorexia, melena, hematemesis, family history of upper gastrointestinal malignancies (UGSM), vomiting, abdominal mass, lymphadenopathy
b. Hsu et al.[6] - includes dysphagia, symptoms suggestive of upper gastrointestinal bleeding, persistent vomiting, unintended weight loss

Safety outcomes

No harms were reported from administering the index test. Alarm signs were found to have a false positive rate of 29.8% (95% CI 16.3 to 48.1%), suggesting that approximately 152 to 480 out of every 1,000 patients examined may be referred for further testing with endoscopy, but will not be found to have gastric cancer. The false negative rate is estimated at 25.1% (95% CI 11.3 to 46.9%), implying that 0 to 33 cases of gastric cancer might be missed for every 1,000 patients.(Appendix Q1.5)

Two of the included studies reported on the adverse events associated with the subsequent confirmatory testing (i.e., endoscopy).[14] In the study by Thomson et al.,[14] a total of 16 endoscopy-related adverse events (e.g., sore throat, nausea, gagging or difficulty of breathing) were reported by 13 out of 1,040 patients (1.2%) which were all resolved. In the study by Melleney et al.,[10] no immediate or late endoscopic complications needing interventions.

Certainty of Evidence

The overall certainty of evidence was rated **very low.** This is due to the wide interval estimates, high risk of bias in the included studies (Appendix Q1.4), indirectness in the target population, and the inconsistency in the index tests used and results reported across studies (Appendix Q1.5). The overall risk of bias in the included studies was deemed high due to uncertainty on the following: unclear sampling strategy, lack of blinding, and not all patients undergoing the reference standard.

RECOMMENDATIONS FROM OTHER GROUPS

Various guidelines have differing recommendations with regards to performing endoscopy in the presence of alarm signs. Owing to cost-effectiveness issues, the 2017 American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) guidelines on dyspepsia do not recommend the use of EGD to investigate alarm features in dyspeptic patients under the age of 60. On the other hand, the Thailand guidelines recommend endoscopy among these patients due to lower local cost of endoscopy.

ADDITIONAL CONSIDERATIONS

Cost

No local health economic evaluation related to this topic was found. Patients' direct medical costs could vary from PHP 500 to PHP 46,000, as estimated. Clinical visits for screening alarm signs and symptoms may involve a consultation fee ranging from PHP 500 to PHP 1,000, depending on the institution or healthcare provider. If alarm signs are positive, an endoscopy may be recommended, with costs ranging from PHP 10,540 to PHP 40,000. Histopathology processing costs range from PHP 125 to PHP 3,000.

It is unclear whether checking for alarm signs followed by EGD will be cost-effective. The 2017 guidelines from the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) did not recommend performing esophagogastroduodenoscopy (EGD) to investigate alarm features in dyspeptic patients under the age of 60 due to low cost-effectiveness, given their very low risk for malignancy. In contrast, the guidelines in Thailand recommended EGD, as the procedure is less expensive compared to North America.[20-21]

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No local studies were retrieved investigating the patient's values and preferences related to the topic. In a cross-sectional study[22] in China investigating the awareness of risk factors and warning symptoms and attitude towards gastric cancer screening among the general public, 47% of participants had a low level of knowledge on the risk factors and warning signs of gastric cancer. The majority of the respondents (83.8%) believe that screening is helpful for the early detection of gastric cancer. This study involved 1200 participants (51.8% women) with an average age of 40.3 years.[22]

In terms of feasibility, Melleny et al.[10] concluded that establishing a system for screening potential gastric cancers using alarm signs and symptoms **may enable rapid detection of gastric cancer** cases but may also **overload the capacity of clinics offering endoscopy** and may increase waiting times for endoscopy as due to high false positive rates.[10]

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GUIDELINE QUESTION 2:

Should we do non-invasive tests to diagnose gastric cancer?

RESEARCH QUESTION: Among patients with alarm signs and symptoms, how accurate are non-invasive tests (imaging and biochemical tests) compared to biopsy/histopathology in diagnosing gastric cancer?

The gold standard for diagnosing gastric cancer is through biopsy, histopathology obtained through esophagogastroduodenoscopy
(Best practice statement)

Among patients with alarm signs and symptoms, we **RECOMMEND AGAINST** the use of non-invasive tests in place of biopsy for diagnosing gastric cancer.

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Strong

CONSIDERATIONS

The panel agreed that non-invasive tests are only a part of the overall process to diagnose cancer, which might include more invasive procedures for confirmation. These non-invasive tests can be used early on or as additional tools for diagnosis. The panel stressed that biopsy, either through surgery or endoscopy, remains to be the most reliable method. They also cautioned against relying on CT scans to diagnose cancer.

KEY FINDINGS

Non-invasive tests, like blood tests (CA19-9, CA72-4, CEA, CA242, CA125) and imaging tests (barium meal, 2D axial CT, MDCT), showed varying levels of accuracy when diagnosing gastric cancer in both symptomatic and asymptomatic patients. These tests, whether used alone or together, had sensitivities ranging from low to moderate, with notably high rates of false negatives. Biochemical tests had poor pooled sensitivities (27% to 67%) but high specificities (86% to 97%). Radiologic tests, such as barium meal examination, 2D axial CT, and MDCT, demonstrated moderate sensitivities (63% to 79%) along with high specificity (91% to 96%). However, the certainty of these accuracy estimates is very low due to serious risk of bias issues.

BACKGROUND

Non-invasive tests range from conventional serum tumor markers (e.g., carcinoembryonic antigen [CEA], cancer antigen 19-9 [CA 19-9]),[1] non-blood-based biomarkers (e.g. saliva, gastric lavage, urine, and stool biomarkers),[2] novel biomarkers (e.g., specific nucleotide sequences and antibodies),[3,4,5] and imaging techniques (e.g., barium swallow, computed tomography, and nuclear imaging).[6] These tests have been studied in relation to screening, diagnosis, prognosis, staging treatment, and surveillance of gastric cancer.

In the Philippines, where geographic and socioeconomic obstacles can restrict access to upper gastrointestinal endoscopy, understanding the potential of non-invasive testing in diagnosing gastric cancer holds significance. This review aimed to assess the accuracy of non-invasive tests, including imaging and biochemical tests, using histopathology as the gold standard for diagnosis. The focus was specifically on conventional tumor markers and radiologic tests for diagnosing symptomatic gastric cancer.

REVIEW METHODS

Literature search was performed on March 31, 2023 on the following electronic databases and trial registries: MEDLINE, Scopus, CENTRAL, and ClinicalTrials.gov. The full search strategy and yield can be found in Appendix Q2.1. A comprehensive search of existing systematic reviews on diagnostic accuracies of non-invasive tests was first performed. A subsequent search for eligible individual diagnostic accuracy studies (cohort or cross-sectional studies) was done in case the obtained systematic reviews were appraised to have low methodologic quality.

Included studies focused on biochemical or radiologic tests for diagnosing suspected gastric cancer in both adults and children, using clinical signs and symptoms. Exclusion criteria involved studies that did not directly compare non-invasive tests to a reference standard (gastric biopsy) obtained endoscopically or surgically. Technologies not widely available in the Philippines, like novel biomarkers, positron emission tomography scans, and image-enhanced endoscopy, were excluded. The review prioritized outcomes such as diagnostic accuracy, adverse events, cost-effectiveness ratios, and downstream health outcomes, with no restrictions on publication date or language.

Risk of bias was appraised using the ROBIS tool for systematic reviews[7] and the QUADAS-2 for individual studies.[8] These can be seen in Appendix Q2.6. Subgroup analyses by non-invasive test type (biochemical or radiologic) were planned.

SUMMARY OF THE EVIDENCE

Evidence Considered

Studies on tumor markers

Three systematic reviews[9,10,11] assessed the diagnostic accuracy of various tumor markers for gastric cancer. The first review, which was conducted by Wang et al. in 2022,[9] included 10 studies, wherein the diagnostic accuracy of combined CA72-4, CA19-9, and CEA was compared against using CA72-4 alone among patients with confirmed gastric cancer and controls (benign gastric lesions or healthy people). The second systematic review by Acharya et al. in 2017[10] summarized the individual diagnostic accuracies of CEA, CA19-9, and CA125 based on 71 studies enrolling patients with esophagogastric cancers. Finally, the 2012 systematic review of Chen et al.[11] included 33 eligible studies, which focused on the diagnostic accuracy of the following tests: CA72-4 (19 studies), CA242 (11 studies), CA199 (25 studies), CA125 (10 studies), CA153 (five studies), and CEA (25 studies). The reference standard utilized in all of these studies was pathological examination of gastric tissue biopsy.

No studies were found specifically assessing the benefit of these tumor markers in terms of improving downstream health outcomes such as reducing gastric cancer morbidity and mortality. However, Acharya et al.[10] estimated the cost-benefit ratio of these tumor markers by asking surgeons to complete a survey that ranked various attributes of these markers. Benefit scores were derived using a multi-criteria decision

analysis that combines diagnostic accuracy, time for result, test consistency across demographics, and patient acceptability.[10]

Studies on radiologic tests

Regarding radiography, the initial search for systematic reviews yielded no relevant studies while a subsequent search for individual studies yielded two eligible studies.[12,13]

In the first study, researchers in the United Kingdom assessed the accuracy of barium meal examination in adults suspected of having gastric disease. At that time, endoscopic biopsy wasn't considered the gold standard for diagnosing gastric cancer, so surgical and postmortem pathologic examinations were used as reference standards.[13] The second study, conducted in Korea, looked at the effectiveness of virtual gastroscopy using multidetector computed tomography (MDCT) and 2D axial CT in diagnosing early gastric cancer. Participants with early gastric cancer were compared to a control group of patients undergoing CT scans for vague abdominal symptoms.[12]

Efficacy Outcomes

Table Q2.1. Diagnostic accuracy of non-invasive tests compared to biopsy for diagnosis of gastric cancer.

Test	No. of Studies (Total Participants)	Sensitivity (95% CI)	Specificity (95% CI)	False Negative Rate (%)	Certainty of Evidence
Conventional biomarkers					
Combined CA19-9, CA72-4, CEA	10 (6574)[9]	57% (56-59%)	81% (79-82%)	42% (41-44%)	**Very low** ⨁◯◯◯
CA72-4	10 (6584)[9]	42% (40-43%)	84% (83-85%)	58% (57-60%)	**Very low** ⨁◯◯◯
CA19-9	25 (4210)[11]	46% (44-48%)	94% (93-95%)	54% (52-55%)	**Very low** ⨁◯◯◯
CEA	25 (4296)[11]	42% (39-44%)	94% (93-95%)	58% (56-61%)	**Very low** ⨁◯◯◯
CA242	11 (2039)[11]	35% (32-39%)	97% (96-98%)	65% (61-68%)	**Very low** ⨁◯◯◯
CA125	10 (1728)[11]	27% (24-30%)	94% (92-95%)	73% (70-76%)	**Very low** ⨁◯◯◯
CA153	5 (1108)[11]	7% (5-10%)	97% (95-98%)	93% (90-95%)	**Very low** ⨁◯◯◯
Radiologic tests					
Virtual gastroscopy using MDCT	1 (162)[12]	79% (69-86%)	91% (82-97%)	21% (14-31%)	**Very low** ⨁◯◯◯

2D axial CT	1 (162)[12]	63% (52-73%)	93% (84-98%)	37% (27-48%)	**Very low** ⊕◯◯◯
Barium meal examination	1 (87)[13]	77% (58-90%)	96% (88-100%)	23% (58-90%)	**Very low** ⊕◯◯◯

*Certainty ratings represent our level of confidence in the given estimates of test accuracy (e.g., high sensitivity, poor specificity, etc.).
CI, confidence interval; *CT*, computed tomography; MDCT, multidetector computed tomography.

Biochemical tests

When used individually, various tumor markers including CA19-9, CA72-4, CEA, CA242, CA125 demonstrated low pooled sensitivities, ranging from 7% (CA153) to 42% (CA72-4), as shown in Table Q2.1.[9,11] Meanwhile, these tests showed high pooled specificity, ranging from 84% (CA72-4) to 97% (CA153 and CA242). Combined use of CA19-9, CA72-4, and CEA improved test sensitivity, albeit still moderate at 57%.[9] Given these estimates, alarmingly high rates of false negative diagnoses are expected (42 to 93%) when biochemical tests are used to diagnose gastric cancer cases compared to gastric biopsy.

Radiologic tests

Diagnostic values of radiologic tests fared better than the biochemical tests discussed above. Based on very low certainty of evidence from one study[13], barium meal examination demonstrated moderate sensitivity at 77% (95% CI 58 to 90%) and high specificity at 96% (95% CI 88 to 100%) for patients with suspected gastric cancer. Based on very low certainty of evidence from another study,[12] sensitivities of virtual gastroscopy using MDCT (79%, 95% CI 69 to 86) and 2D axial CT (63%, 95% CI 52 to 73) and were likewise moderate, while specificities were comparably high (91 to 93%). However, false negative rates ranging from 21 to 37% may still be expected when these tests are used to diagnose patients with suspected gastric cancer.

Certainty of Evidence

The certainty of evidence for both biochemical and radiological tests was rated as **very low.**

Most studies were downgraded twice for serious indirectness, enrolling healthy individuals and being primarily conducted in China with a high prevalence of gastric cancer, potentially influencing accuracy estimates. Inconsistency was downgraded due to high statistical and clinical heterogeneity. Using the QUADAS-2 tool for the radiologic tests, the study by Segal et al. was rated high risk for bias in three domains, and publication bias was suspected due to a small sample size. For Kim et al.'s study, high risk of bias was identified in patient selection and index test domains, considering that the MDCT was done for preoperative staging.[9, 11-13]

RECOMMENDATIONS FROM OTHER GROUPS

No explicit recommendations have been issued by other guideline groups[14,15,16,17] regarding the use of tumor markers or radiologic tests for the diagnosis of gastric cancer. To obtain a definitive diagnosis, other guideline groups recommend upper GI endoscopy with biopsy.[14,15]

Indirectly, to answer the clinical question: “What are the biomarkers which are useful in surveillance and management of gastric neoplasia?”, the Singapore clinical guidelines[16] state that *“serum biomarkers, such as pepsinogen levels and microRNA, may be useful for the identification of individuals at high risk for gastric*

cancer." Biomarker testing is also mentioned in the US National Comprehensive Cancer Network 2022 clinical guidelines[17] within the context of tailoring treatment approaches, while imaging modalities are discussed primarily for staging purposes.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

Costs for tumor markers were as low as PHP 250 (CEA) to as high as PHP 4,490 (CA19-9), while barium meal examination costs ranged from PHP 500 to 1,445. Abdominal CT scan may be between PHP 5,025 to 12,400. Table Q2.2 below summarizes the estimated direct medical costs of non-invasive tests for gastric cancer based on publicly available data from various government hospitals in the Philippines.

Table Q2.2. Estimated costs and availability of non-invasive tests at different government hospitals in the Philippines.*

Test	Hospital and location (income class)			
	East Avenue Medical Center,[46] Quezon City, Metro Manila (1st class)	Region II Trauma and Medical Center,[47] Bayombong, Nueva Vizcaya (1st class)	Far North Luzon General Hospital and Training Center,[48] Luna, Apayao (2nd class)	Dr. Jose Rizal Memorial Hospital,[49] Dapitan, Zamboanga Del Norte (3rd class)
CEA	750	1500	715	250
CA125	750	1500	N/A	2050
CA153	N/A	1500	N/A	N/A
CA19-9	N/A	N/A	N/A	4490
CA72-4	N/A	N/A	N/A	N/A
CA242	N/A	N/A	N/A	N/A
Barium meal examination	1445	500	N/A	N/A
Abdominal CT scan	10,238	5,025†	N/A	12,400

**All prices are in Philippine pesos (PHP),* †excluding professional fee of radiologist

Cost-effectiveness

No local cost-effectiveness studies on this topic were found.

Cost-benefit ratios for CEA, CA19-9, and CA125 were calculated by Acharya et al.[10] based on five performance criteria ranked by relative importance: sensitivity, specificity, predictive ability for cancer recurrence, predictive ability for metastasis, and test consistency. For the purpose of this evidence review, benefit scores of the tumor markers were recomputed using ratings solely for sensitivity, specificity, and consistency. Cost-benefit maps were similarly derived by comparing the updated benefit scores with their associated costs, as published in the same paper.

According to the cost-benefit map presented below (Figure Q2.1), CA-125 exhibited the highest level of benefit; however, it was also associated with the highest financial cost. On the other hand, CEA demonstrated a comparable level of benefit with the lowest financial cost. Conversely, CA19-9 was deemed the least desirable option, as it had both low benefit and low cost scores.

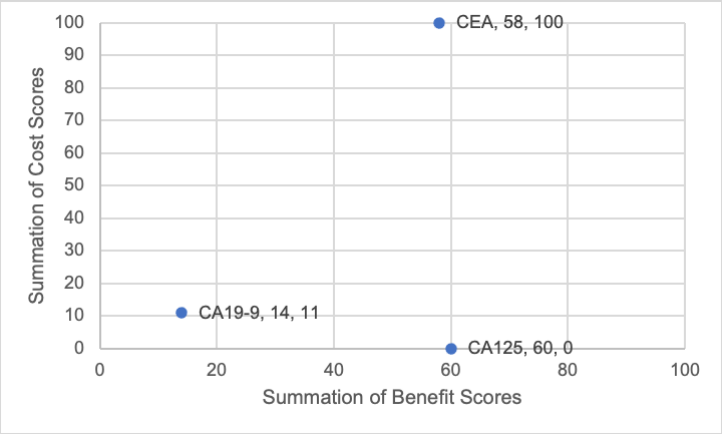

Figure Q2.1. Cost-benefit map illustrating cumulative benefit, taking into account sensitivity, specificity, and consistency, of three biomarkers,[10] while also considering their respective financial costs.

Patient's Values and Preferences

There's uncertainty about whether patients consider diagnostic accuracy for gastric cancer important when assessing individuals suspected to have it. False negative rates in tests range from 23% to 73%.[9,11,13] Missing an early-stage diagnosis has significant consequences, causing clinical issues and financial burdens. Endoscopic biopsy is cost-effective and often preferred, providing additional value in ruling out other potential diseases for symptomatic patients with various diagnoses.

Equity, Acceptability, and Feasibility

Discouraging non-invasive testing is expected to promote health equity by avoiding unnecessary tests, especially in less affluent areas where outsourcing makes them more expensive. While the tests are generally acceptable to both patients and physicians due to their less invasive nature, recommending their use, especially biochemical markers, may not be practical currently, as they are unavailable in surveyed government hospitals.[46-49]

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GUIDELINE QUESTION 3:

Should we use FDG-PET/CT[6] or endoscopic ultrasound (EUS) on top of contrast CT to guide preoperative staging in patients with gastric cancer?

RESEARCH QUESTION: Among patients diagnosed with gastric cancer, how safe, accurate, and effective is contrast CT alone compared to contrast CT with adjunctive diagnostic modalities (EUS, FDG-PET/CT) in preoperative staging?

Among patients with gastric cancer, we **RECOMMEND the use of multidetector computed tomography (MDCT)** for staging gastric cancer prior to surgery.

Certainty of Evidence: Low ⊕⊕◯◯
Strength of Recommendation: Strong

Among patients with early gastric cancer, we **SUGGEST the use of EUS** as an *adjunct* to MDCT in areas where it is available and technical expertise is present.

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Weak

Among patients with gastric cancer, we **DO NOT RECOMMEND the *routine* use of FDG-PET/CT** as an adjunct to MDCT for staging.

Certainty of Evidence: Low ⊕⊕◯◯
Strength of Recommendation: Strong

CONSIDERATIONS

CT scans, particularly multidetector CT (MDCT), are the standard diagnostic tools known for high sensitivity and specificity. However, the evidence certainty was downgraded to "Low" in reviewed studies, mainly retrospective, due to imprecision and wide confidence intervals. Despite consensus concerns about limited procedure availability, a shortage of trained specialists, and the rare benefit of endoscopic ultrasound for early-stage gastric cancer, CT scans, especially MDCT, remain crucial for determining metastatic makeup. The panel emphasized that FDG-PET is not ideal due to false positives, and standard CT scans are sufficient for detecting metastatic diseases, making FDG-PET unnecessary. In cases like node-positive and intraperitoneal metastatic gastric cancer, CT scans may sometimes miss lesions. The panel noted that FDG-PET scans are not necessarily consistently more accurate in these instances based on the reviewed studies.

[6] *F-fluorodeoxyglucose Positron-emitted Tomography/Computed Tomography (FDG-PET/CT)

KEY FINDINGS

Preoperative assessment of gastric cancer is vital for determining the optimal therapeutic approach based on tumor invasion depth (T), lymph node involvement (N), and distant metastasis (M). Accurate staging guides the selection of procedures, ranging from less invasive options like endoscopic mucosal resection for early cases to extensive surgery or neoadjuvant chemotherapy for advanced cases.

Current evidence from 18 studies, encompassing 2,054 patients, suggests that supplementing CT with endoscopic ultrasound (EUS) may enhance diagnostic accuracy for T and N staging, while adding FDG PET/CT alongside CT may improve accuracy for N and M staging. However, these findings are affected by serious imprecision, inconsistency, and indirectness in the included studies. Notably, prior studies did not identify direct harms associated with EUS and FDG PET/CT.

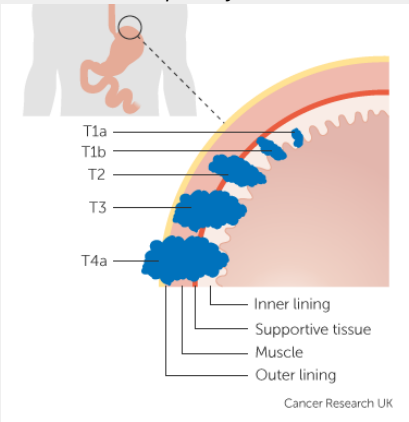
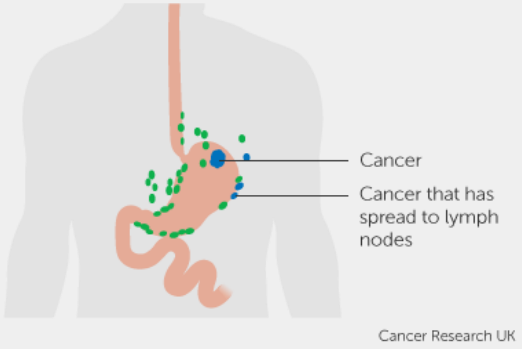
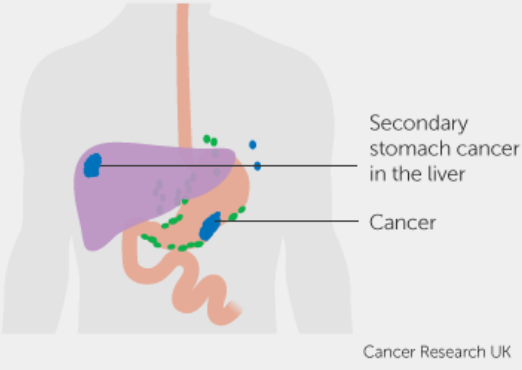
BACKGROUND

Early detection, accurate preoperative staging, and standardized curative surgery significantly impact the overall survival rate in gastric cancer. Achieving a detailed clinical stage is crucial to identifying suitable candidates for surgery, determining the need for neoadjuvant therapy, and assessing those who may benefit from palliative management.

The widely used TNM system (Table Q3.1) by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) categorizes gastric cancer based on Tumor (T), Nodes (N), and Metastasis (M). Early gastric cancer is defined as cancer limited to the submucosa without invasion beyond, irrespective of lymph node involvement. Initial staging involves contrast-enhanced CT scans of the abdomen, thorax, and pelvis to assess invasion depth and lymph node metastasis, crucial criteria guiding surgical resection. While the NCCN guidelines do not specify modalities, additional preoperative imaging like FDG-PET/CT and EUS are suggested for detecting metastasis and locoregional staging.

The review focuses on evaluating the accuracy, safety, and efficacy of supplementing routine CT with EUS and/or FDG-PET/CT for gastric cancer staging, aiming to determine whether this enhances the precision of preoperative staging.

Table Q3.1. TNM Staging system for gastric cancer.

Component		Description
T (Tumor) *Size or direct extent of the primary tumor* 	**T0**	No evidence of tumor
	T1	Tumor has grown into the stomach wall– within the inner layers/mucosae of the stomach (T1a) or into the submucosa (T1b)
	T2	Tumor has grown into the muscularis propria (muscle layer of the stomach)
	T3	Tumor has grown through all the muscle layers into the connective tissue outside the stomach (outer lining of the stomach)
	T4	Tumor has broken through the outer lining of the stomach–serosa (T4a) or organs surrounding the stomach (T4b)
N (Nodes) *Degree of spread to regional lymph nodes* 	**N0**	no regional lymph nodes metastasis (no lymph nodes containing cancer cells)
	N1	regional lymph node metastasis present (at some sites, tumor spread to closest or 1 to 2 regional lymph nodes near the stomach)
	N2	cancer cells in 3 to 6 nearby lymph nodes
	N3	tumor spread to more distant or numerous regional lymph nodes (cancer cells in 7 to 15 nearby lymph nodes [N3a] or in ≥16 nearby lymph nodes [N3b]
M (Metastasis) *Metastasis describes whether the cancer has spread to a different part of the body.* 	**M0**	no distant metastasis (cancer has not spread to other organs)
	M1	metastasis to distant organs (cancer has spread to other parts of the body beyond the regional lymph nodes)

Source: TNM staging for stomach cancer Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) https://www.cancerresearchuk.org/about-cancer/stomach-cancer/stages/tnm-staging
Amin M, Edge S. AJCC Cancer Staging Manual. 8th Edition. Springer 2017.

REVIEW METHODS

A systematic search was done on April 30, 2023, using MEDLINE, Cochrane Library, and Google Scholar with combined keywords, medical subject headings (MeSH) and free text terms related to "endoscopic ultrasound," "multi-detector computed tomography," and "gastric adenocarcinoma". The full search strategy and yield is detailed in Appendix Q3.1.

For this review, studies were considered direct evidence if they involved adjunctive EUS or FDG-PET/CT to contrast CT scan compared to contrast CT scan alone and reported on any the following outcomes: diagnostic accuracy, safety/adverse events, cost-effectiveness, or patient-reported outcomes (e.g., symptom severity, quality of life scores). Efficacy outcomes were included since accurate staging would equate to better clinical management. We excluded studies that did not report sufficient data to calculate diagnostic accuracy measures as well as case series, non-systematic review articles, and abstracts or letters.

Risk of bias of the diagnostic accuracy studies were appraised using QUADAS-2. Summary estimates were computed externally through a web-based app (MetaDTA v2.01; https://crsu.shinyapps.io/dta_ma/). The study estimates of pooled sensitivity and specificity were plotted on forest plots using Review Manager 5 (RevMan 5. Version 5.4.1, The Cochrane Collaboration, 2020). The area under the receiver operating characteristic curve (AUC) was also calculated to compare the overall accuracy between tests. A preferred test has an AUC close to 1, while a poor test has an AUC close to 0.5.[18]

SUMMARY OF THE EVIDENCE

Evidence Considered

Of the 372 titles and abstracts screened, we found no study that directly compared CT versus CT with EUS or CT with FDG-PET/CT for gastric cancer preoperative staging. However, 18 observational studies were considered eligible for this review—12 for EUS, 6 for FDG-PET/CT, and 2 for EUS+MDCT vs. EUS.[2-13] The 12 EUS studies were previously included in a network meta-analysis of gastric cancer clinical stage diagnostic tests.[14]

The detailed characteristics of the included studies are presented in Appendix Q3.3. The 12 studies involved a total of 2,054 adult patients diagnosed with gastric adenocarcinoma and pre-surgical staging with MDCT and EUS. The majority of patients were male (n = 1,438, 70%) with ages ranging from 53 to 70 years old. The most common tumor location among the examined participants was within the antrum/lower part of the stomach, comprising about 40% of the total sample size (n=822). The reference standard for gastric cancer diagnosis was confirmation by histopathological analysis of surgical specimens. For FDG-PET/CT accuracy, a total of 647 adult patients were included in the analysis from 6 studies. The majority of the patients were male (n=334, 52%), with ages ranging from 55 to 78 years old. Confirmation with histopathology post gastrectomy was the basis for comparison as reference standard.

Outcomes assessed in the studies focused on tumor staging (T stage), lymphadenopathy involvement assessment (N stage), and distant metastasis (M stage). However, downstream clinical outcomes like reduction in mortality, progression-free survival, or patient-reported outcomes were not evaluated. The accuracy of EUS, MDCT, and the combination of EUS with MDCT was compared against confirmation through histopathological analysis of surgical specimens as the reference standard. T and N staging followed the 4th to the 7th edition of the TNM classification.[15] For M staging, the accuracy of MDCT, EUS, and FDG-PET/CT were similarly compared against histopathologic staging.

Efficacy Outcomes

Table Q3.2. Accuracy of EUS, MDCT, EUS+MDCT and FDG-PET/CT for T, N and M staging in patients with gastric cancer.

Critical Outcomes	Basis (Number of Studies; n=patients)	Diagnostic accuracy estimates				Interpretation	Certainty of Evidence*
		Sn/Sp	95% CI	LR+/LR-	95% CI		
Accuracy for T staging							
EUS	8 n=1,324	Sn 70.9%	41.8 - 89.2%	LR+ 19.61	2.337 - 164.4	Moderate Sn	**Low** ⊕⊕◯◯
		Sp 96.4%	70.2 - 99.7%	LR- 0.30	0.135 - 0.680	High Sp	
MDCT	8 n=1,694	Sn 47.2%	19.6 - 76.7%	LR+ 16.51	2.560 - 106.5	Poor Sn	**Low** ⊕⊕◯◯
		Sp 97.1%	85.1 - 99.5%	LR- 0.54	0.293 - 1.006	High Sp	
EUS + MDCT	2 n=152	Sn 90.1%	81.5 – 95.0%	LR+ 7.84	0.873 – 70.502	High Sn	**Very Low** ⊕◯◯◯
		Sp 88.5%	39.2 – 98.9%	LR- 0.11	0.054 – 0.229	High Sp	
Accuracy for N staging							
EUS	11 n=1,151	Sn 83.7%	68.5 - 92.5%	LR+ 2.43	1.106 - 5.332	High Sn	**Low** ⊕⊕◯◯
		Sp 65.5%	36.9 - 86.1%	LR- 0.25	0.109 - 0.631	Moderate Sp	
MDCT	8 n=1,694	Sn 71.4%	60.5 - 80.2%	LR+ 2.39	1.637 - 3.499	Moderate Sn	**Low** ⊕⊕◯◯
		Sp 70.2%	55.3 - 81.7%	LR- 0.41	0.311 - 0.535	Moderate Sp	
EUS+MDCT	2 n=152	Sn 96.0%	4.2 - 100%	LR + 12.80	6.508 - 25.19	High Sn	**Very Low** ⊕◯◯◯
		Sp 92.5%	86.2 - 96.1%	LR - 0.04	0 - 18.654	High Sp	
FDG-PET/CT	3 n=300	Sn 72.0%	45.0 - 89.0%	LR + 10.70	0.223 - 513.64	Moderate Sn	**Low** ⊕⊕◯◯
		Sp 93.0%	18.0 - 100%	LR - 0.30	0.131 - 0.71	High Sp	
Accuracy for M staging							
EUS	3 n=734	Sn 98.7%	85.9 - 99.9%	LR + 1.26	0.88 - 1.783	High Sn	**Low** ⊕⊕◯◯
		Sp 21.6%	5.2 - 57.9%	LR - 0.06	0.004 - 0.981	Low Sp	
MDCT	4 n=1,020	Sn 94.5%	54.8 - 99.6%	LR + 15.53	2.969 - 81.257	High Sn	**Low** ⊕⊕◯◯
		Sp 93.9%	72.7 - 98.9%	LR - 0.06	0.005 - 0.720	High Sp	
FDG-PET/CT	3 n=442	Sn 21.7%	11.0 - 38.4%	LR + 1.74	0.651 - 4.631	Low Sn	**Moderate** ⊕⊕⊕◯
		Sp 87.5%	74.8 - 94.3%	LR - 0.90	0.728 - 1.099	High Sp	

*Certainty ratings represent our level of confidence in the given estimates of test accuracy (e.g., high sensitivity, poor specificity, etc.).
CI, confidence interval.

In evaluating the accuracy of diagnostic modalities for staging gastric cancer, key findings emerge. Regarding T staging, endoscopic ultrasound (EUS) exhibits higher sensitivity (70.9%) compared to multidetector computed tomography (MDCT) (47.2%), with EUS+MDCT showing increased sensitivity (90.1%). For N staging, EUS demonstrates higher sensitivity (83.7%) but lower specificity (65.5%) compared to MDCT (sensitivity: 71.4%, specificity: 70.2%). Combining EUS+MDCT enhances sensitivity (96.0%) and specificity (92.5%). (See Appendix Q3.6-A) Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has comparable sensitivity (71.6%) but higher specificity (93.3%) for N staging than MDCT. (See Appendix Q3.6-B) In M staging, EUS sensitivity (98.7%) surpasses MDCT (94.5%), while FDG PET/CT shows higher sensitivity (21.7%) and specificity (87.5%) than MDCT (sensitivity: 14.4%, specificity: 75%). These findings underscore the varied diagnostic performance of different modalities across T, N, and M staging in gastric cancer. (See Appendix Q3.6-C)

Safety outcomes

The potential harms associated with low accuracy in certain diagnostic tests for gastric cancer staging are considerable. Tests with low sensitivity, like MDCT for T staging and FDG-PET/CT for M staging, may lead to false negatives, causing understaging, delayed diagnosis, and progression to advanced cancer stages. Conversely, tests with low specificity, exemplified by EUS for M staging, may yield false positives, exposing patients to unnecessary overtreatment-related morbidity.

In EUS, involving semi-blind maneuvers during endoscopy, potential harms include rare but serious adverse events such as perforation, bleeding, and infection. Cervical esophageal perforations were reported in a small percentage of cases, associated with factors like older age, difficult intubation history, use of radial echo-endoscopes, and less experienced EUS operators. Infections and bleeding are more commonly associated with EUS-guided fine needle aspiration and other interventional procedures during EUS.[17]

Regarding FDG-PET/CT, radiation exposure from 18[F]-FDG is considered within acceptable limits, and no adverse events were reported in the included studies. However, the decision to administer FDG should be carefully weighed, considering diagnostic benefits against potential risks.

To mitigate the limitations of individual tests, a complementary and combined approach involving multiple diagnostic modalities may enhance overall sensitivity. Despite these considerations, it's essential to acknowledge the potential harms associated with false positives and negatives, guiding clinicians in optimizing diagnostic strategies for gastric cancer staging.[32]

Certainty of evidence

The overall certainty of evidence for test accuracy of EUS and FDG-PET/CT were **low to very low**. Downgrading occurred due to serious indirectness and imprecision. There was noted high imprecision since confidence intervals of both tests overlapped.

Most of the studies were of low risk of bias. Of the 12 studies on EUS, the methodology for patient selection was unclear in only four (33%) studies[2,3,4,9] and considered high in one (8%) study due to the exclusion of early-stage gastric cancer cases.[12] Three studies [2,4,6] were at unclear risk of bias for flow and timing because it was unclear if there was an inappropriate interval between the index test and reference standard. Four studies (33%) were at high risk of bias in terms of flow and timing domain since not all of the participants were included in the analysis for both EUS and MDCT as well as the presence of applicability issues in patient selection.[2,4,6,11] All 6 studies on PET CT were appraised to be of high methodologic quality.

RECOMMENDATIONS FROM OTHER GROUPS

FDG-PET/CT

Other international guidelines (i.e., ESMO 2022, NCCN 2022) have issued strong recommendations ***against*** the routine use of FDG-PET/CT for preoperative staging in gastric cancer.[16] While FDG-PET/CT imaging may improve staging by detecting involved lymph nodes or metastatic disease, it may not be informative in patients with mucinous or diffuse tumors due to lower tracer uptake.

EUS

NCCN states endoscopic ultrasound may be utilized if early-stage disease is suspected or if early versus locally the advanced disease needs to be determined. Contrast-enhanced CT, on the other hand, was recommended as initial staging and risk assessment workup for gastric cancer.[1]

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No local economic evaluation studies on the topic were found.

Costs for a whole abdomen CT scan are approximately PHP 10,000.[28,20] FDG-PET/CT Scan prices in the Philippines range from PHP 40,000 to 60,000, excluding the professional fees of the reader.[30,31] EUS on the other hand costs approximately PHP 50,000 to 70,000 excluding the professional fees of the operator. While these direct costs may give guidance on the expenses that can be incurred by patients, factors such as expenses incurred from additional confirmatory testing need also be considered. Moreover, for false negative tests, the cost of morbidity from an untreated disease might be cumbersome. For a false positive test, the cost of treatment and their side effects might also be substantial.

Table Q3.3. Price of Imaging Diagnostic Tests for Gastric Cancer in the Philippines.

Diagnostic Test	Price (PHP)
MDCT	5,100 - 10,237.50
EUS	50,000 - 70,000
FDG-PET/CT	40,000 - 60,000

Cost-effectiveness

While the economic evidence for gastroesophageal cancer (GOC) staging using endoscopic ultrasound (EUS) is limited, a 2019 systematic review by Yeo et al. suggests that incorporating EUS as a complementary staging technique could be cost-saving (around PHP 141,600 to 241,900 per patient, 2017 price year) and yield greater quality-adjusted life years (0.0019-0.1969 more QALYs) compared to strategies without EUS.[19] However, the review emphasizes the need for more health economic research and high-quality data. Regarding FDG-PET/CT for gastric cancer, its cost-effectiveness in the local context remains unclear. A 2012 study by Smyth et al. suggests potential cost savings of approximately PHP

735,000 per patient by adding FDG-PET/CT to standard staging for locally advanced gastric cancer, primarily by avoiding futile gastrectomies in patients with occult metastases.[27] Another study also supports the cost-effectiveness of PET CT in preventing unnecessary staging laparoscopies or futile treatment attempts.[25]

Patient's values and preferences, equity, acceptability, feasibility

In the Philippines, access to endoscopic ultrasound (EUS) and FDG-PET/CT is limited, with only a few institutions offering these services, and a scarcity of trained professionals and operators for such procedures. According to the 2022 registry of the Philippine Society of Digestive Endoscopy (PSDE), there are only 10 endoscopy centers with EUS and 16 EUS practitioners nationwide, mainly concentrated in the National Capital Region (81%, 13/16), and only 3 in the provinces of Rizal, Albay, and Benguet.[7] Despite a lack of evidence on the attitudes of Filipino patients or clinicians towards EUS for gastric cancer, studies from other regions indicate positive opinions about its necessity for evaluating both early and advanced gastric cancer. However, recognized barriers such as the scarcity of experienced endosonographers, low service availability, limited accessibility, perceived utility, high cost, and a shortage of trained endosonographers pose challenges to the widespread use of EUS.[20,21]

[7] **Institutions with EUS:** Philippine General Hospital, Rizal Medical Center, National Kidney and Transplant Institute, St. Luke's Medical Center - Global City, St. Luke's Medical Center - Quezon City, Chinese General Hospital, University of Santo Tomas Hospital, Southern Philippines Medical Center, Our Lady of Lourdes Hospital, The Medical City

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GUIDELINE QUESTION 4:

Should we use a multidisciplinary team approach for patients with gastric cancer?

RESEARCH QUESTION: Among patients with gastric cancer, how effective is a multidisciplinary team approach in improving gastric-cancer related outcomes?

Among patients with gastric cancer, we **RECOMMEND the use** of a **multidisciplinary team** approach.

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Strong

CONSIDERATIONS

Despite low certainty, the consensus panel acknowledged potential benefits of Multidisciplinary Team (MDT) discussions for advanced gastric cancer, enhancing clinical decision-making. While MDT was valuable for addressing misconceptions and facilitating discussions on patient management, some cases may proceed without extensive MDT discussions. Patients not falling into these categories were seen to benefit the most. From the patients' perspective, the MDT approach was advantageous for their welfare and well-being, but integrating MDT into standardization and policy-making was suggested to alleviate costs. The panel highlighted potential harms, such as overstaging, and concerns about feasibility and availability in low-resource areas, emphasizing equity issues.

KEY FINDINGS

One randomized controlled trial (RCT) and 6 non-randomized trials investigated the effectiveness of a multidisciplinary team (MDT) approach compared to standard oncologic care in diagnosing and treating gastric cancer. MDT characteristics varied, involving specialists from various medical fields in regular meetings to expedite diagnosis confirmation, improve clinical staging accuracy, and finalize individualized treatment plans. The MDT approach resulted in lower 1-year mortality, shorter time from diagnosis to treatment initiation, increased early gastric cancer detection, and decreased risk of understaging/undertreatment. MDT may be as good as or better than standard care for improving overall survival, though it was associated with a higher risk of overstaging/overtreatment. Certainty of evidence is very low due to bias, imprecision, and heterogeneity, indicating that further studies are likely to change effect estimates.

BACKGROUND

Due to the recurrence and local or distant spread of gastric cancer, a comprehensive approach involving surgery, adjuvant, and neoadjuvant treatments like chemotherapy and radiotherapy is essential. This necessitates a Multidisciplinary Team (MDT) comprising specialists from diverse medical fields who collaboratively develop individualized diagnostic and treatment plans.[1,2] MDT meetings streamline care processes, reduce treatment delays, and ensure decisions align with guidelines or clinical experience. While MDT is widely considered the standard of care, its effectiveness varies across cancer types and settings. For gastric cancer patients, particularly those in early-stage or palliative settings, it is crucial to assess whether the MDT approach improves survival and clinical outcomes, especially since organized MDT is not yet the norm in many Philippine institutions.[3] This review aims to justify the adoption of the MDT

approach across different facilities in the country and address key considerations such as team composition and optimal implementation.

REVIEW METHODS

A systematic search was done on May 4, 2023 in MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) using a combination of keywords, MeSH terms, and free text search related to gastric cancer and interdisciplinary/multidisciplinary teams. We also searched for ongoing studies about this topic in the NIH *clinicaltrials.gov.* The full search strategy is detailed in Appendix Q4.1.

This review considered eligible articles such as meta-analyses, systematic reviews, randomized controlled trials (RCTs), and non-randomized studies of the effects of interventions (NSRI) with before-and-after designs that reported on outcomes related to a multidisciplinary team approach for managing diagnosed gastric cancer patients. Exclusions encompassed studies enrolling patients with esophagogastric or other gastrointestinal cancers, while observational studies were included if they reported on outcomes like the reduction in gastric cancer-related morbidity and mortality, quality of life, cost-effectiveness, hospital readmission, and survival time. The review assessed the risk of bias using Cochrane ROB 1[4] for RCTs and ROBINS-I for non-randomized studies. Meta-analysis, employing a random effects model, aimed to derive a single pooled effect estimate (e.g., hazards ratio, risk ratio, odds ratio) for each outcome, with subgroup analysis conducted when feasible based on gastric cancer stage (i.e., early vs. advanced stage). The overall certainty of evidence was evaluated following the GRADE approach.

SUMMARY OF THE EVIDENCE

Evidence Considered

Randomized controlled trials

A Chinese open-label randomized controlled trial included 328 patients with previously-untreated metastatic gastric, gastroesophageal, or esophageal cancer, comparing early interdisciplinary supportive care (ESC) to standard oncologic care (SC).[6] ESC involved a multidisciplinary team meeting patients 14 days before treatment initiation and regularly during first-line treatment, while the SC group was managed by the attending GI medical oncologist, with referrals to a nutritionist or psychologist made upon request. Primary outcome: overall survival (OS) over 42 months, and secondary outcomes included progression-free survival (PFS), objective response rate (ORR), adverse events, quality of life (QoL) using European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ C30),[7] nutritional and psychological assessment scores.

Non-randomized trials

Six non-randomized trials were identified,[3,8-12] comparing outcomes of patients treated with a multidisciplinary team (MDT) to those without, with one being prospective.[12] Studies involved early gastric cancer, intent for resection or cure, and advanced or late-stage gastric cancer, with one study covering all stages. The comparison group received standard care before MDT establishment, while the intervention group was managed post-MDT creation. One unique prospective study aimed to determine MDT's accuracy in clinical staging compared to final histopathological staging.[12] MDT composition varied, including specialists from surgery, medical oncology, pathology, gastroenterology, radiation oncology, radiology, anesthesiology, clinical nurse specialists, thoracic surgery, dietitians, psychologists, an MDT coordinator, and attending physicians. MDT meeting frequency ranged from weekly to monthly, primarily focused on

diagnosis confirmation, staging, recommendation of additional tests, and individualized treatment plans. Efficacy outcomes comprised overall survival (expressed as hazard ratios [HR]),[3,6,8-11] mortality at 1 and 3 years,[6,8,11] progression-free survival,[6] early gastric cancer detection,[9] time to treatment, and staging accuracy.[8,12] Safety outcomes included mild and serious adverse events, overstaging, and undertreatment.[6,8,12] The characteristics of included studies are summarized in Appendix Q4.3.

Efficacy Outcomes

Table Q4.1. Summary of outcomes of MDT for gastric cancer.

CRITICAL OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Overall survival	RCTs only (n=246)	HR 0.76	0.55, 1.04	MDT is better than or as good as no MDT	**Low** ⊕⊕◯◯
	3 NRSIs* only (n=957)	HR 0.86	0.46, 1.61	Inconclusive	**Very Low** ⊕◯◯◯
Mortality at 1 year	2 NRSI, 1 RCT (n=891)	RR 0.68	0.55, 0.85	MDT is better than no MDT	**Very Low** ⊕◯◯◯
Mortality at 3 years	3 NRSI, 1 RCT (n=1285)	RR 0.93	0.84, 1.03	MDT is as good as no MDT	**Very Low** ⊕◯◯◯
Progression-free survival	1 RCT (n=306)	HR 0.80	0.62, 1.03	MDT is better or as good as no MDT	**Low** ⊕⊕◯◯
Adverse events (mild)	1 RCT (n=306)	RR 0.92	0.72, 1.14	MDT is better than no MDT	**Low** ⊕⊕◯◯
Adverse events (serious)	1 RCT (n=306)	RR 1.07	0.74, 1.51	Inconclusive	**Low** ⊕⊕◯◯
Overstaging/ overtreatment	2 NRSI (n=299)	RR 1.51	1.11, 2.05	MDT is more harmful than no MDT	**Very Low** ⊕◯◯◯
Understaging/ undertreatment	2 NRSI (n=299)	RR 0.74	0.55, 0.98	MDT is better than no MDT	**Very Low** ⊕◯◯◯
Time to treatment (from endoscopy to chemotherapy initiation)	1 NRSI (n=100)	MD -51.6 days lower	-57.0, -46.2	MDT is better than no MDT	**Very Low** ⊕◯◯◯
Detection of early gastric cancer	1 NRSI (n=371)	OR 3.00	1.63, 5.53	MDT is better than no MDT	**Very Low** ⊕◯◯◯
Quality of life	1 RCT (n=328)	Compared to baseline scores, MDT patients had increased emotional function scores (+5.87 points [95%CI 0.05, 11.69] and cognitive functioning scores (+5.77		Inconclusive	**Very Low** ⊕◯◯◯

		points [95%CI 0.28, 11.25] at 9 weeks. Scores indicate 'little to no benefit' in QOL		

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio; **HR:** hazards ratio.
*__NRSI__, non-randomized studies of interventions **

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

Multidisciplinary team (MDT) involvement in gastric cancer treatment shows potential benefits, but the certainty of evidence is very low due to serious bias, imprecision, and inconsistency. Overall survival analysis involving 1,203 patients from four studies[3,6,8,11] demonstrated a 27% reduction in annual death risk, but the wide confidence interval crossed 1. Subgroup analysis by gastric cancer stage did not show significant differences. MDT led to significantly lower 1-year mortality (RR 0.72), but 3-year mortality rates were equivalent. Progression-free survival data suggested a 20% reduction in the annual risk of progression (HR 0.80). Quality of life scores improved slightly with MDT, but clinical significance was questionable. Early gastric cancer detection increased post-MDT implementation (OR 2.63). Time to treatment was significantly shorter with MDT, reducing the time between endoscopy and chemotherapy initiation. Certainty of evidence for these outcomes was low due to various biases and issues. (See Figures Q4.6-A-F,H)

Safety outcomes

Mild and serious adverse events within a 9-week period showed no significant difference between MDT and no MDT groups. For mild adverse events, the risk ratio was 0.92 (95%CI 0.72 to 1.14), and for serious adverse events, the risk ratio was 1.07 (95%CI 0.74 to 1.51). Staging accuracy, based on very low-certainty evidence from two non-randomized studies, suggests a higher risk of overstaging/overtreatment with MDT (43.9% vs. 30.6% for non-MDT), with a risk ratio of 1.34 (95%CI 0.81 to 2.20). However, fewer patients were understaged/undertreated with MDT compared to non-MDT (30.9% vs. 43.1%), with a risk ratio of 0.74 (95%CI 0.55 to 0.98). The certainty of evidence for these outcomes is very low. (See Figure Q4.6-G Forest plot)

Certainty of evidence

The overall certainty of evidence for both efficacy and safety outcomes is **very low**. Certainty was downgraded due to imprecision in effect estimates, with confidence intervals crossing 1.00, serious risk of bias associated with the non-randomized nature of the studies, and heterogeneity arising from differences in MDT intervention characteristics. Even considering only data from the randomized controlled trial, the overall certainty of evidence remains **low** due to imprecision and risk of bias related to deviations in intended interventions, particularly non-compliance to treatments in 28-33% of patients.

RECOMMENDATIONS FROM OTHER GROUPS

Based on clinical practice guidelines from other countries, recommendations on use of the MDT approach in the management of gastric cancer were generally made with moderate to high strength of recommendation, but with low certainty of evidence based on nonrandomized studies and expert consensus. The European Society of Medical Oncology (ESMO) emphasizes the mandatory need for multidisciplinary treatment planning in gastric cancer, advocating core membership from various specialties. The Korean Practice Guidelines suggest a multidisciplinary approach for resectable locally-advanced gastric cancer and gastric outlet obstruction, with a conditional recommendation and low-level evidence. The National Cancer Center Network (NCCN) supports multidisciplinary treatment decision-making, providing recommendations for MDT meeting conduct. (See Appendix Q4.7) The Chinese Society of Clinical Oncology recommends MDT discussions to determine optimal treatment regimens, particularly in complex clinical scenarios, based on strong expert consensus. These guidelines highlight the importance of a collaborative, multidisciplinary approach in managing gastric cancer cases.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

While the direct costs of organizing Multidisciplinary Team (MDT) conferences for gastric cancer in the Philippines are challenging to quantify, several considerations are pertinent to this topic. Specialists dedicating time to MDT meetings may entail remuneration, potentially adding to patients' expenses. Some institutions organizing MDTs might pass on additional costs to patients for meeting platforms and conduct. Furthermore, the association of the MDT approach with an increased risk of overstaging and subsequent overtreatment may lead to additional patient expenses for diagnostics, treatments, and interventions, with potential indirect costs such as time. Recommending unnecessary tests can impact health equity by prolonging waitlists and increasing waiting times for essential procedures, potentially disadvantageous to patients who urgently require these diagnostics.

Patient's values and preferences, equity, acceptability, feasibility

The geographic distribution of cancer care specialists in the Philippines reveals a regional disparity, with the highest density in the National Capital Region and the lowest in the Bangsamoro Autonomous Region in Muslim Mindanao, as noted in a study by Eala et al. (2022).[18] Additionally, certain subspecialties, including surgical oncology, radiation oncology, and hospice and palliative medicine, are unavailable in several regions. Implementing MDT universally may exacerbate these inequities. Moreover, while MDT meetings aim to enhance clinical staging and treatment selection for improved outcomes, studies in this review report low compliance rates with MDT-recommended interventions, suggesting potential knowledge gaps in how patient values and preferences are incorporated into decision-making.[6,8] This concern aligns with findings from a UK ethnographic study on decision-making in the context of MDTs for head-and-neck cancer patients.[19]

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GUIDELINE QUESTION 5:

Should we use non-surgical hemostatic interventions in patients with unresectable gastric cancer with tumoral bleeding?

RESEARCH QUESTION: Among patients with unresectable gastric cancer presenting with tumoral bleeding, how effective are non-surgical hemostatic interventions in improving survival and bleeding control?

Shared decision making for the palliative control of tumor bleeding by endoscopic techniques and/or radiotherapy should be discussed to the patient as deemed necessary.
(Good practice statement)

Among patients with unresectable gastric cancer with tumor bleeding, we **SUGGEST the use** of **hemostatic spray powder or transarterial embolization** (TAE), where accessible, as *bridging therapy* for more definitive treatment for tumor bleeding.

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Weak

CONSIDERATIONS

The panel acknowledged the limited effects of interventions on patients with lower functional status (ECOG 3+), especially when quality of life is already low. Endoscopic treatments, such as clips, were deemed suitable for cases of unresectable bleeding. Concerns about significant harms from transarterial embolization (TAE), like spleen infarction and pyloric stenosis, were noted. TAE was favored by the panel, but its use was contingent on a low risk of the bleeding impacting other organs.

Possible bias in Pittayanon's study, which supported Hemospray, was recognized, given its comparable subject numbers (57) to other studies (50-80 patients). Notably, Hemospray was not administered in addition to standard treatments but provided to non-responders. Cost considerations played a role. Hemospray was viewed as more manageable for patients, while radiotherapy presented challenges due to limited accessibility outside Metro Manila, with added costs for transit and logistics. The panel recommended exploring all modalities, emphasizing a best practice statement rather than endorsing a specific procedure despite overall benefit. The consensus was to opt for non-surgical hemostatic interventions where feasible and accessible, considering cost-effectiveness, physician training, logistical support, and other practical factors.

KEY FINDINGS

Transcatheter Arterial Embolization (TAE):

Four observational studies, involving 119 patients (55 to 72 years old) with bleeding from advanced gastric cancer, explored varied TAE procedures. Clinical success (bleeding control within 2 weeks to 30 days) was observed in 75% (58-98%) of cases, with a 23% (15-31%) rebleeding rate within 30 days. One-month survival was noted in 88% (76-97%), and major complications occurred in 4% (0-14%). Patients with

successful TAE had higher odds of one-month survival (93% vs. 65%; OR 6.7 [2.2-21.4]). Certainty of evidence for TAE benefits and harms is very low.

Endoscopic Treatment (Hemostatic Spray Powder):

Three RCTs, involving 139 patients, compared hemostatic spray powder (TC-325) to standard endoscopic therapy for bleeding advanced gastric cancer. Significant benefits with TC-325 were observed for immediate hemostasis [OR 20.57 (3.19, 132.53)], but no impact on the proportions of patients needing blood transfusion. Subgroup analysis found no significant differences in 30-day mortality [RR 1.25 (0.47, 3.33)], 30-day rebleeding [RR 0.46 (0.09, 2.32)], and length of hospital stay [mean difference 3.77 days (-1.31, 8.86)]. Certainty of evidence for hemostatic spray powder is very low.

Radiation:

Fourteen observational studies and one non-randomized control trial (746 patients) assessed palliative radiotherapy for bleeding control in advanced gastric cancer. Bleeding response to radiotherapy was 72% (61-81%), with a rebleeding rate of 30% (17-45%), 30-day mortality of 42% (10-78%), overall mortality of 85% (62-98%), and serious adverse events in 3% (1-7%). Certainty of evidence for palliative radiotherapy is very low.

Medications:

No evidence was found for proton pump inhibitors, vasoactive agents (octreotide and somatostatin), and Tranexamic acid in treating tumor bleeding in unresectable gastric cancer.

INTRODUCTION

Bleeding in unresectable gastric cancer poses significant challenges, contributing to morbidity and mortality. The complexities arise from extensive lesions, high rebleeding rates, and substantial transfusion needs.[1,2] Common palliative modalities include radiotherapy, transarterial embolization, endoscopic interventions (such as hemostatic powder spray), and medical/pharmacologic management.[1] Despite various approaches, there is no established standard of care for treating bleeding in unresectable gastric cancers. Surgery remains recognized as an effective option for managing bleeding complications in gastric cancer patients.[1,2]

REVIEW METHODS

A systematic search was done from the date of the last search April 1, 2023 up to August 16, 2023 using MEDLINE and CENTRAL with a combined MeSH and free text search using the terms gastric cancer/stomach cancer, malignant/tumor bleeding/hemorrhage, and for the specific interventions, including: radiotherapy, transarterial embolization, endoscopic interventions such as hemostatic powder and argon plasma coagulation, and tranexamic acid (Appendix Q5.1). Systematic reviews, observational studies and randomized control trials that analyzed the following nonsurgical interventions with standard of care (e.g., surgery, other active control) for the treatment of bleeding were included in this review. Outcomes of interest include treatment/success rate, rebleeding rate, and need for transfusion and mortality/survival.

Risk of bias of the studies were appraised using the Cochrane Risk of Bias tool version 1 (Appendix Q5.4).[3] Summary effect estimates were calculated, which included either relative risk (RR) or odds ratio (OR) using

Review Manager 5 (RevMan 5. Version 5.4.1, The Cochrane Collaboration, 2020) for studies with available comparisons. For studies that only included a single cohort, pooled incidence/event rates were calculated using *metaprop* command in Stata/MP version 14.0 (StataCorp, TX, USA). Certainty of evidence was rated using the GRADE approach.

RESULTS

Table Q5.1. Summary of outcomes for non-surgical hemostatic interventions.

CRITICAL OUTCOMES	BASIS (No and Type Of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Transarterial embolization					
Clinical success*	4 observational (n=119)	Pooled rate = 75%	58, 98%	**Inconclusive** TAE will result in bleeding control in 58-98% of patients. Rates unknown in patients not treated with TAE.	**Very Low** ⊕◯◯◯
Rebleeding rate (30 days)	3 observational (n=110)	Pooled rate = 23%	15, 31%	**Inconclusive** Rebleeding is estimated to occur in 23% of patients treated with TAE. Rates unknown in patients not treated with TAE.	**Very Low** ⊕◯◯◯
Survival (30 days)	3 observational (n=110)	OR 6.89	2.22, 21.4	**Benefit** (from 156 to 328 more per 1000 patients will survive among those where TAE is successfully performed)	**Very Low** ⊕◯◯◯
Serious adverse events / major complications	3 observational (n=110)	Pooled rate = 4%	0, 14%	**Inconclusive** Major complications are estimated to occur in 0 to 14% of patients treated with TAE. Rates unknown in patients not treated with TAE.	**Very Low** ⊕◯◯◯
Endoscopic Treatment (e.g. Hemostatic Spray Powder Application)					
Immediate Hemostasis	2 RCTs (n=77)	OR 20.57	3.19,132.53	**Benefit** (from 237 more to 419 more patients with have immediate hemostasis)	**Very Low** ⊕◯◯◯
Mortality (30 days)	3 RCTs (n=136)	RR 1.06	0.66,1.7	**Inconclusive** (from 170 fewer to 350 more deaths)	**Very Low** ⊕◯◯◯
Rebleeding (30 days)	3 RCTs (n=136)	RR 0.46	0.09,2.32	**Inconclusive** (from 274 fewer to 398 more patients will rebleed)	**Very Low** ⊕◯◯◯
Length of hospitalization	3 RCTs (n=136)	mean difference 3.77 days	-1.31,8.86	**Inconclusive** (from 1.31 less days to 8.86 more days of hospitalization)	**Very Low** ⊕◯◯◯
Blood Transfusion requirements	2 RCTs (n=77)	RR 0.85	0.64,1.12	**Inconclusive** (from 281 fewer to 94 more patients will have more blood transfusion requirements)	**Very Low** ⊕◯◯◯

CRITICAL OUTCOMES	BASIS (No and Type Of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Palliative radiotherapy					
Response to radiotherapy**	14 observational studies, 1 nonrandomized clinical trial (n=746)	Pooled rate = 72%	61-81%	**Inconclusive** (Palliative RT will result in bleeding response in 61-81% of patients. Rates unknown in patients not treated with RT).	**Very Low** ⊕◯◯◯
Rebleeding rate (30 days)	4 observational studies (n=142)	Pooled rate = 30%	17-45%	**Inconclusive** (Rebleeding is estimated to occur in 17-45% of patients who were treated with palliative RT. Rates unknown in patients not treated with RT.)	**Very Low** ⊕◯◯◯
Mortality (30 days)	5 observational studies, 1 nonrandomized clinical trial (n=146)	Pooled rate = 42%	10-78%	**Inconclusive** (30 day mortality is estimated to occur in 10-78% of patients who were treated with palliative RT. Rates unknown in patients not treated with RT.)	**Very Low** ⊕◯◯◯
Overall mortality (follow-up: 21-103 months)	6 observational studies (n=313)	Pooled rate = 84%	62-98%	**Inconclusive** (Overall mortality is estimated to occur in 62-98% of patients who were treated with palliative RT. Rates unknown in patients not treated with RT.)	**Very Low** ⊕◯◯◯
Serious adverse events	11 observational studies (n=508)	Pooled rate = 3%	1-7%	**Inconclusive** (Serious adverse is estimated to occur in 1-7% of patients who were treated with palliative RT. Rates unknown in patients not treated with RT.)	**Very Low** ⊕◯◯◯

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio; **HR:** hazards ratio.
* Clinical success was defined as either survival without recurrent bleeding after 14 days (Cho 2020), cessation of bleeding symptoms within 3 days (Park 2017) or until 30 days after TAE (Elmokadem 2017), or discharge from hospital without needing blood transfusion for 30 days (Kimura 2018).
** Response to radiotherapy was defined as absence of rebleeding or drop in hemoglobin or hemodynamic instability within a defined time period.

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

A. Transcatheter arterial embolization (TAE)

Evidence Considered

Four retrospective observational studies comprised the evidence base for TAE (Appendix Q5.3.1).[4,5,6,7] A total of 119 patients with gastric cancer-related GI bleeding with an average age of 55-72 years were examined. All patients underwent embolization after endoscopic and angiographic evaluations. Two of the studies were performed in Korea[4,7], one in Egypt[5], and one in Japan[6].

TAE procedures were performed by experienced interventional radiologists using a variety of embolic materials/tools (e.g., microcoils, gelatin sponge, polyvinyl alcohol) at the discretion of the operator and approaches. Most of the studies used gel sponge as embolic material. Outcomes reported included the following: clinical success, mortality (30-241 days), complications, transfusion requirement, and rebleeding rates. Clinical success was defined as either survival without recurrent bleeding after 14 days,[4] cessation of bleeding symptoms within 3 days[7] or until 30 days after TAE[5], or discharge from hospital without needing blood transfusion for 30 days.[6]

Efficacy outcomes

The pooled clinical success rate, drawn from four studies, was 75% (95% CI 58 to 89%), exhibiting significant variability in estimates (I2=63.2%). Elmokadem's study reported a perfect 100% clinical success rate in 9 out of 9 patients, while Cho (2020), Park (2017), and Kimura (2018) reported rates of 72.4%, 65%, and 56%, respectively. In terms of rebleeding within 30 days, the combined rate, based on three studies, stood at 23% (95% CI 15 to 31%), with uniformity across studies as all rebleeding events occurred within this timeframe.[4,5,7] Additionally, TAE demonstrated a one-month survival rate of 88% (95% CI 76 to 97%; I2=48.4%). Comparing survival rates between successful TAE and clinical failure highlighted a significantly higher 1-month survival (93.2% vs. 64.7%) among those with clinical success (OR 6.89 [95% CI 2.22 to 21.4]), considering pooled results from three studies. Elmokadem's study, however, reported a 241-day follow-up with 6 out of 9 patients surviving.[4-7]

Safety outcomes

Based on pooled results from 3 studies,[4,6,7] 5 out of 107 patients experienced a major complication, corresponding to a rate of 4% (95%CI 0 to 14%). These included 2 cases of 3 cases of splenic infarction, 1 case of pyloric stenosis, and 1 case of procedure-related stomach wall perforation that required gastrectomy.

Certainty of evidence

The overall certainty of evidence on the efficacy and safety of TAE is **very low** (Appendix Q5.5.1). Reasons for downgrading include study design limitations (observational studies only), inconsistency (varied TAE protocols and embolic materials used depending on the operator and institution), and indirectness (no comparison group).

B. Endoscopic Treatments

Evidence Considered

For Argon Plasma Coagulation (APC), there is a lack of systematic reviews, randomized control trials, or observational studies directly comparing its efficacy against the standard of care for treating bleeding in advanced gastric cancers.

In contrast, Hemostatic Spray Powder has been investigated in three randomized control trials involving a total of 136 adult patients with malignancy-related upper GI bleeding.[8-10] These trials assessed the use of TC-325 hemostatic spray powder, also known as Hemospray, in comparison to the standard of care or standard endoscopic therapy, which could include various thermal therapies, electrocoagulation, injection treatments, or hemoclipping. The outcomes evaluated encompassed 30-day rebleeding, defined by a significant drop in hemoglobin levels to less than 7g/dL, the need for transfusion, or the presence of hemodynamic instability. Other measured outcomes included 30-day mortality, immediate hemostasis (timed control of bleeding upon application of the hemostatic spray powder during endoscopy), the proportion of patients requiring blood transfusion, and the length of hospital stay.

Efficacy outcomes (Hemostatic Spray Powder)

Regarding Hemostatic Spray Powder (TC-325) compared to the standard of care for malignancy-related upper GI bleeding, a subgroup analysis of three randomized control trials (RCTs) showed no significant difference in 30-day mortality (RR 1.06 [95%CI 0.66 to 1.7]). Pooled risk ratios for 30-day rebleeding did not conclusively favor TC-325 over the standard of care (RR 0.46 [95%CI 0.09 to 2.32]), but significant heterogeneity was observed. One of the RCTs by Pittayanon 2023 reported better rebleeding rates with TC-325, although the study excluded patients with poor functional status (ECOG score of 3).[10] Tumor characteristics and bleeding stigmata identified during endoscopy were consistent across the three RCTs.

Regarding the average length of hospitalization, no significant difference was found between TC-325 and the control group (mean difference 3.77 days [95%CI -1.31 to 8.86 days]) based on three RCTs. On the other hand, the odds of achieving immediate hemostasis were significantly higher in patients treated with TC-325 compared to the control (97.7% vs. 57.6%; OR 20.6 [95%CI 3.19 to 132.5]) based on two RCTs. Subgroup analysis of blood transfusion requirements from two RCTs did not show a significant difference between the hemostatic spray group and the standard of care (RR 0.85 [95%CI 0.64 to 1.1]).[8-10]

Safety outcomes

There were no reported mild or serious adverse outcomes documented with the use of hemostatic spray powder across the 3 RCTs.

Certainty of evidence

The overall certainty of evidence on the efficacy and safety of hemostatic spray is **very low** (Appendix Q5.5.2). Reasons for downgrading include inconsistency (crossover from one intervention group to the other for treatment of persistent bleeding, varied decision to use endoscopic therapy and heterogeneity of results across studies), and indirectness (1 study provided data for both upper and lower GI malignancy bleeding while another study included data from all upper GI malignancy aside from primary gastric cancer) and imprecision (wide confidence intervals).

C. Radiotherapy

Evidence Considered

Evidence included 14 observational studies[11-21,23-25] and 1 non-randomized control study[22] from a recently published systematic review[1] which enrolled a total of 746 patients with advanced gastric cancer treated with palliative radiotherapy for control of bleeding (Appendix Q5.3.3). The age of the patients included ranged from 33-95 years old, with males comprising ~63.9% of the included patients. At least 35.9% of the patients were identified to have an Eastern Cooperative Oncology Group (ECOG) score of 3 and above. Most of the patients received chemotherapy either during or after radiotherapy. Most of the studies included institutions from Asia (8 from Japan, 3 from Korea, 2 from Singapore, 1 from HK) and 1 from the UK.

There were different palliative radiotherapy regimens, in single or multiple courses but the most common regimen was 30 Gy in 10 fractions, ranging from a single 8 Gy fraction dose to 42 Gy over 20 fractions.[1] Outcomes measured in the studies included: (a) response to RT, defined as absence of rebleeding or drop in hemoglobin or hemodynamic instability within a defined time period; (b) rebleeding rate within a defined time period; (c) mortality; and (d) serious adverse events, mostly reported based on the Common Terminology Criteria for Adverse Events (CTCAE) used in cancer therapy.

Efficacy outcomes

The aggregated findings from 14 studies examining palliative radiotherapy for bleeding control in advanced gastric cancer revealed a pooled response rate of 72% (61-81%), though with considerable heterogeneity at 86.59%.[11-25]

Regarding rebleeding after radiotherapy, a pooled rate of 30% (95% CI 17-45%) was observed across four studies, with notable heterogeneity between them. The reported rebleeding rates varied, with Sugita in 2021 documenting 15%, and Asakura in 2010 reporting a higher rate of 50%..[12,13,15,19]

In terms of 30-day mortality after radiotherapy, a pooled rate of 42% (95% CI 17-45%) was calculated from five studies, reflecting substantial heterogeneity (I2=94.7%). The study by Mitsuhashi in 2021 reported a relatively lower 11% 30-day mortality rate, whereas Asakura in 2010 indicated a considerably higher 97% mortality within the same timeframe. Furthermore, the overall mortality rate across six studies, with follow-ups ranging from 21 to 103 months, stood at 84% (95% CI 62-98%). While five of the pooled studies reported rates from 85-93%, Takeda in 2022 deviated with an overall mortality of 46%.

Safety outcomes

The pooled rate for serious adverse events associated with RT was 3.0% (95%CI 1.0 to 7.0%) based on 11 studies which included a total of 508 patients.[12,13,14,16,17,19,20,21,22,24,25] These included severe anorexia (n=7), bleeding abnormalities (n=5), perforation (n=3), severe gastritis (n=2), fatal hemorrhage post-RT (n=1), severe nausea (n=1), and elevation of creatinine (n=1). Mild adverse events were common (36% [95%CI 26 to 47%]) and were either gastrointestinal symptoms (nausea, vomiting, anorexia) or hematologic abnormalities (cytopenias).

Certainty of Evidence

The overall certainty of evidence on the efficacy and safety of palliative RT is **very low** (Appendix Q5.5.3). Reasons for downgrading include study design limitations (observational studies, hence pooled estimates

only), inconsistency (palliative RT in different protocols with or without concurrent chemotherapy), and indirectness (no comparison group).

D. Medications

Despite our current literature search, no applicable systematic reviews, randomized controlled trials or observational studies were retrieved with the use of medications (including proton pump inhibitors, vasoactive agents (Octreotide and Somatostatin) and Tranexamic acid in the treatment of tumor bleeding in patients with unresectable gastric cancer (Appendix Q5.1).

RECOMMENDATIONS FROM OTHER GROUPS

Currently, there is no society guideline endorsing a particular modality for effectively palliating bleeding complications in advanced gastric cancers. In 2014, the Indian Council for Medical Research issued a consensus statement outlining management strategies for bleeding complications without specific recommendations.[26] Meanwhile, the Brazilian Gastric Cancer Association, in 2021, suggests palliative gastric resection over nonsurgical interventions for treating bleeding in advanced gastric cancer.[27]

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No local economic evaluation studies on nonsurgical interventions for bleeding gastric cancer were found. Estimated costs for these procedures are outlined in Table Q5.2.

Hemospray (Cook Medical) hemostatic spray powder costs Php 41,470 per unit for a single-use endoscopic procedure. The actual cost of therapeutic endoscopy ranges from Php 14,960 to around Php 40,000 in Manila's tertiary centers. Not all endoscopists have the required expertise in using hemostatic spray powders for bleeding gastric tumors.

Embolization procedure costs range from PHP 46,500 to 200,000, depending on tumor extent and planning, limited to tertiary centers with fluoroscopy and trained interventional radiologists. Radiotherapy session costs vary from PHP 3,000 to PHP 12,000, with multiple sessions (5-10), incurring additional planning, laboratory testing, and monitoring costs throughout the treatment.

Table Q5.2. Estimated costs of non-surgical hemostatic interventions in the Philippines.

Non-Invasive Diagnostic Test	Price (PHP)
Hemospray (single-use)	41,470
Therapeutic endoscopy	14,960 - 40,000
Embolization	46,500 - 200,000
Radiotherapy (3,000-12000 per session for 5-10 sessions)	15,000 - 120,000

Patient's Values And Preference, Equity, Acceptability, And Feasibility

No relevant studies on patient acceptability for the reviewed interventions were identified. Assessing the impact on quality of life is crucial, considering the recognized importance of addressing psycho-social burden alongside potential survival benefits.[28]

Accessibility poses a significant challenge, with limited infrastructure and technology available mainly in tertiary centers, resulting in restricted rural access. Out-of-pocket spending on procedures, especially radiotherapy, remains high. The Philippines has a scarcity of oncologists, with 0.32 medical oncologists, 0.15 surgical oncologists, 0.09 radiation oncologists, 0.13 gynecologic oncologists, and 0.03 hospice and palliative medicine (HPM) specialists per 100,000 Filipinos. Geographic concentration of specialists in the National Capital Region further exacerbates the issue.[29]

The latest census by the Philippine Society of Digestive Endoscopy and Philippine Society of Vascular and Interventional Radiology indicates 528 active members/endoscopists and approximately 150 interventional radiologists, translating to 0.48 gastroenterologists and 0.14 interventional radiologists per 100,000 Filipinos.

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GUIDELINE QUESTION 6:

Should we do mass screening for *H. pylori* infection in asymptomatic individuals?

RESEARCH QUESTION: Among asymptomatic individuals, how safe, accurate, and effective is mass screening compared to targeted screening for detecting *Helicobacter pylori* infection and decreasing *H. pylori*-related morbidity and gastric cancer incidence?

Among asymptomatic individuals, we **SUGGEST AGAINST mass screening** for *H. pylori.*

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Weak

CONSIDERATIONS

The consensus panel opposed mass screening for gastric cancer in the Philippines due to a lack of local evidence of high prevalence. Mass screening was considered less feasible and not cost-effective in the absence of substantial incidence data. Instead, the panel favored individualized screening under specific conditions, deeming it more realistic and sustainable. Certainty of evidence for screening benefits was low, despite prevalent strains not proven carcinogenic.

Screening specifically for high-incidence areas was not recommended primarily due to the absence of local data describing the distribution of *H. pylori* across the country. Nonetheless, doing epidemiological studies on *H. pylori* in the Philippines was identified as a key priority area for policymakers/government agencies.

KEY FINDINGS

Gastric cancer incidence and mortality

A systematic search produced two studies on H. pylori screening's effect on gastric cancer incidence and mortality. Pooled estimates revealed a 45% reduction in gastric cancer risk after H. pylori eradication. However, evidence certainty was downgraded to low due to indirectness and variations in intervention characteristics.

Dyspepsia symptoms and quality of life

Six randomized controlled trials assessed H. pylori screening and eradication impact on dyspepsia symptoms, consultation rates, ulcer incidence, and quality of life. Pooled estimates showed a 14% reduction in dyspepsia symptoms. Quality of life demonstrated little to no difference. Evidence certainty was moderate for dyspepsia symptoms and quality of life but downgraded to low. For dyspepsia consultation and ulcer incidence, the level of evidence was low and downgraded to very low due to various factors.

Cost-effectiveness

Nine cost-effectiveness studies analyzed *H. pylori* screening and eradication, grouping them based on prevalence/risk status. In high-risk populations, screening using serology was cost-effective, with an ICER as low as Php88K/QALY. In low-risk populations, cost-effectiveness was dependent on willingness to pay,

with dominance observed at a threshold of PHP >3.2M or >3-fold 2022 GDP. Certainty of evidence for cost-effectiveness was low due to methodological differences and lack of specific data on screening tools.

INTRODUCTION

Gastric cancer stands as the third leading cause of global cancer-related deaths, exhibiting a significant rise after the age of 50, particularly in regions with heightened prevalence such as Korea, China, and Japan.[1] In the Philippines, it holds the 11th position among causes of cancer-related deaths, with a reported incidence rate of 4.13 cases per 100,000 individuals, also ranked as having the 13th highest incidence rate.[2]

The classification of H. pylori as a class I carcinogen underscores its substantial impact on stomach cancer risk, elevating it 3-6 times. However, the outcomes of H. pylori infection manifest with considerable variation, ranging from chronic gastritis to gastric neoplasia. In the Philippines, H. pylori prevalence is documented at 34%, with notable divergence observed among dyspeptic patients, ranging from 26.5% to 79.9%.[3]

Despite the high prevalence of HP, the incidence of gastric cancer in the Philippines remains relatively low, mirroring a phenomenon recognized globally as the "African enigma."[4] This paradox, observed in various regions worldwide, suggests that factors such as the oncogenic potential of the H. pylori strain, host response, genetic factors, and environmental influences collectively modulate the inflammatory processes initiated by H. pylori infection. Local studies in the Philippines have identified a predominant Western cagA-positive strain, which is associated with a lower carcinogenic risk.[5]

Preventive measures and early interventions could significantly impact healthcare consumption and overall public health. Recognizing this, the International Agency for Research on Cancer (IARC) emphasizes the need for countries to allocate resources to gastric cancer control. The IARC recommends exploring the feasibility of introducing population-based H. pylori screening and eradication programs into national agendas. The purpose of this review is to assess the effectiveness and cost-effectiveness of H. pylori screening in mitigating gastric cancer incidence and related outcomes.[6]

REVIEW METHODS

A systematic search was performed from April 30,2023 to July 7, 2023 using MEDLINE, Cochrane Library and Google Scholar. A comprehensive search was conducted using a standardized set of terms, applied as MeSH and text-words in Pubmed for individual studies or pooled or meta-analyses on mass screening of Helicobacter pylori infection and gastric cancer. The search terms were “Helicobacter pylori” or Helicobacter pylori infection”, “symptomatic patients”,“high risk patients”; “mass screening”, “targeted screening” for the intervention and “randomized controlled trial”, “clinical trial”, metaanalysis” and “systematic review”. Title, abstract and full text (as required) were screened to identify studies that met selection criteria. References of selected papers were further scanned. Cross-referencing and search for ongoing trials registered at clinicaltrials.gov were done. No language restrictions or other limits applied.

The titles and abstracts of the papers identified by the initial search were screened for appropriateness to the review question. Articles were assessed for directness and the following data were extracted: geographical location, country of origin, number of centers, method used to confirm H pylori infection, type of H pylori eradication regimen used, duration of treatment, eradication rate, duration of follow-up, subsequent occurrence of gastric cancer and mortality from gastric cancer. The systematic search on effectiveness of H pylori screening vs no screening on gastric cancer incidence and mortality included meta-analyses, systematic reviews and clinical trials. The search for cost-effectiveness data included meta-

analyses, systematic reviews, randomized controlled trials and modeling studies on cost effectiveness comparing mass screening to either no screening or screening of symptomatic patients or both were included. Outcomes of interest included quality adjusted life years, incremental cost effectiveness ratio and diagnostic accuracy.

Data on intervention (screening vs no screening), HP eradication vs no eradication, eradication rate, screening test used and cost were extracted. Cost of screening, screening tool and valuation of incremental cost-effectiveness ratio (ICER) were converted to Philippines pesos using online currency converter (www.xe.com). Risk of bias was assessed using Cochrane risk of bias assessment criteria (handbook16) by recording the method used to generate the randomization schedule and performance of allocation concealment, whether blinding was implemented for participants, staff, and outcome assessment; what proportion of subjects completed follow-up; and whether there was evidence of selective reporting of outcomes.

SUMMARY OF THE EVIDENCE

Evidence Considered

Studies on gastric cancer incidence and mortality

There were no clinical trials or cohort studies that directly investigated effectiveness of screening vs. no screening for H pylori on gastric cancer incidence and mortality. The search yielded 7 studies (N=8,323) on asymptomatic high-risk groups given HP eradication regimen vs no eradication/antacids/vitamins/placebo.[7,11-12,14-20] All studies were included in the meta-analysis of randomized trials by Ford et al. 2020[1], with the addition of the study by Wong et al. 2022[19] which reported 26.5 yr follow-up results from one of the included studies in the Ford 2020 review. This newer trial investigated the effect of screening and eradication vs no eradication of HP positive cases among high prevalence or high-risk groups/populations on the development of gastric cancer.

Six studies were from Asia (Japan,[16] China,[7,12,14,17,18,20] South Korea[11]) while one came from a high prevalence region in Colombia (Narino, Colombia).[15] Among the studies in the systematic review, only 3 studies were included in assessing the effect of screening and eradication on gastric mortality.[7,11,12,14,20]

Studies on *H. pylori* related morbidity

There were 6 RCTs on population-based *H. pylori* screening comparing HP screening and eradication vs no screening among HP positive low risk population. A total of 57,297 participants were included in the assessment of the following outcomes: dyspepsia symptom improvement,[8-10,13,22] consultation rates for dyspepsia,[8-10,21-22] ulcer incidence,[8-9] and quality of life.[8-9,13,21] The study by Bomme (2017) was an extension trial of Hansen (2008) with 13 years follow-up data, while the study by Harvey (2010), was an extension trial of Lane (2004) with 7 years follow-up data. Duration of follow-up ranged from 2 to 15 years. Studies were conducted in low-risk populations / low HP prevalence countries (Denmark and the United Kingdom).

Efficacy Outcomes

Table Q6.1. Summary of outcomes on *H. pylori* screening.

OUTCOME	NO AND TYPE OF STUDIES, PARTICIPANTS	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Incidence of gastric cancer (follow-up: 4 to 22 yrs)	7 RCTs (n=8,323)	**RR 0.55**	0.42, 0.71	**BENEFIT** 45% reduction in gastric cancer incidence with screening *(from 21 to 10 fewer cases)*	Low ⊕⊕◯◯
Deaths from gastric cancer (follow-up: 9.2 to 22 yrs)	4 RCTs (n=6,301)	**RR 0.66**	0.46, 0.95	**BENEFIT** 34% reduction in gastric cancer-related deaths with screening *(from 12 to 1 fewer deaths)*	Low ⊕⊕◯◯
Incidence of dyspepsia symptoms (follow-up: 2 to 13 yrs)	3 RCTs (n=12,218)	**RR 0.86**	0.71, 1.05	**TREND TOWARDS BENEFIT** *H. pylori* screening as good as or better than no screening *(from 60 fewer to 10 more cases with dyspepsia)*	Very Low ⊕◯◯◯
Dyspepsia consultation (follow-up: 1 to 13 yrs)	3 RCTs (n=21,737)	**RR 1.00**	0.77, 1.30	**EQUIVALENT** *H. pylori* screening as good as no screening *(from 8 fewer to 11 more dyspepsia consultations)*	Very Low ⊕◯◯◯
Incidence of peptic ulcer disease (follow-up: 13 yrs)	1 RCTs (n=12,530)	**RR 0.88**	0.71, 1.10	**EQUIVALENT** *H. pylori* screening as good as no screening *(from 8 fewer to 3 more cases with peptic ulcer)*	Very Low ⊕◯◯◯
Improvement in quality of life	5 RCTs	**Pooled effect not derived** No difference in QOL in 3 RCTs SF-36 Physical Component Score: 0.2-0.5 points SF-36 Mental Component Score 0.4-0.9 points PGWB 0.86 points		**EQUIVALENT** *H. pylori* screening as good as no screening	Low ⊕⊕◯◯

The risk in the intervention group (H. pylori screening) and its 95% confidence interval is based on the assumed risk in the comparison group (no screening) and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio.

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

Incidence of gastric cancer

Based on pooled data from 7 RCTs involving 8,323 HP-positive participants, HP eradication vs. no eradication resulted in 45% reduction in the risk of developing gastric cancer (RR 0.55 [95%CI 0.42 to 0.71]).[7,11,14-16,18,20] The level of evidence was moderate but downgraded to low due to indirectness (primarily investigates effect of eradication vs no eradication), inconsistencies in the results, and different intervention characteristics (treatment regimens, duration).

Deaths from gastric cancer

Data from 4 RCTs[7,11,12,14,20] involving 6,301 participants that investigated population-based screening and HP eradication on mortality risk from gastric cancer showed 34% reduction in the risk of dying from gastric cancer among patients who had HP eradication versus (RR 0.66 [95%CI 0.46, 0.95]). All studies involved the Asian participants. The certainty of evidence was downgraded to low due to indirectness and heterogeneity related to different intervention characteristics.

***H. pylori*-related morbidity**

Pooled estimate showed 14% reduction in dyspepsia symptom rate (RR 0.86 [95%CI 0.71 to 1.05]) with screening.[8-10,13,22] Only the study of Hansen 2008-Bomme 2017 reported ulcer incidence in mass screening, which showed a 12% lower ulcer rate among patients who had screening and eradication (RR 0.88 [95% CI 0.71 to 1.10]).[8,9] In terms of dyspepsia consultations, no significant difference was found between HP screening and no screening (RR 1.00 [95% CI 0.77 to 1.30]).[8-10,21,22] Pooled effect estimates for these outcomes were affected by imprecision in the confidence intervals.

Quality of life

Quality of life was assessed using a questionnaire (SF-36) with 8 domains, computing for the physical component summary and mental component summary. However, a pooled effect estimate could not be derived due to variations in reporting across the 3 included RCTs.[8,9,13,21] Moayyedi et al. 2001 reported the standard deviations and the perceived general well-being, Bomme et al. 2017 reported mean scores, and Wildner-Christensen et al. 2003 reported median scores.

Across all studies, there were no significant differences between screening and no screening in terms of quality-of-life scores in the short- and long-term follow-up. The mean difference in PCS scores were 0.2[8,9] and 0.5.[21] The mean difference in PGWB reported by Moayyedi was 0.86.[13]

Safety outcomes

No safety issues reported on screening using the serology, stool antigen or urea breath test. Issue with development of antibiotic resistance was evaluated in the Taipei consensus (2020) but noted inconclusive evidence on the effect of mass eradication therapy on antibiotic resistance in the community.

Certainty of evidence

The overall certainty of evidence was rated **low** to **very low** across the critical outcomes. Five studies, 4 studies in the systematic review (Choi 2020, Wong 2004, Wong 2012, You 2006-Li 2019) and the new randomized controlled trial (Wong 2022) were at low risk of bias. Two studies included in the analysis by Ford were at high risk of bias particularly on blinding and unclear outcome assessment, while one study

included in the systematic review (Saito 2005) had unclear risk of bias due to incomplete data reported. There was high risk of bias in the Danish studies (Wildner 2008, Bomme 2017) due to appropriateness of randomization due to higher rates of baseline dyspepsia rates in the screened vs the no screening arm, which could have affected the results.

The level of evidence was moderate for dyspepsia symptoms rates and quality of life but downgraded to low due to imprecision, differences in measuring outcomes, validity of randomization (higher baseline dyspepsia rates in the screened group), and inconsistencies in reporting of results. The level of certainty for dyspepsia consultation rates and ulcer incidence rates were low but further downgraded to very low due to differences in measuring outcomes, validity of randomization, inconsistencies in data, and reporting of results.

RECOMMENDATIONS FROM OTHER GROUPS

The 2022 European Helicobacter Study Group (EHSG) in Maastricht VI report emphasizes the integration of population-based *H. pylori* test-and-treat programs into healthcare priorities, especially in regions with intermediate to high gastric cancer incidence. The report suggests that such programs are cost-effective in populations with intermediate or high gastric cancer incidence, backed by a 94% agreement and a moderate level of evidence. Similarly, the 2020 Taipei Global Consensus recommends screening and eradicating *H. pylori* for gastric cancer prevention in populations with high incidence or high risk, supported by an 84% agreement and a low level of evidence. The strategy of screen-and-treat for *H. pylori* is considered most cost-effective in young adults in regions with a high incidence of gastric cancer, supported by an 84% agreement and a low level of evidence. Additionally, the second Asia-Pacific Consensus Guidelines advocate for screening and treating *H. pylori* in communities with a high incidence of gastric cancer, with 100% agreement and a level of evidence classified as IB.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No local economic evaluation studies on non-invasive tests for *H. pylori* were found. Table Q6.2 below gives current price ranges for these tests based on publicly available data from hospitals and diagnostic centers.

Table Q6.2. Price of Non-Invasive Diagnostic Tests for *H. pylori* in the Philippines.

Non-Invasive Diagnostic Test	Price (PHP)
Urea Breath Test (13C/14C)	3,700 - 11,100
Serology	295 - 5,750
Stool Antigen Test	2,200 - 2,910
EGD with histology	6,000 - 15,000

Cost-effectiveness

Nine studies, encompassing 11,926,891 participants, investigated the cost-effectiveness of *H. pylori* screening and eradication versus no screening. In high-risk populations (N=11,893,900 participants), including meta-analyses,[30] randomized controlled trials,[31] and economic simulation studies,[32] the cost analysis favored serology as the diagnostic test, showing an incremental cost-effectiveness ratio (ICER) of Php88K/QALY. The diagnostic accuracy of serology was reported at 85-93% sensitivity and 79-90% specificity. In low-risk populations (N=6 studies),[8-10,13,22,33,34] the analysis suggested that screening might not be cost-effective, with an estimated cost of Php1,000,000 per life-year saved. The evidence level was low, influenced by variations in cost analysis, health perspectives, and currency conversion without adjusting for inflation and discount rates. The findings underscore the importance of tailoring H. pylori screening strategies to the prevalence and risk of gastric cancer in specific populations.

Patient's Values And Preference, Equity, Acceptability, And Feasibility

No local studies addressing the acceptability, feasibility, and equity of *H. pylori* screening were identified. To facilitate large-scale implementation of screening and eradication programs, a multi-tiered approach has been proposed.[36] Policymakers play a crucial role in identifying feasible methods for participant identification and invitation, along with establishing effective screening and referral systems. General practitioners need proper feedback and knowledge about diagnostic tests and eradication regimens to enhance treatment outcomes. Target communities should be mobilized through risk communication and education on lifestyle habits. Patient adherence may hinge on awareness of the disease and screening purpose, as studies in China[37,38] and the United Arab Emirates[39] found poor knowledge of H. pylori in the general population, emphasizing the need for health education campaigns. Asymptomatic status and lack of knowledge about testing procedures contribute to reluctance for screening.[37]

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GUIDELINE QUESTION 7:

Should we use non-invasive tests to diagnose active *H. pylori* infection in patients with dyspepsia?

RESEARCH QUESTION: Among patients with dyspepsia, how accurate, safe and effective are non-invasive tests in diagnosing active *H. pylori* infection?

Among adults with dyspepsia without alarm signs and symptoms, we **RECOMMEND the test-and-treat strategy** in the non-invasive testing of *H. pylori* infection.

Certainty of Evidence: Low ⊕⊕◯◯
Strength of Recommendation: Strong

Among adults with dyspepsia without alarm signs and symptoms, we **RECOMMEND the use of stool antigen tests** to diagnose *H. pylori* infection.

Certainty of Evidence: Low ⊕⊕◯◯
Strength of Recommendation: Strong

Among adults with dyspepsia without alarm signs and symptoms, we **SUGGEST the use of 13C or 14C UBT** to diagnose *H. pylori* infection.

Certainty of Evidence: Low ⊕⊕◯◯
Strength of Recommendation: Weak

Among adults with dyspepsia without alarm signs and symptoms, we **SUGGEST AGAINST** the use of **serology** to diagnose *H. pylori* infection.

Certainty of Evidence: Low ⊕⊕◯◯
Strength of Recommendation: Weak

Among children with dyspepsia without alarm signs and symptoms, we **RECOMMEND AGAINST** non-invasive testing (13C/14C UBT, serology, stool antigen test) for *H. pylori* infection.

Certainty of Evidence: Low ⊕⊕◯◯
Strength of Recommendation: Strong

CONSIDERATIONS

Despite the low certainty of evidence, the consensus panel strongly recommends the stool antigen test (SAT) due to its cost-effectiveness and ease of implementation, making it a preferable option. Among the tests documenting active infection (RUT, SAT, UBT), SAT is more readily available than UBT and exhibits sensitivity comparable to the others. In cases where patients present with alarm signs and symptoms, the consensus suggests conducting endoscopy and testing for *H. pylori* using the rapid urease test (RUT).

Noninvasive testing in the pediatric population was not recommended by the consensus panel, since the presence of *H. pylori* in the pediatric population was not directly associated with risks for peptic ulcer or gastric cancer. Those who would test positive for *H. pylori,* especially if there were no alarm signs, had very low to nonexistent risk levels for peptic ulcer and gastric cancer. Most cases were noted to end up as functional abdominal pain as well. Thus, confirmatory testing through invasive tests is done only when alarm signs and symptoms are evident.

KEY FINDINGS

The guideline question is supported by evidence from 96 studies assessing the diagnostic accuracy of non-invasive tests and five randomized controlled trials comparing the effectiveness of a "test-and-treat" strategy versus endoscopy for diagnosing *H. pylori* infection in dyspeptic patients.

The findings suggest low certainty of evidence, indicating that the "test-and-treat" strategy is associated with higher *H. pylori* eradication rates than endoscopy, but without a significant advantage in improving quality of life or resolving dyspepsia symptoms.

The 13C UBT demonstrates moderate-to-high sensitivity and specificity in diagnosing *H. pylori* infection in dyspeptic patients, with similar accuracy observed in children but to a slightly lesser extent. The 14C UBT shows moderate to high sensitivity and specificity, but no specific studies for children are available. Serology is moderately to highly sensitive and specific for diagnosing *H. pylori* infection, with slightly reduced accuracy in children compared to the general population. The stool antigen test displays moderate to high sensitivity and specificity, with a similar trend observed in children but with slightly reduced accuracy.

There is a lack of direct studies assessing harm associated with these tests. Among them, 13C UBT shows the lowest false negative rates (3.3%) and false positive rates (5.7%), while serology is associated with the highest false negative rate (10.8%) and false positive rate (15.6%). In children, stool antigen tests are linked to higher false negative results at 27.9%.

Overall, the certainty of evidence for both the "test-and-treat" strategy and test accuracy is considered low.

BACKGROUND

Helicobacter pylori (H. pylori) is a Gram-negative bacterium found in the stomach, contributing to conditions like gastritis, peptic ulcers, and gastric cancer. Globally, H. pylori infection prevalence is 44.3%, higher in adults than children. In the Philippines, the prevalence is 34% in the general population and 26.5–79.9% in dyspeptic patients.[1-3] Transmission occurs through oral ingestion and direct exposure. Two diagnostic pathways for dyspepsia are upper esophagogastroduodenoscopy (EGD), which is the gold standard in diagnosis despite not always a feasible option, and the "test-and-treat" strategy, using non-endoscopy tests followed by eradication therapy if positive. *H. pylori* eradication therapy benefits symptom improvement and reduces peptic ulcer development.[5] Invasive methods (histology, culture, rapid urease test) require

endoscopy, while non-invasive tests (serology, stool antigen, urea breath test) offer alternatives, considering factors like patient condition, cost, and availability.[6,8,9] This review synthesizes evidence on the accuracy and efficacy of non-invasive tests, comparing the "test-and-treat" strategy with endoscopy for *H. pylori* diagnosis and management.

REVIEW METHODS

A comprehensive and systematic search was conducted from May 13, 2023, to July 24, 2023, using databases such as MEDLINE, Cochrane Library, and Google Scholar. The search focused on keywords related to alarm symptoms, non-invasive tests, *H. pylori*, test-and-treat, esophagogastroduodenoscopy, accuracy, sensitivity, specificity, diagnosis, adverse effects, harm, cost-effective, and cost-effectiveness. Ongoing studies were sought in NIH clinicaltrials.gov, and local studies were explored in the Health Research and Development Information Network (HERDIN). The review included studies assessing the accuracy of non-invasive tests for *H. pylori* in dyspeptic patients, encompassing both adults and children. Exclusion criteria comprised patients with specific medical histories, such as antibiotic intake, previous surgeries, or use of certain medications. Additionally, studies evaluating the benefits of non-invasive test-and-treat strategies compared to esophagogastroduodenoscopy (EGD) were included. Outcomes of interest encompassed H. pylori eradication effectiveness, symptom relief, diagnostic accuracy, side effects, and cost-effectiveness. The quality of the included studies was evaluated using tools like AMSTAR-2,[10] Cochrane ROBINS-1, and QUADAS-2,[11] while the GRADE tool assessed the overall quality of evidence and certainty. Statistical analyses, including pooled estimates and subgroup analyses, were performed using Review Manager and Meta-DiSc 2.0 software.[13]

SUMMARY OF THE EVIDENCE

Evidence Considered

The search identified 8,010 citations from various databases, leading to the retrieval of 176 articles, with 101 studies included in the review. The breakdown of studies comprised 73 cross-sectional studies, 22 prospective studies, 5 randomized controlled trials (RCTs), and 1 retrospective study. Notably, most diagnostic accuracy studies were previously featured in a 2018 high-quality review by Best et al.[14] One local study was excluded due to inaccessible content despite attempts to contact the author. The incorporated studies utilized endoscopy with histology as the reference standard for comparing non-invasive test accuracy. Among the included RCTs, five explored the outcomes of the "test-and-treat" strategy versus endoscopy in adults. Efficacy outcomes spanned *H. pylori* eradication, resolution of dyspepsia, improvement in quality of life, and cost-effectiveness. However, no similar studies were identified that enrolled children.

Efficacy Outcomes

Efficacy Outcomes of “Test-and-Treat” Strategy versus Endoscopy

Five RCTs reported on the effectiveness of “test-and-treat” strategy compared to EGD in treatment of adults with *H. pylori* infection and dyspepsia. Low certainty evidence from 1 study suggests that “test-and-treat” results in higher eradication rates than endoscopy. However, other studies showed that there appears to be no clear advantage in terms of impact on patients’ quality of life and resolution of dyspepsia symptoms.

Table Q7.1. Effectiveness of "Test-and-treat" Strategy versus Endoscopy in the Management and Diagnosis of *H. pylori* Infection

Critical Outcomes	Basis (Number of Studies; n=patients)	Results	Interpretation	Certainty of Evidence
Eradication of *H. pylori* infection	1 n=250	• "test-and-treat" group: 46/194 (23%) vs endoscopy group: 30/186 (16%) (RR 1.47 [95%CI 0.97, 2.22])[15]	Inconclusive	Low ⊕⊕◯◯
Resolution of dyspepsia	5 n=1832	• Improvement of dyspesia scores in both groups[15-19] • Better dyspepsia scores and lesser consultations to physicians in the "test-and-treat" group[15,16] • "test-and-treat" group paid more dyspepsia-related visits (3.06) vs Endoscopy group (2.28) (p=0.005)[19]	Inconclusive	Low ⊕⊕◯◯
Quality of life	3 n=874	• Improvement of quality of life on both groups with no statistically significant difference[16, 18, 19]	No significant difference	Moderate ⊕⊕⊕◯

In terms of eradicating H. pylori infection, one randomized controlled trial (RCT) indicated that 23% of patients in the "test-and-treat" group were negative for H. pylori after one month, compared to 16% in the endoscopy group, although the difference was not statistically significant (RR 1.47 [95% CI 0.97, 2.22]).[15] Regarding the resolution of dyspepsia, studies using the Glasgow dyspepsia severity scoring system demonstrated improvement in symptoms in both groups, with significantly better scores in the "test-and-treat" group according to Heaney, et al.[16] Another study by McColl, et al. showed no significant difference in the average change in dyspepsia scores between the two groups after 12 months.[17] A longer follow-up of 6.7 years by Lassen et al still showed no significant difference in alleviation of dyspepsia symptoms.[18] Duggan, et al. reported that fewer patients in the endoscopy group consulted for dyspepsia compared to the "test-and-treat" group,[15] while Arents, et al. found the opposite result with more dyspepsia-related visits in the "test-and-treat" group.[19]

In terms of quality of life, three RCTs demonstrated improvement in both groups, as measured by the SF36 health survey questionnaire, with significant improvements in physical role functioning for the "test-and-treat" group.[16,18,19] Similar results were reported by Arents, et al., noting improvement in most categories of the SF36 health questionnaire in both groups with no statistically significant differences. Long-term follow-up (up to 6.7 years) by Lassen et al revealed no significant difference in the quality of life between the groups based on the gastrointestinal symptom rating scale and psychological general well-being index.[18]

Diagnostic accuracy of non-invasive tests

Table Q7.2 summarizes the sensitivity, specificity, and likelihood ratios obtained from the different non-invasive tests in adults and children.

Table Q7.2. Diagnostic accuracy of non-invasive diagnostic tests for *H. pylori* Infection

Test accuracy	Basis (Number of Studies; n=patients)	Effect Estimates			Certainty of Evidence*
		Sn (95% CI)	Sp (95% CI)	LR+/LR-	
Adults					
13C UBT	38 n=5123	**96.7%** (93.9 - 98.2%)	**94.3%** (91.5 - 96.2%)	16.694/0.035	Low ⊕⊕◯◯
14C UBT	20 n=1837	**92.5%** (89.3 - 94.8%)	**92.8%** (89.4 - 95.1%)	12.834/0.081	Low ⊕⊕◯◯
Serology	31 n=4255	**89.2%** (84.1 - 92.8%)	**84.4%** (79.1 - 88.5%)	5.715/0.128	Low ⊕⊕◯◯
Stool antigen test	28 n=3294	**83.1%** (76.2 - 88.3%)	**91.6%** (86.3 - 94.9%)	9.873/0.184	Low ⊕⊕◯◯
Children					
13C UBT	7 n=809	**94.2%** (85.3 - 97.6%)	**93.5%** (85.8 - 97.1.%)	14.444/0.062	Low ⊕⊕◯◯
Serology	8 n=522	**88.2%** (81.7 - 92.6%)	**83.0%** (71.1 - 90.7%)	5.192/0.143	Low ⊕⊕◯◯
Stool antigen test	5 n=429	**72.1%** (42.8 - 89.9%)	**94.5%** (65.7 - 99.4%)	13.209/0.295	Low ⊕⊕◯◯

The accuracy of the 13C urea breath test (UBT) was evaluated by 38 studies, revealing a high sensitivity of 96.7% and a high specificity of 94.3%. The positive likelihood ratio (LR+) was 16.96, and the negative likelihood ratio (LR-) was 0.04. Subgroup analysis for children, based on seven studies, indicated a high sensitivity of 94.2% and a high specificity of 93.5%.[20-58]
For the 14C UBT, 20 studies demonstrated a high sensitivity of 92.5% and a high specificity of 92.8%. No significant heterogeneity was found. There were no studies evaluating 14C UBT among children.[59-77]

The accuracy of serology, assessed by 31 studies, showed a high sensitivity of 89.2% and a high specificity of 84.4%. In children, eight studies demonstrated high sensitivity (88.2%) and high specificity (83.0%).[23, 25, 30, 46, 48, 51, 53, 57, 66, 71, 78-97]

Stool antigen test, evaluated by 28 studies, showed a high sensitivity of 83.1% and a high specificity of 91.6%.[20, 36, 38, 43, 53, 58, 78, 81, 95, 98-115] Subgroup analysis for children, based on five studies, revealed a moderate sensitivity of 72.1% and high specificity of 94.5%.

Safety outcomes

There were no direct studies assessing the adverse effects or harm associated with non-invasive *H. pylori* tests. To indirectly evaluate potential harm, the review computed pooled false positive rates (FPR) and false negative rates (FNR) for the tests. False positives may lead to unnecessary medication prescription (overtreatment), while false negatives may result in untreated *H. pylori* infection and complications (undertreatment).

Table Q7.3 summarizes estimated FNR and FPR based on the studies. The 13C urea breath test (UBT) showed the lowest FNR (3.3%) and FPR (5.7%), followed by stool antigen test and 14C UBT. Serology had the highest FNR (10.8%) and FPR (15.6%). In children, stool antigen tests had a higher false negative rate (27.9%) than 13C UBT (5.8%) and serology (11.8%). These findings emphasize the importance of considering misdiagnosis risks in clinical decision-making.

Table Q7.3. False negative and false positive results of non-invasive diagnostic tests for *H. pylori* infection

Critical Outcomes	Basis (Number of Studies; n=patients)	Effect Estimate		Certainty of Evidence
		False negative (95%CI)	False positive (95%CI)	
Adults				
13C UBT	38 n=5123	**3.3%** (1.8 - 6.1%)	**5.7%** (3.8 - 8.5%)	**Low** ⨁⨁◯◯
14C UBT	20 n=1837	**7.5%** (5.2 - 10.7%)	**7.2%** (4.9 - 10.6%)	**Low** ⨁⨁◯◯
Serology	31 n=4255	**10.8%** (7.6 - 15.9%)	**15.6%** **(**11.5 - 20.9%)	**Low** ⨁⨁◯◯
Stool antigen test	28 n=3294	**6.9%** (11.7 - 23.8%)	**8.4%** (5.1 - 13.7%)	**Low** ⨁⨁◯◯
Children				
13C UBT	7 n=809	**5.8%** (2.4 - 14.7%)	**6.5%** (2.9 - 14.2%)	**Low** ⨁⨁◯◯
Serology	8 n=522	**11.8%** (7.4 - 18.3%)	**17.0%** (9.3 - 28.9%)	**Low** ⨁⨁◯◯
Stool antigen test	5 n=429	**27.9%** (10.1 - 57.2%)	**5.5%** (0.6 - 34.3%)	**Low** ⨁⨁◯◯

*Certainty ratings represent our level of confidence in the given estimates of test accuracy (e.g., high sensitivity, poor specificity, etc.). *CI*, confidence interval.

Certainty of Evidence

The overall certainty of evidence for diagnostic accuracy was rated **low** for all tests due to serious risk of bias and inconsistency. Most of the included studies had unclear or high risk of bias from patient selection (e.g., did not include a consecutive or random sample of participants), index test (unclear if index tests were interpreted without knowledge of biopsy results and using pre-specified thresholds), and flow and timing (unclear interval between conduct of the index test and reference standard).

RECOMMENDATIONS FROM OTHER GROUPS

Various international groups have formulated recommendations regarding non-invasive diagnostic tests for *H. pylori* infection, with some endorsing the use of UBT, serology, and stool antigen tests. In Taiwan, the urea breath test (UBT) and stool antigen test (SAT) are recommended for accurately detecting *H. pylori* infection. The UBT is preferred for patients with bleeding peptic ulcers. The European Helicobacter and Microbiota Study Group suggests using serological tests with high accuracy for non-invasive *H. pylori* diagnosis. The urea breath test is the best option for confirming eradication, and monoclonal SAT is an alternative. The World Gastroenterology Organisation recommends non-invasive tests when endoscopy is not required or available.

For children, the ESPGHAN and NASPGHAN strongly **recommend against** antibody-based tests (IgG, IgA) for H. pylori in various bodily fluids. Citing low sensitivity in children aged 2-6 years (44%), sensitivity improves to 77% in ages 7-11 years and 93% in adolescents. (On the other hand, the Japanese Society for Pediatric Gastroenterology recommends the 13C-urea breath test and stool antigen test as strong diagnostic options for active *H. pylori* infection. They advise against using anti-*H. pylori* antibodies as single diagnostic tests. For a more accurate diagnosis, they recommend using more than two tests, such as a combination of breath test and stool test or a biopsy-based and non-invasive test.

The 2017 ACG Guidelines and the Maastricht Consensus strongly recommend a test-and-treat strategy for adults but do not extend the same recommendation to children.[120,122]

According to the Maastricht V/Florence Consensus, a test-and-treat strategy is appropriate for uninvestigated dyspepsia, dependent on regional H. pylori prevalence and cost-benefit factors. This approach is not suitable for patients with alarm symptoms or older individuals.

ESPGHAN-NASPGHAN strongly advises against a "test-and-treat" strategy for H. pylori infection in children due to limited evidence, despite unanimous expert agreement. Similarly, JSPGHAN discourages the use of this approach in asymptomatic children to prevent gastric cancer, supported by evidence at level C and full expert consensus. Additionally, JSPGHAN recommends against employing a "test-and-treat" strategy in asymptomatic children residing with an H. pylori-infected adult who underwent eradication therapy to prevent reinfection, with evidence at level B and unanimous expert agreement, though the strength of this recommendation is considered weak.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No local economic evaluation studies on non-invasive tests for *H. pylori* were found. Table Q7.4 below gives current price ranges for these tests based on publicly available data from hospitals and diagnostic centers.

Table Q7.4. Price of Non-Invasive Diagnostic Tests for *H. pylori* in the Philippines.

Non-Invasive Diagnostic Test	Price (PHP)
Urea Breath Test (13C/14C)	3,700 - 11,100
Serology	295 - 5,750
Stool Antigen Test	2,200 - 2,910
EGD with histology	6,000 - 15,000

Cost-effectiveness

Analyzing the cost-effectiveness of the "test-and-treat" strategy versus direct endoscopy, Duggan, et al. found that the "test-and-treat" approach is most effective across a broad range of endoscopy costs and willingness-to-pay thresholds, specifically if the willingness to pay exceeds GBP 500 / PHP 35,954 but remains below GBP 2,000 / PHP 143,817.[15] In terms of non-invasive diagnostic tests, Holmes, et al. conducted a cost-effectiveness analysis, revealing that the incremental cost-effectiveness ratios of the urea

breath test (UBT), serology, and stool antigen test were similar to an empiric trial of proton pump inhibitor among patients with uninvestigated dyspepsia.[123] In the United States, a study by Vakil, et al. on non-invasive *H. pylori* testing methods in children with dyspepsia showed that the UBT was significantly more expensive compared to other diagnostic tests such as endoscopy and serology. The incremental cost of 13C UBT and serology compared to endoscopy was USD 126 and USD 11, respectively, with a small difference in cost-effectiveness between endoscopy and 13C UBT and serology noted.

Implementation Issues

Several factors can impact the practicality of non-invasive *H. pylori* tests in the Philippines. Serology, the most widely available and cost-effective option, cannot distinguish between past and current infections. Qualitative tests may remain positive for up to 3 years post-treatment, and quantitative levels may persist for 6 to 12 months after treatment.[126] Urea breath tests (UBT) may face availability challenges in hospitals, with limited applicability to the general population. UBT could be beneficial for patients on anticoagulants, with low platelet counts, or at high risk of cardiac complications. However, it is not recommended for children due to low specificity and sensitivity, and challenges in compliance. Despite concerns about COVID-19 transmission, precautions such as oral care screening have helped mitigate risks during UBT.[127] Patient acceptability favors UBT, with high satisfaction rates compared to endoscopy.[17] Factors influencing UBT accuracy include the presence of *Helicobacter heilmannii*, certain infections causing false positives, and recent antibiotic or bismuth compound use leading to potential false negatives.[128] Stool antigen tests are widely available and less expensive, posing fewer risks than serology. However, patient reluctance to handle stool samples may affect the test's acceptability in routine medical practice.[129]

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GUIDELINE QUESTION 8:

Should we use the 14-day triple therapy in patients with *H. pylori* infection?

RESEARCH QUESTION

Among patients with H pylori infection, how effective and safe is 14-day triple therapy compared to novel drug combinations in patients with *H. pylori* infection?

Among adults and children with *H. pylori* infection, we **SUGGEST using** the 14-day concomitant triple therapy containing clarithromycin

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Weak

Among adults with *H. pylori* infection, we **SUGGEST using** alternative regimens*.

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Weak

Among children with *H. pylori* infection, we **SUGGEST using** alternative regimens*.

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Weak

*Other regimens that were found to be more effective than 14D standard triple include the following:

- **Adults:** 14D clarithromycin-based sequential, 14D levofloxacin-based sequential, 10D bismuth-containing quadruple, 14D bismuth-containing quadruple, 7D vonoprazan-containing triple therapy
- **Children:** 14D sequential therapy, bismuth-based quadruple therapy

CONSIDERATIONS

The 14-day triple therapy is suggested for both adults and children, aligning with common practice. However, the panel lowered the strength of this recommendation due to concerns about the increasing clarithromycin resistance in the country. The certainty of evidence was reduced because local data on the actual figures of this increase was unavailable, and routine testing was not commonly performed locally, creating an information gap. The panel also aimed to provide guidance on alternative regimens, acknowledging variations for adults and children. Alternative regimens were typically reserved for retreatment and were noted to be costlier than the 14-day triple therapy. While considering the inclusion of probiotics in recommendations for children, a decision was deferred due to insufficient clinical data supporting their use.

KEY FINDINGS

Limited data on clarithromycin-resistant *H. pylori* strains in the Philippines underscores the need for current rates assessment. Two meta-analyses for adults and pediatric patients found that 14-day triple therapy had a 77% eradication rate in Asian countries, with alternative regimens showing rates above 90%. These alternatives included sequential levofloxacin-based triple therapy, modified concomitant bismuth-based quadruple therapy, and hybrid clarithromycin-based quadruple therapy, all more effective than standard triple therapy for adults. Pediatric patients on clarithromycin-based triple therapy achieved a 74.2% eradication rate, while regimens with at least 90% effectiveness included sequential therapy with probiotics, bismuth-containing quadruple therapy, PPI+clindamycin+nitroimidazoles, and concomitant therapy. Safety rankings favored probiotic-containing regimens. Certainty of evidence ranged from low to very low due to various study limitations.

BACKGROUND

The current standard for first-line H. pylori treatment involves triple therapy comprising a proton pump inhibitor (PPI), clarithromycin, and amoxicillin/metronidazole. However, due to escalating clarithromycin resistance and rising eradication therapy failure rates, alternative regimens, including levofloxacin therapy, are under exploration, particularly in regions with high clarithromycin resistance.

The 2017 American College of Gastroenterology (ACG) guidelines, recognizing a low level of evidence supporting current regimens, strongly recommend bismuth-based or levofloxacin-based therapy in the USA where antibiotic resistance is prevalent. In the Philippines, the extent of clarithromycin resistance remains uncertain, necessitating clarification of potential benefits and risks associated with maintaining these specific therapies.

This evidence summary aims to summarize current available evidence and recommendations about the safety and efficacy of a 14-day triple therapy compared to novel drug combinations in patients with *H. pylori* infection.

Definition of Terms

a. *H. pylori eradication rate.* Proportion of patients meeting criteria for cure from *H. pylori* infection.
b. *Reduction in H. pylori-related mortality*. Proportion of patients with death due to complications related to untreated/persistent *H. pylori* infection such as gastric cancer.
c. *Reduction in H. pylori-related morbidity*. Proportion of patients with persistent symptoms such as dyspepsia or other GI symptoms related to *H. pylori* infections.
d. Antibiotic resistance
e. *Low clarithromycin resistance*. Clarithromycin resistance rate of < 15%.

REVIEW METHODS

A comprehensive approach was taken to address the clinical question, involving the evaluation of existing clinical practice guidelines (CPG) through the AGREE II tool. Simultaneously, extensive literature searches were conducted on May 3, 2023 using the Ovid platform and different electronic databases, employing relevant indexing terms and variable truncations. No language restrictions were applied. The full literature search strategy executed in Ovid is outlined in Appendix Q8.1. Systematic reviews/meta-analyses published in the past six years were initially screened, followed by a search for recent primary studies, particularly clinical trials. Salvage or rescue therapies were excluded from consideration.

Furthermore, efforts were made to identify local studies on clarithromycin-resistant *H. pylori* strains, the effectiveness of triple therapy, and studies on cost/cost-effectiveness. Searches were conducted in Herdin, Acta Medica Philippina, the Philippine Journal of Gastroenterology, and the research repository of the Joint Committee on Research and Research Education (JRRE) of the Philippine Society of Gastroenterology (PSG), the Philippine Society of Digestive Endoscopy (PSDE), and the Hepatology Society of the Philippines (HSP) (https://giresearch.ph/). The Antimicrobial Resistance Surveillance Reference Laboratory (https://arsp.com.ph) was consulted for national trends in antimicrobial resistance.
Finally, ongoing trials were explored through the U.S. National Library of Medicine's ClinicalTrials.gov website using specific query parameters related to Helicobacter pylori, triple therapy, or 14-day regimens.

SUMMARY OF THE EVIDENCE

Incidence of clarithromycin-resistant H pylori strains

A recent global meta-analysis of 247 clinical studies on *H. pylori* clarithromycin resistance reported an overall pooled resistance rate of 27.53% (95% CI, 25.41% to 29.69%) based on 20,936 isolates, with notable heterogeneity. Time trend analyses indicated an increase from 24.28% (2010-2017) to 32.14% (2018-2021). An earlier southeast Asia-focused meta-analysis found primary resistance at 10%, secondary resistance at 15%, with an increasing trend from 13% (2006-2008) to 21% (2012-2016).

In a 2015 ASEAN consensus survey, the estimated prevalence of clarithromycin resistance in the Philippines was 2%.[2] A recent publication classified the Philippines as an area with low clarithromycin resistance (<5%), but data sources were unspecified. Local studies in the Philippines are limited; a 2004 study found no resistance in 14 isolates, while a more recent cohort study reported a high rate of 28.6%.[3] The latter study included patients irrespective of proton pump inhibitor exposure. Eradication rates were not available in these studies.

In the 2004 study, patients with no prior antibiotic or *H. pylori* eradication treatment showed no clarithromycin resistance. In contrast, a more recent study revealed high resistance rates across different isolation sites, with no socioeconomic details provided. The absence of clarithromycin resistance in the 2004 study was attributed to patients' challenges in affording antibiotics, (i.e., 70% *H. pylori* patients were unemployed with average incomes below the poverty line) while socioeconomic profiles were not consistently presented in the more recent studies, limiting insights into resistance factors.[4]

Evidence Considered

Evidence regarding the effectiveness of 14-day triple therapy were based on 3 recent systematic reviews with network meta-analyses.[6-8]

For adults, data from the 2022 NMA by Zamani et al. were extracted, including 25 randomized controlled trials (RCTs) out of a total of 121 involving treatment-naive adult patients (n=34,759) diagnosed with *H. pylori* infection through molecular methods (e.g., 13 or 14C-UBT, histology, rapid urease test) but not serology.[8] The primary outcome was the eradication rate, assessed at least 4 weeks after completing treatment. Efficacy estimates were presented as risk ratios (RR) with 95% credible intervals (CrI), where RR > 1 indicated a significant benefit compared to triple therapy.

For children, data from the 2023 NMA by Liang et al. were utilized.[6] This review included a total of 163 RCTs involving pediatric patients (n = 18,257) diagnosed with *H. pylori* infection through various methods. Among these, 132 RCTs directly compared clarithromycin-based triple therapy. The primary outcome was

the eradication rate, assessed at least 2 weeks after treatment. Regimens by duration (e.g., 7-day, 10-day, or 14-day) were not distinguished at the time of writing. Effect estimates were expressed as odds ratios (ORs) with 95% confidence intervals for pairwise analysis, and treatments were ranked based on efficacy and safety using surface under the cumulative ranking (SUCRA) values, where higher values indicated superiority.

Efficacy outcomes

In Asia, the estimated overall eradication rate for 14-day triple therapy against H. pylori was **77% (95% CrI 72.8 to 81.2%)**.[8] Notably, treatment regimens with eradication rates exceeding 90% included **sequential levofloxacin-based triple therapy** (98.7% [88.9 to 100%]), **modified concomitant bismuth-based quadruple therapy** (93.1% [84.0 to 100%]), and **hybrid clarithromycin-based quadruple therapy** (90.3% [84.0 to 97.3%]).

Three unpublished local studies (two randomized controlled trials and one prospective cohort) assessed the success rate of *H. pylori* treatment using standard 14-day triple therapy with omeprazole (40 mg BID), clarithromycin (500 mg BID), and amoxicillin (1 g BID).[9-11] The pooled estimate for eradication rate was 77% (95% CI, 66 to 86%), demonstrating significant variability across studies (I2 = 83.7%, P<0.001).

Comparisons between 14-day triple therapy and other regimens were made using the network meta-analysis by Zamani et al.[8] The following regimens showed higher effectiveness in eradicating *H. pylori*: 14-day clarithromycin-based sequential therapy, 14-day levofloxacin-based sequential therapy, and bismuth-containing quadruple therapy (Table Q8.1). While no significant differences were observed between 14-day standard triple therapy and certain alternative regimens, the **14-day triple therapy was superior to 7-day triple therapy** (78.2% vs. 69.0%) based on **low** certainty evidence, and there was very low certainty evidence suggesting the superiority of 14-day over 10-day therapy (70.7% vs. 65.5%).

For children, the overall eradication rate of clarithromycin-based triple therapy was **74.2% (95% CI, 71.4 to 76.9%)**. Regimens with at least a 90% eradication rate included **sequential therapy with probiotics** (93.2% [95% CI, 89.7 to 96.8%]), **bismuth-containing quadruple therapy** (93.2% [95% CI, 91.3 to 95.1%]), PPI+clindamycin+nitroimidazoles (90.9% [95% CI, 88.3 to 93.5%]), and **concomitant therapy** (90% [95% CI, 81.7 to 98.3%]).[6] Clarithromycin-based triple therapy was significantly better than some regimens, while others showed no significant differences in terms of effectiveness (Table Q8.2). Probiotic-containing therapies, sequential therapy, and the combination of PPI, amoxicillin, and nitrofuran drugs achieved better cure rates compared to clarithromycin-containing triple therapy (Appendix Table Q8.7.4).[6]

Safety outcomes

In adults, data from 59 randomized controlled trials (RCTs) reviewed by Zamani et al. involving 8,600 participants indicated that most regimens had similar risks for causing adverse effects leading to treatment withdrawal.[8] Compared to 14-day triple therapy, only two regimens were associated with a significantly higher risk of adverse events: concomitant clarithromycin-based quadruple therapy for 14 days (RR 2.72 [95%CrI 1.05 to 7.03]) and 10 days (RR 1.92 [95%CrI 1.01 to 3.59]) (Appendix Table Q8.7.1).

As for pediatric patients, data on adverse event rates from 116 studies reviewed by Liang et al. for safety outcomes are not available. The total side effects rate was used as the safety evaluation index, and probiotic-containing regimens, specifically sequential therapy with probiotics (SUCRA 98.5%) and triple therapy with probiotics (SUCRA 85.9%), ranked the highest. In contrast, clarithromycin-based triple therapy ranked 7th (SUCRA 37.8%) among the 10 eradication regimens (Appendix Table Q8.7.2).

Table Q8.1. Effectiveness of different treatment regimens compared to 14-day clarithromycin-containing triple therapy in terms of cure rates in adult patients.

OUTCOME	BASIS (No and Type Of Studies, Total Participants)	EFFECT ESTIMATE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Eradication rate					
14-day clarithromycin-based sequential therapy	3 RCTs (n=869)	RR 1.13	1.01, 1.25	**Better than 14-day triple** (from 9 to 217 more cases with cure)	**Low** ⊕⊕◯◯
14-day levofloxacin-based sequential therapy	3 RCTs (n=543)	RR 1.33	1.22, 1.46	**Better than 14-day triple** (from 191 to 399 more cases with cure)	**Low** ⊕⊕◯◯
10-day bismuth-containing quadruple therapy	1 RCT (n=1,080)	RR 1.73	1.25, 2.38	**Better than 14-day triple** (from 226 to 1000 more cases with cure)	**Low** ⊕⊕◯◯
14-day bismuth-containing quadruple therapy	1 RCT (n=270)	RR 1.28	1.06, 1.54	**Better than 14-day triple** (from 36 to 320 more cases with cure	**Low** ⊕⊕◯◯
7-day vonoprazan-containing triple therapy*	3 RCTs (n=791)	RR 1.21	1.11, 1.30	**Better than 14-day triple** (from 82 to 224 more cases with cure)	**Low** ⊕⊕◯◯
10-day clarithromycin-based sequential therapy	11 RCTs (n=3,690)	RR 1.04	0.98, 1.09	**Equivalent with 14-day triple** (from 16 fewer to 74 more cases with cure)	**Very Low** ⊕◯◯◯
7-day modified bismuth-containing quadruple therapy	1 RCT (n=243)	RR 0.65	0.35, 1.22	**Equivalent with 14-day triple** (from 536 fewer to 181 more cases with cure)	**Very Low** ⊕◯◯◯
14-day modified bismuth-containing quadruple therapy	1 RCT (n=200)	RR 1.32	0.88, 1.98	**Equivalent with 14-day triple** (from 86 fewer to 706 more cases with cure)	**Low** ⊕⊕◯◯
7-day clarithromycin-based triple therapy	8 RCTs (n=1,763)	RR 0.88	0.83, 0.94	**Not better than 14-day triple** (from 117 to 41 fewer cases with cure)	**Low** ⊕⊕◯◯
10-day clarithromycin-based triple therapy	2 RCTs (n=365)	RR 0.93	0.83, 1.02	**Not better than or equivalent with 14-day triple** (from 111 fewer to 13 more cases with cure)	**Very Low** ⊕◯◯◯

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CrI).**CrI:** credible interval; **OR:** odds ratio; **RR:** risk ratio; **HR:** hazards ratio.
* Effect estimates derived from studies comparing vonoprazan regimen with 7-day triple

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

Table Q8.2. Effectiveness of different treatment regimens compared to clarithromycin-containing triple therapy in terms of cure rates in pediatric patients.

OUTCOME	BASIS (No and Type Of Studies, Total Participants)	EFFECT ESTIMATE*	95% CrI	INTERPRETATION	CERTAINTY OF EVIDENCE
Eradication rate					
bismuth-containing quadruple therapy	26 RCT (n=2,395)	OR 0.25	0.19, 0.32	**Better than triple therapy**	**Low** ⊕⊕◯◯
concomitant therapy	1 RCT (n=101)	OR 2.99*	0.86, 11.94	**Better than triple therapy**	**Very Low** ⊕◯◯◯
sequential therapy	35 RCTs (n=3,680)	OR 0.37	0.30, 0.46	**Better than triple therapy**	**Low** ⊕⊕◯◯
sequential therapy with probiotics	1 RCT (n=209)	OR 0.19	0.08, 0.41	**Better than triple therapy**	**Very Low** ⊕◯◯◯
triple therapy with probiotics	53 RCTs (n=6,183)	OR 0.31	0.26, 0.37	**Better than triple therapy**	**Low** ⊕⊕◯◯
PPI, amoxicillin and nitrofuran drugs	2 RCTs (n=250)	OR 0.55	0.27, 1.11	**As good as triple therapy**	**Very Low** ⊕◯◯◯
PPI, clindamycin and nitroimidazoles	1 RCT (n=95)	OR 0.86	0.56, 1.29	**As good as triple therapy**	**Very Low** ⊕◯◯◯
PPI, amoxicillin and nitroimidazoles	18 RCTs (n=2535)	OR 2.56	1.95, 3.38	**Not better than triple therapy**	**Low** ⊕⊕◯◯
PPI, amoxicillin and nitroimidazoles	18 RCTs (n=2535)	OR 2.56	1.95, 3.38	**Not better than triple therapy**	**Low** ⊕⊕◯◯

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio.

NOTE: The ORs (95% CIs) were lifted from the league comparison table/chart which presents the results of the network meta-analysis by Liang et al. The columns (H pylori regimens) are read from left to right; where an OR > 1 signifies that the top left regimen is better in comparison.

GRADE Working Group Certainty of Evidence

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

Certainty of evidence

For the subgroup analysis in adults, certainty of evidence across different treatment comparisons ranged from low to very low due to a serious risk of bias, with 20-40% of the included studies exhibiting issues related to deviations in intended interventions or missing outcome data. Additionally, since the studies were conducted outside the Philippines, the certainty of evidence was further downgraded for indirectness.

RECOMMENDATIONS FROM OTHER GROUPS

International or local clinical guidelines and consensus reports typically recommend clarithromycin-containing triple therapy as the primary treatment for *H. pylori* infection for a duration of 14 days in areas with low clarithromycin resistance. However, alternative eradication regimens are suggested if clarithromycin resistance is known or observed.

The treatment recommendations for *H. pylori* infection vary across clinical guidelines and depend on the resistance status. In areas with low clarithromycin resistance, **bismuth quadruple therap**y or **clarithromycin-containing triple therapy** is suggested as the first-line empirical treatment, with a treatment duration of 14 days. The American College of Gastroenterology proposes multiple regimens, including Clarithromycin-Based Triple Therapy, emphasizing local resistance rates, and the Canadian guidelines favor 14-day Concomitant Non-Bismuth Quadruple Therapy as a primary option, suggesting PPI triple therapy in areas with low clarithromycin resistance. For standard triple therapy, involving a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole, the duration is also 14 days. The European Helicobacter and Microbiota Study Group *suggests* **Bismuth Quadruple Therapy or Non-Bismuth Concomitant Quadruple Therapy**, emphasizing bismuth therapy in areas with high or unknown clarithromycin resistance.[12] Additionally, various sequential, concomitant, and hybrid therapies, including levofloxacin and fluoroquinolone-based regimens, are outlined with different durations based on specific protocols. The Korean College of Helicobacter Research *recommends* a **14-day course of Clarithromycin-Containing Triple Therapy** as the first-line treatment, with various options such as standard triple, sequential, and concomitant therapy.

The Japanese Society for Pediatric Gastroenterology *suggests* a **proton pump inhibitor (PPI)-based triple regimen with amoxicillin and clarithromycin** as the first-line therapy for *H. pylori* infection when strains are susceptible to clarithromycin or susceptibility is unknown. In cases of clarithromycin resistance, they *recommend* a **PPI-based triple regimen with amoxicillin and metronidazole**. The use of probiotics for improving eradication rates is deemed **unclear**, but they acknowledge its effectiveness in preventing side effects like diarrhea.

On the other hand, the European Society for Paediatric Gastroenterology and North American Society for Pediatric Gastroenterology provide a range of first-line therapy options for *H. pylori* infection. This includes **14-day clarithromycin-based triple therapy**, **PPI + amoxicillin + metronidazole**, or **bismuth-based regimens**. The strength of their recommendation is **strong**, with moderate to low quality of evidence for suggested regimens and low quality for duration. The guideline emphasizes consensus on the listed regimens as first-line therapy. (*Table 2 in the Joint ESPGHAN and NASPGHAN guidelines)*

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

There were no local economic evaluation studies found on the various treatment regimens for *H. pylori*. Table Q8.3 reflects the 2023 Drug Price Reference Index (DPRI) as available for the listed drugs below, while Table Q8.4 displays the publicly available data on retail prices for select drugs as of October 2023.

Table Q8.3. 2023 Drug Price Reference Index in the Philippines

Drug name	2023 DPRI*		
	Lowest	Median	Highest
Proton pump inhibitors			
Lansoprazole			
30 mg capsule	15.70	22.00	28.00
Omeprazole			
20 mg capsule	0.68	0.78	14.00
40 mg capsule	2.55	3.89	48.00
40 mg powder for injection vial + 10 mL solvent	3.14	20.50	240.00
Pantoprazole			
40 mg tablet	7.50	10.00	18.00
Antibiotics			
Amoxicillin			
500 mg capsule	1.06	1.38	4.00
100 mg/mL, 15 mL oral drops	16.50	18.08	22.00
250 mg/5 mL, 60 mL oral suspension	17.00	22.00	90.00
Clarithromycin			
125 mg/5 mL, 50 ml oral suspension bottle	88.00	140.00	220.00
250 mg/5 mL, 50 ml oral suspension bottle	380.00	547.50	663.00
500 mg tablet	6.00	10.50	36.50
Clindamycin			
150 mg capsule	3.00	5.20	6.50
300 mg capsule	4.00	5.00	35.00
150 mg/mL, 2 mL solution for injection ampule	45.00	70.57	198.00
150 mg/mL, 4 mL solution for injection ampule	38.79	52.89	370.00
75 mg/5 mL, 60 mL oral suspension bottle	437.94	455.88	473.82
Levofloxacin			
500 mg tablet	3.48	5.63	42.00
750 mg tablet	10.29	12.89	62.00
5 mg/mL, 100 mL solution for injection vial	63.22	79.13	935.00
5 mg/mL, 150 mL solution for injection vial	507.31	625.00	894.27
Metronidazole			
500 mg Tablet	0.91	1.30	15.00
125 mg/5 mL, 60 mL oral suspension bottle	18.50	22.00	60.00
5 mg/mL, 100 mL solution for injection vial	10.44	13.00	79.86

*Reflects acquisition costs including landed cost, packaging, drug content, quality assurance, manufacturing overheads, and Food and Drug Administration (FDA) fees. It is computed based on the prevailing public tender prices of the previous year reflected in the actual Purchase Orders (POs) submitted by the DOH Retained Hospitals, RHOs, Central Office Bids and Awards Committee (COBAC) and Philippine International Trading Corporation (PITC) Pharma Inc. (PPI) to the DOH. Only data coming from reputable suppliers are considered in the database.

Table Q8.4. 2023 Retail prices in the Philippines

Drug Name	Retail Price
Proton pump inhibitors	
Dexlansoprazole	
30 mg capsule	94.50
60 mg capsule	119.00
Esomeprazole	
20 mg tablet	40.75 - 136.50
40 mg tablet	55.50 - 157.00
Lansoprazole	
15 mg tablet	68.00
20 mg capsule	35.00
30 mg capsule	38.00 - 94.50
60 mg capsule	119.00
30 mg powder for injection	984.00
Omeprazole	
10 mg capsule	37.00
20 mg capsule	12.00 - 49.75
40 mg capsule	25.00 - 73.25
40 mg powder for injection vial	485.00 - 801.00
Pantoprazole	
20 mg tablet	80.00
40 mg tablet	39.75 - 116.00
40 mg power for injection vial	675 - 1,088.50
Rabeprazole	
10 mg tablet	79.00
20 mg tablet	26.00 - 105.75
Potassium-competitive acid blocker	
Vonoprazan	
10 mg film-coated tablet	126.00
20 mg film-coated tablet	138.50
Antibiotics	
Amoxicillin	
250 mg capsule	5.50 - 9.00
500 mg capsule	5.40 - 18.00
100 mg/mL, 10 mL oral drops	84.50 - 93.25
100 mg/mL, 15 mL oral drops	
100 mg/mL, 20 mL oral drops	131.00
125 mg/5 mL, 60 mL oral suspension	108.50
125 mg/5 mL, 105 mL oral suspension	129.75
250 mg/5 mL, 105 mL oral suspension	157.50 - 173.75
250 mg/5 mL, 60 mL oral suspension	100.90 - 160.00
Clarithromycin	
125 mg, 25 ml oral suspension	528.00
125 mg/5 mL, 25 ml granules for suspension	290.50
125 mg/5 mL, 35 ml oral suspension bottle	414.75
125 mg/5 mL, 50 ml oral suspension bottle	871.00
125 mg/5 mL, 70 ml oral suspension bottle	676.00 - 937.00
250 mg/5 mL, 25 ml oral suspension bottle	687.00
250 mg/5 mL, 35 ml oral suspension bottle	620.00
250 mg/5 mL, 50 ml oral suspension bottle	679.00 - 1,442.00
250 mg/5 mL, 70 ml oral suspension bottle	1,050.75 - 1,200.00
250 mg tablet	48.75 - 127.25
500 mg tablet	48.25 - 261.00

Drug Name	Retail Price
Clindamycin	
150 mg capsule	21.00 - 76.00
300 mg capsule	27.00 - 110.25
150 mg/mL, 2 mL solution for injection ampule	375.00 - 464.75
150 mg/mL, 4 mL solution for injection ampule	895.00 - 1,874.00
75 mg/5 mL, 60 mL granules for oral solution	699.75
Levofloxacin	
500 mg tablet	40.20 – 226.00
750 mg tablet	95.00 - 295.00
5 mg/mL, 100 mL solution for injection vial	1,836.75
5 mg/mL, 150 mL solution for injection vial	1,780.75
250 mg/5 mL, 50 ML solution for infusion	891.50
Metronidazole	
500 mg Tablet	14.00 - 47.00
25 mg/mL, 60 mL suspension	125.50
125 mg/5 mL, 60 mL oral suspension bottle	151.75
500 mg/100 mL vial	286.50

Patient's Values And Preference, Equity, Acceptability, And Feasibility

Selecting the optimal first-line therapy for *H. pylori* infection is intricate due to evolving antibiotic resistance and varied cure rate thresholds. While the World Gastroenterology Organization proposes ≥80% eradication,[19] others advocate ≥90%.[12,20] The efficacy of clarithromycin-containing regimens diminishes with clarithromycin resistance, yet local data on resistance rates is lacking.[21] Success hinges on patient adherence and economic factors. In the Philippines, antibiotic self-medication ranges from 31% to 66%, with shared antibiotics linked to misconceptions and concerns. These challenges underscore the complexity of achieving successful H. pylori eradication and highlight the need for more comprehensive local data.[22]

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GUIDELINE QUESTION 9:

Should we use confirmatory tests to decrease incidence of gastric cancer in patients who completed eradication treatment?

RESEARCH QUESTION: Among patients who completed eradication treatment for *H. pylori*, how effective is confirmatory testing (urea breath test, stool antigen test) compared to no testing in decreasing incidence of gastric cancer, *H. pylori* related morbidity, and drug resistance rates?

Good Practice Statements:

- In adults and children who completed eradication treatment for H. pylori infection, clinicians should consider doing tests of cure using urea breath test or stool antigen test to confirm eradication of *H. pylori.*
- Biopsy-based testing for cure may be considered only if there are other indications for a repeat EGD.
- Tests of cure should be done at least 4 weeks after the completion of antibiotic therapy and after proton pump inhibitor (PPI) therapy has been withheld for 1-2 weeks.

CONSIDERATIONS

In the absence of direct evidence, the consensus adopted an approach involving a detailed analysis of the question and the synthesis of available information to construct a good practice statement. Emphasis was placed on the importance of timing, discouraging retesting for those with negative results but advocating it for positive results both before and after treatment. Once a negative outcome is achieved, retesting is considered unnecessary unless symptoms resurface. Challenges related to logistics, particularly costs and test availability, were notable, especially in provincial areas. The decision to consolidate pediatric and adult statements was justified by the non-practice of test-and-treat in pediatrics due to non-standardized UBT tests and the absence of routine stool antigen tests in the Philippines. Nonetheless, the imperative for local studies and eradication therapy was emphasized.

KEY FINDINGS

No direct evidence was found comparing confirmatory testing against no testing for *H. pylori* eradication therapy outcomes, but the consensus suggests that confirmatory testing may bring overall benefit based on indirect evidence. Confirmatory testing becomes crucial in identifying treatment failure, enabling retreatment, and potentially reducing gastric cancer incidence and mortality, as eradication of *H. pylori* has demonstrated these benefits. High failure rates in local data (23%) emphasize the importance of identifying such cases in the Philippines. A negative confirmatory test aids in considering alternative diagnoses for persistently symptomatic patients. The optimal test or testing interval remains unclear, but urea breath test, monoclonal stool antigen test, and endoscopic-based tests are all highly sensitive and specific. In pediatrics, ELISA-based stool antigen tests show superior accuracy. In terms of timing of testing, the accuracy is optimized with testing delayed at least 4 weeks post-antibiotic therapy and 1-2 weeks off proton pump inhibitors. Test of cure has demonstrated cost-effectiveness in preventing *H. pylori* complications, especially in gastric ulcer bleeding, in other countries.

BACKGROUND

Eradication of *H. pylori* is crucial for reducing gastric cancer risk.[1] However, persistent infection after treatment is common and increasing failure rates have been reported.[5] Tests of cure or testing to confirm eradication after completing eradication therapy is recommended by most guidelines.[2,3,4] However, these recommendations are mostly intuitive.[2,5] Routine documentation is lacking locally unless patients revisit for other reasons or persistent symptoms. The impact of documenting *H. pylori* eradication on patient outcomes remains uncertain. Determining the optimal test, cut-off values, and testing intervals is necessary for effective post-treatment assessment. Clarifying these aspects could enhance the management of *H. pylori* infection and contribute to improved patient outcomes.

REVIEW METHODS

A systematic search was done on March 28, 2023 (updated on July 22, 2023) on electronic databases MEDLINE, Cochrane Library, and Google Scholar. A combination of keywords and free text search related to *Helicobacter pylori*, eradication, gastric cancer, resistance, and test of cure were used. For local studies, HERDIN was searched using the search term *Helicobacter pylori*. The repository of the Joint Committee on Research and Research Education of the Philippine Society of Gastroenterology, Philippine Society of Digestive Endoscopy and Hepatology Society of the Philippines (https://giresearch.ph/) was also searched for unpublished local studies. References of relevant CPGs and publications were also screened for potential inclusion in the review. Additional hand searching of references was also done.

To assess if doing confirmatory testing offers net benefit, we aimed to include studies that reported on the impact of any non-invasive diagnostic test for confirming eradication of *H. pylori t*esting compared to no testing on clinical outcomes (e.g., reduction of gastric cancer rates). To answer the question regarding which test to use and when to test, we also looked for studies comparing various confirmatory testing strategies (e.g., UBT vs. SAT) or timing intervals (e.g., 4 weeks vs. 8 weeks post-treatment). Eligible study designs were randomized controlled trials (RCTs), non-randomized trials, cohort, or cross-sectional studies.

SUMMARY OF THE EVIDENCE

Evidence Considered

No evidence was found directly comparing confirmatory testing (using any test) versus no testing in terms of how it affected the outcomes of interest (e.g. reduction in gastric cancer cases, reduction in *H. pylori* related symptoms). Similarly, there were no studies that specifically compared different testing strategies (e.g., UBT vs. SAT, UBT at 4 weeks vs. UBT at 8 weeks).

Since no direct evidence was found, a synthesis of indirect evidence from 38 studies to inform this guideline recommendation was done. These studies encompassed research into the effect of *H. pylori* eradication on reducing gastric cancer risk (n=2), estimates of failure rates associated with *H. pylori* eradication therapy in the Philippines (n=3), studies cited by other clinical practice guidelines justifying their recommendations (n=3), and studies summarizing the accuracy of *H. pylori* testing for detecting persistent infection post-treatment among adult or pediatric patients, including factors influencing test accuracy (e.g., PPI use, antibiotic treatment) (n=30).

Efficacy outcomes

Confirmatory testing for *H. pylori* eradication may indirectly impact the reduction of gastric cancer cases, as eradication itself has been linked to decreased gastric cancer incidence and mortality.[1] Although no direct studies specifically attribute testing of cure to reduced gastric cancer cases, the identification of persistent infection through confirmatory testing allows for appropriate retreatment. Local data from three studies revealed a higher failure rate of 23% with standard triple therapy in the Philippines, exceeding rates documented in other countries.[6-8]

In adults, both urea breath test (UBT) and stool antigen test (SAT) demonstrated high accuracy for detecting persistent *H. pylori* infection, with UBT showing a sensitivity of 94% and specificity of 100%, and SAT exhibiting a sensitivity of 94% and specificity of 97%.[31] However, SAT accuracy may decrease with proton pump inhibitor (PPI) use and active bleeding.[37]

In the pediatric population, a review of 20 studies, mainly conducted in Japan, assessed the accuracy of various diagnostic tests to confirm *H. pylori* eradication, as outlined in the 2020 Japanese Society for Pediatric Gastroenterology, Hepatology, and Nutrition (JSPGHAN) guidelines.[11-30] According to the findings, urea breath test (UBT) and stool antigen test (SAT) demonstrated substantial accuracy, ranging from 94.1% to 100% for UBT and 86.7% to 100% for SAT ELISA.[10] These tests serve as robust evidence of the success of eradication therapy in children. On the other hand, serology exhibited moderate sensitivity (70.6%) and poor specificity (32.1%). For a comprehensive overview of test accuracy estimates, refer to Table Q9.1 below.

Table Q9.1. Diagnostic accuracy of various tests for confirming *H. pylori* eradication.

Type of test	Test	Sensitivity	Specificity
Children*			
Non invasive	13C-UBT [12, 16-20]	94.1-97.6%	92.3-98.8%
	14C-UBT [21]	100%	100%
	Polyclonal SAT ELISA [14-16, 20, 22-27]	86.7-100%	97.5-98.1%
	Monoclonal SAT ELISA [13, 14, 28-30]	95.6%	95.1-95.8%
	SAT IC [11, 21, 25, 28, 29]	60-75%	96.3-100%
	Anti-*H. pylori* IgG [13, 20]	77.8%	32.1%
Invasive	Culture method [12]	70.6%	100%
	Histological examination[12]	100%	92.3%
Adults**			
Non invasive	^{13}C-UBT[13] Or ^{14}C-UBT [31]	94%	100%
	SAT IC [31]	94%	97%
Invasive	Rapid Urease Test (RUT) [31]	100%	100%

*Values obtained from 2020 JSPGHAN guidelines[10]
**Estimates from Vaira 2002[31] and Gisbert 2004[37]
Abbreviations: Polyclonal SAT ELISA = Stool Antigen Test ELISA using a polyclonal antibody; Monoclonal SAT ELISA = Stool Antigen Test ELISA using monoclonal antibody; Monoclonal SAT IC = Stool Antigen Test immunochromatography using a monoclonal antibody

Various diagnostic tests for *H. pylori* confirmation, including culture, histology, rapid urease test (RUT), urea breath test (UBT), and stool antigen testing, rely on a sufficient bacterial density, and false negatives may result from reduced bacterial load due to antimicrobial use and proton pump inhibitors (PPIs) effects. Most clinical practice guidelines (CPGs) recommend delaying confirmatory H. pylori testing for at least 4 weeks after completing antibiotic therapy. This allows any remaining bacteria not fully eradicated to repopulate the stomach, reaching sufficient numbers for detection and reducing the risk of false negatives. The increased pH induced by PPIs may decrease bacterial urease activity. By 4 weeks, a negative UBT's accuracy ranges from 98% to 100%.

In adults, stool antigen testing (SAT) is accurate for confirming *H. pylori* eradication 4-8 weeks after therapy (sensitivity = 86%, specificity = 92%).[37] The accuracy of SAT is impacted by proton pump inhibitor use and the presence of active bleeding, reducing sensitivity and specificity. Performing SAT less than 4 weeks after treatment may lead to decreased accuracy, emphasizing the recommendation to delay testing beyond 4 weeks to minimize false positive results.[37] Additionally, monoclonal SAT is more accurate than polyclonal SAT.

RECOMMENDATIONS FROM OTHER GROUPS

Various guidelines, including those by ACG, Maastricht VI/Florence consensus, ESPGHAN/NASPGHAN, and JSPGHAN, recommend conducting a test of cure after *H. pylori* treatment.[2,4,10,39] This involves using highly sensitive and specific tests like UBT, SAT, or biopsy-based methods, particularly when considering persistent *H. pylori* infection. Invasive tests (biopsy-based rapid urease or histopathology) may be considered if there are other indications for repeat endoscopy. However, these tests are advised at least 4 weeks post-antibiotic completion and at least 2 weeks after discontinuing proton pump inhibitor (PPI) use to enhance accuracy. Serological tests detecting anti-*H. pylori* antibodies are not recommended for confirming eradication due to their limitations.

For adults, the 2017 ACG Clinical Guideline suggests testing for eradication using a urea breath test, fecal antigen test, or biopsy-based testing at least 4 weeks after completing antibiotic therapy, with a recommended 1-2 week withholding of PPI therapy. The 2022 European Helicobacter and Microbiota Study Group and Consensus panel emphasizes the importance of not using antibiotics or bismuth in the short-term post-eradication follow-up (4-6 weeks), and suggests stopping proton pump inhibitors 14 days before testing. The use of urea breath test, monoclonal SAT, and noninvasive tests are strongly recommended, while serology is not considered suitable for testing eradication success. The 2018 Bangkok Consensus Report recommends noninvasive tests to confirm H. pylori eradication in duodenal ulcers.

In children, both the 2016 Joint ESPGHAN/NASPGHAN Guidelines and the 2020 JSPGHAN guidelines recommend assessing the outcome of *H. pylori* therapy at least 4 weeks after completion. The recommended tests for confirming eradication include the 13C-UBT or a 2-step monoclonal stool *H. pylori* antigen test. The use of endoscopy biopsy specimens, serological tests, and testing for active infection within four weeks post-eradication therapy are discouraged.[10,39]

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No local economic evaluation studies on non-invasive tests for *H. pylori* were found.

Table Q9.2 below gives current price ranges for various non-invasive tests based on publicly available data from hospitals and diagnostic centers.

Table Q9.2. Price of Non-Invasive Diagnostic Tests for *H. pylori* in the Philippines.

Non-Invasive Diagnostic Test	Price (PHP)
Urea Breath Test (13C/14C)	3,700 - 11,100
Serology	295 - 5,750
Stool Antigen Test	2,200 - 2,910
EGD with histology	6,000 - 15,000

Cost-effectiveness

Tests of cure for H. pylori have demonstrated cost-effectiveness in cases of bleeding peptic ulcers, leading to fewer recurrent bleeding incidents and a reduced need for antisecretory therapy. However, post-treatment testing with 13C UBT was found to lack cost-effectiveness in patients with **uncomplicated duodenal ulcers**.[44] This approach proved notably more expensive than clinical follow-up, irrespective of the cost per care setting (ranging from approximately 8,000 to 12,000 PHP in low-cost scenarios to 20,900 to 37,600 PHP in high-cost scenarios). The cost-effectiveness assessment considered various factors such as cure rates of eradication treatment, the cost of the urea breath test, and the sensitivity and specificity of the test to detect eradication.

Patient's values and preferences, equity, acceptability, and feasibility

No local studies have investigated the patient's values and preferences, equity, acceptability, and feasibility regarding the implementation of post-eradication testing for *H. pylori*. However, a study involving 87 patients with *H. pylori*-associated peptic ulcer disease revealed that the majority (90%) preferred undergoing confirmatory testing if asymptomatic, rather than delaying testing until symptoms recurred.[46] This patient preference for confirmation of cure from a carcinogenic bacteria has been acknowledged in the ACG 2017 guidelines as a significant factor supporting the need for routine confirmatory testing.[2] Post-treatment testing is valuable not only in deciding whether to pursue alternative diagnoses in persistently symptomatic patients after negative confirmatory tests, such as in cases of functional dyspepsia, but also in gathering data on *H. pylori* eradication success rates and the effectiveness of current antibiotic regimens.[2] Regarding patients' potential preferences for confirmatory tests, a survey study of 462 patients in the UK indicated that about 75% would be content to provide a stool sample or breath test, especially if informed that these tests are more accurate than blood serology.[45]

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GUIDELINE QUESTION 10:

Should we do monitoring and surveillance of precancerous lesions?

RESEARCH QUESTION: Among patients diagnosed with premalignant gastric lesions, how effective is periodic monitoring using EGD in decreasing gastric cancer-related mortality and morbidity?

Among patients with gastric premalignant conditions, we **SUGGEST periodic surveillance** using upper gastrointestinal endoscopy

Certainty of Evidence: Very Low ⊕◯◯◯
Strength of Recommendation: Weak

Atrophic gastritis: within 3 years
Gastrointestinal metaplasia: within 3 years
Dysplasia: endoscopic resection, if available, or annual surveillance

CONSIDERATIONS

Concerns were raised about the specificity of the target populations in the draft recommendations, which could pose challenges in implementation. Difficulty in identifying the specific subset of patients was anticipated, particularly in a low-incidence country like the Philippines. To address this, the final draft recommendations suggested that endoscopy for surveillance be conducted every three years, considering the low incidence rate. The consensus emphasized the need for improvement not only in equipment but also in the quality of training for those performing endoscopy to enhance surveillance quality. Given the faster development of gastric cancer compared to some other cancers, surveillance was highlighted as beneficial in avoiding false positives in diagnosis, reducing the risks and anxieties associated with additional tests like biopsy, and impacting overall prevention and diagnostic costs.

KEY FINDINGS

The effectiveness of surveillance for gastric premalignant conditions was assessed using indirect evidence from 10 observational studies. While two studies focused on patients with gastric premalignant conditions, the remaining eight studies involved patients diagnosed with gastric cancer, comparing outcomes between those with repeated surveillance and those without. Results showed a 48% reduction in the risk of 5-year mortality among patients with gastric cancer undergoing repeated screening.[4,10,13] Survival rates were higher for those with premalignant lesions who underwent surveillance, and repeated endoscopy detected gastric cancer in 1-2% of the population. Additionally, repeated screening increased the odds of detecting early gastric cancer and significantly reduced the incidence of advanced gastric cancer. Cost-effectiveness studies suggested surveillance every 3 years for patients aged 50 to 69 may be cost-effective.[29-32] The certainty of evidence was very low, mainly due to concerns about indirectness, study design, and imprecision.

BACKGROUND

Gastric cancer ranks 11th in cancer incidence (3.1 per 100,000) and 13th in cancer-related mortality (2.6 per 100,000) in the Philippines.[1] The Correa cascade outlines stages from gastritis to invasive adenocarcinoma, each associated with an increased risk of gastric cancer.[2,3] Surveillance endoscopy can detect invasive lesions early, potentially improving survival.[4] In a Korean study, localized gastric cancer cases had a 92.4% five-year survival rate.[4] Screening and surveillance increase the odds of diagnosing localized gastric cancer.[6] The optimal surveillance interval varies; in Korea, a 2-year interval is supported,[8] while in contrast, the Netherlands progression risk is low for atrophic gastritis and intestinal metaplasia. Surveillance endoscopy's efficacy depends on factors like lesion type and prevalence settings.[9]

REVIEW METHODS

We conducted a systematic search in electronic databases MEDLINE, CENTRAL and Google Scholar using a combined MeSH and free text search related to, “gastric premalignant conditions,” “gastric premalignant lesions,” “gastric intestinal metaplasia,” “atrophic gastritis,” “gastric dysplasia,” and “surveillance endoscopy” (Appendix Q10.1). We also did a hand search of bibliographies of relevant articles. We searched for observational studies or non-randomized trials that looked at different surveillance strategies using upper gastrointestinal endoscopy to determine the optimal timing and interval of surveillance to decrease mortality and incidence of gastric cancer. We included studies that looked at the efficacy of repeated endoscopic follow-up on the survival and incidence of neoplastic progression among patients with patients with gastric premalignant lesions, as well as patients diagnosed with gastric adenocarcinoma.

SUMMARY OF THE EVIDENCE

Evidence Reviewed

Ten studies were used as evidence base to inform this guideline recommendation. Of the 10 studies, 8 were performed in Asia (6 in Korea,[11,12,14,17,19,20] 1 in Japan,[13] 1 in China[10]) and 2 in Europe.[4,18] Six were retrospective cohort studies[11-14,15,17-18] involving patients diagnosed with gastric cancer (68% to 91% Stage I) and then grouped by surveillance strategy (e.g., endoscopic screening vs. no screening) or surveillance interval (e.g., annual, biennial, every 4.5 yrs). Only 4 were prospective studies[4,10,16,18] with 2 studies specifically involving patients with premalignant gastric lesions.[4,16]

A total of 29,022 participants were included across studies. The average age of participants ranged from 40 to 60 years, except for 1 study by Park et al. (2016)[18] which specifically enrolled adults < 40 years old. About 60% (range: 46 to 69%) were males. Critical outcomes assessed included incidence of screen-detected gastric cancers,[10,11,17] proportion of premalignant gastric lesions progressing to cancer,[4,16] overall survival,[10,12,14] and mortality rate at 5 years.[10-13]

Two of the studies included patients with gastric premalignant lesions.[4,16] The study by Whiting et al. (2002) followed an annual surveillance strategy,[4] while the study by den Hollander et al. (2018) followed up patients every 2 years, annually and at 6-monthly intervals, for patients with extended AG/IM, low grade dysplasia, and high grade dysplasia, respectively.[16] Four of the included studies compared the outcomes of frequent/repeated (annual, biennial) and infrequent (more than 2 years) surveillance strategies among patients already diagnosed with gastric cancer.[11,12,17,18] Three other studies extended the comparison of surveillance to beyond 4 years,[13,14,15] while one study from China employed a fixed screening strategy of every 4.5 years.[10]

Efficacy outcomes

Table Q10.1. Summary of outcomes of surveillance endoscopy for premalignant gastric lesions.

CRITICAL OUTCOMES	BASIS (No and Type Of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIDENCE
Overall survival	3 observational* (n=4,097)	HR 0.49	0.39, 0.63	**Benefit** (from 47 to 61% reduction in annual mortality risk)	**Very low** ⊕◯◯◯
Mortality at 5 years	5 observational (n=2,901)	RR 0.52	0.38, 0.72	**Benefit** (from 211 to 96 fewer deaths per 1,000 patients)	**Very low** ⊕◯◯◯
Detection of early gastric cancer cases	8 observational (n=6,101)	OR 4.74	2.22, 10.11	**Benefit** (from 191 to 420 more EGC per 1,000 patients)	**Very low** ⊕◯◯◯
Detection of advanced gastric cancer cases	7 observational (n=5,537)	OR 0.25	0.14, 0.44	**Benefit** (from 312 to 172 fewer AGC per 1,000 patients)	**Very low** ⊕◯◯◯
Incidence of gastric cancer	5 observational (n=82,561)	Patients w/ premalignant gastric lesions: 1.4% to 9.7% Patients w/o known lesions: 0.44% to 1.93%			**Very low** ⊕◯◯◯

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio; **HR:** hazards ratio.
*nested case-control studies

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

Gastric cancer incidence in individuals with premalignant lesions was investigated by Whiting et al. (2002), revealing a **9.7%** occurrence over a decade in 144 UK patients.[4] Notably, cases predominantly arose from intestinal metaplasia (11%) and atrophic gastritis (18%). Conversely, a study in a low-incidence European region, with a mean 57.1 months follow-up, demonstrated a minimal **1.4%** progression to neoplastic lesions in those with atrophic gastritis, intestinal metaplasia, and/or dysplasia.[16]

Examining individuals without known lesions, community studies involving 29,477 participants reported surveillance endoscopy incidence rates ranging from 0.47% to 1.93%, with higher estimates observed in Chinese participants (1.93%) compared to Korean volunteers (0.47%).[10] Moreover, the 'infrequent screening' group (no endoscopy within 2 years) exhibited a 50% higher incidence (0.59%) compared to the 'repeated screening' group (endoscopy within 2 years - 0.29%).[17] Noteworthy risk factors included age over 40 years, a family history of gastric cancer, and male gender.

Analyzing overall survival, pooled results from 2,901 participants indicated a 48% relative risk reduction in mortality for those undergoing repeated screening compared to no screening. Additionally, annual surveillance in UK patients aged 40 years and older demonstrated a notably higher 5-year survival rate

(50% vs. 10%) compared to open access endoscopy.[4] Three studies explored different screening intervals: within 1-2 years (repeated screening group) versus more than 2 years (infrequent screening). A Korean study reported a significantly higher overall 5-year survival rate of 86% in the repeated screening group compared to 86.1% in the infrequent screening group (p = 0.030).[11] This aligns with another study showing a cumulative 5-year survival rate of 87.3% in the repeated screening group, compared to 83% in the infrequent screening group.[12] Similarly, a Japanese study revealed cumulative 5-year survival rates of 96.5% and 71% in the repeated and infrequent screening groups, respectively (p<0.01).[13] In China, screen-detected gastric cancer cases exhibited a higher 5-year cumulative survival of 63.7% compared to 36.4% in patients diagnosed at the initial endoscopy. While overall mortality was reduced by over 40%, there was no observed reduction in gastric cancer-related mortality, possibly attributed to the perceived wide 4.5-year intervals leading to diagnoses in advanced stages.[10] The combined findings from three observational studies yielded a hazard ratio (HR) for overall survival of 0.49 (95% CI 0.39 to 0.63), favoring repeated screening (Appendix Q10.6-B). Univariate analysis results indicated significant associations between overall survival and factors such as the history of endoscopic evaluation, its interval, patient age, and BMI. Notably, the risk for mortality increased with a prolonged interval between the last endoscopy and the diagnosis of gastric cancer. Moreover, results from a multivariate analysis reinforced these findings, demonstrating a noteworthy reduction in the hazards ratio in groups subjected to screening within 2 years of gastric cancer diagnosis compared to those screened more than 2 years after the diagnosis.

Surveillance for early gastric cancer proves instrumental, demonstrated by findings from eight observational studies involving 6,101 participants, resulting in an almost fivefold increase in the odds of detection (OR 4.74 [95%CI 2.22 to 10.11]) (Appendix Q10.6-C).[4,10-12,14,15,,17,18] While significant heterogeneity was observed (I2 = 96%), sensitivity analyses consistently affirm the substantial benefit of surveillance, with exclusion or inclusion of specific studies yielding higher odds ratios (OR 6.13 [95%CI 2.63 to 14.30] and OR 5.38 [95%CI 1.31 to 22.17, p=0.02], respectively).[11,12,15,17,18] Notably, in a UK study, annual surveillance of gastric premalignant conditions was associated with a fivefold increase in the odds of detecting early gastric cancer. Despite these encouraging results, the study's limited population size cautions against recommending a nationwide surveillance program. Conversely, frequent endoscopic surveillance displayed remarkable efficacy, detecting early gastric cancer in 80% of cases compared to a mere 7.6% in patients with infrequent surveillance. Grouping studies by surveillance strategy underscored the importance of shorter intervals, revealing a 74% detection rate for an endoscopic interval within 1-2 years, as opposed to 51% for intervals exceeding 2 years.

For the detection of advanced gastric cancer, analysis of seven observational studies (n=5,537) unveiled a significant reduction in odds with surveillance (OR 0.25 [95%CI 0.14 to 0.44]) (Appendix Q10.6-E).[4,10,11,12,14,17,18] However, for patients with previously diagnosed premalignant gastric lesions, the proportion of advanced gastric cancers did not significantly differ between those under annual surveillance and those in the open access group (OR 1.00 [95%CI 0.44 to 2.24]).[4] Univariate analysis identified multiple risk factors, including age,[12,17] male gender, shorter endoscopic screening interval,[12] previous gastric examination, presence of intestinal metaplasia, and family history.[17] Multivariate analysis further pinpointed age, the presence of intestinal metaplasia, and a history of previous gastric examination as independent risk factors.[17]

Safety outcomes

None of the included studies reported adverse events during the endoscopic procedures. Other studies have identified several adverse events during endoscopy. Cardiopulmonary complications are the most commonly observed, accounting for approximately 60% of unplanned events and occur in up to **0.6%** of EGD procedures. These may be patient-related (advanced age, ASA grade 3 or above,) procedure-related

(difficult intubation of the esophagus, prolonged procedure, and prone position), or sedation-related (oversedation, paradoxical restlessness or agitation, hypotension dysrhythmia and aspiration pneumonia). This ranges from transient hypotension, hypoxia or vasovagal episodes. Upper GI endoscopy carries a high risk of aerosol generation and hence airborne infection such as COVID-19 is also a possibility. Postprocedural symptoms such as sore throat, abdominal pain, nausea, dental trauma, and temporomandibular joint dislocation may also be experienced after endoscopy. Perforation may be a life-threatening complication. Minor bleeding after taking mucosal biopsies is also possible, but the risk of clinically significant bleeding is exceedingly low.[19] Perforation (1.2-5.2%) and bleeding (immediate - 7%; delayed - 0.15%) may be more commonly observed as a complication of endoscopic mucosal dissection as treatment for early gastric cancer.[20] Finally, a potential adverse event of upper GI endoscopy is a missed lesion. A miss rate of 9.4% of cancer cases during endoscopy was observed in a meta-analysis.[19]

Certainty of Evidence

Overall certainty of evidence was rated **very low** due to serious indirectness (most studies did not specifically include patients with premalignant gastric lesions), serious inconsistency (high heterogeneity estimates and different intervention characteristics) and study design limitations (retrospective cohort).

RECOMMENDATIONS FROM OTHER GROUPS

No surveillance is recommended for patients with mild to moderate gastric atrophy (GA) or gastric intestinal metaplasia (GIM) limited to the antrum or 1 location.[21,22,24,25] Surveillance is recommended for patients with GA or GIM limited to the antrum plus strong family history of gastric cancer, persistent *H. pylori* infection,[21,22] or incomplete IM[20] every 3 years.

In China, low risk patients are recommended to undergo surveillance every 3 years and every 1-2 years if with a family history of gastric cancer.[23] Surveillance every 3 years is recommended for patients with advanced AG or GIM,[21,22,24,25] while surveillance every 1-2 years is recommended for these patients with family history of gastric cancer.[21,22] On the other hand, annual surveillance for patients with high risk OLGA/OLGIM III/IV (moderate to severe atrophy or intestinal metaplasia), and a more intensive surveillance for these patients with a family history are recommended in China.[23] Six-monthly, 12-monthly intervals are recommended for patients with low grade dysplasia and high grade dysplasia, respectively.[21,22]

In Japan, the risk of gastric cancer is assessed clinically before initial endoscopic examination. Suspicious lesions for early gastric cancer are examined endoscopically for histological type, size, depth of invasion and presence or absence of scar. Patients identified as having high clinical and endoscopic risk of developing gastric cancer are recommended to undergo endoscopic surveillance every 1 to 3 years.[26]

The Korean National Cancer Screening Program currently recommends gastric cancer screening at 2-year intervals for individuals starting at age $\geq$ 40 years old. The current policy is employed due to the high prevalence of *H.pylori* infection in the region and consequently may have a high chance of unrevealed glandular atrophy or intestinal metaplasia.[27] There was, however, insufficient evidence to recommend surveillance endoscopy at intervals of less than 2 years in patients with intestinal metaplasia.[28]

Table Q10.2. Recommendations from other groups

	AGA 2020[24,25]	ESGE 2019[21]	BSG 2019[22]	China 2022[23]	Japan 2022[26]	Korea 2023[27,28]
Atrophic Gastritis (AG)	Not well-defined and should be decided based on individual risk assessment and shared decision making.	**Mild to moderate atrophy restricted to the antrum:** no evidence to recommend surveillance (moderate quality evidence, strong recommendation)	**AG or GIM limited to gastric antrum:** Surveillance not recommended .	**Low risk:** every 3 years **Low risk + family history:** every 1-2 years	Repeated gastric cancer screening every 1–3 years for patients with high clinical and endoscopic risk	Every 2 years starting at age 40 years old
	Advanced AG: Every 3 years	**Advanced AG** (severe atrophic changes or intestinal metaplasia in both antrum and corpus, OLGA/OLGIM III/IV): High quality endoscopy every 3 years (low quality evidence, strong recommendation)		**High risk (OLGA/OLGIM III/IV):** Annual **High risk (OLGA/OLGIM III/IV) + family history:** more intensive		
		Advanced stages of atrophic gastritis + family history of gastric cancer: More intensive follow-up (e.g. every 1 – 2 years after diagnosis) (low quality evidence, weak recommendation)				
Gastric intestinal metaplasia (GIM)	"AGA suggests against routine repeat short-interval (1 year) endoscopy with biopsies for the purpose of risk stratification" (Conditional; Very low)	**IM at a single location:** Increased risk for gastric cancer does not justify surveillance in most cases, particularly if a high-quality endoscopy with biopsies has excluded advanced stages of atrophic gastritis (moderate quality evidence, strong recommendation)	**AG or GIM limited to antrum + strong family history of gastric cancer or persistent H. pylori infection**: Surveillance every 3 years (low quality of evidence; grade of recommendation: strong; level of agreement: 93%). **Extensive AG or GIM** (affecting the antrum and body): Surveillance every 3 years (low quality of evidence; grade of recommendation: strong; level of agreement: 100%			
	"AGA suggests against routine use of endoscopic surveillance" (Conditional; Very Low)	**IM at a single location + family history of gastric cancer, or with incomplete IM, or with persistent H. pylori gastritis:** Endoscopic surveillance with chromoendoscopy and guided biopsies every 3 years (low quality evidence, weak recommendation)				
Dysplasia		**LGD:** Every 12 months* (low quality evidence, strong recommendation)	**LGD:** Annual ** (low quality of evidence; grade of recommendation: strong; level of agreement: 100%).			
		HGD: Every 6 months* (low quality evidence, strong recommendation)	**HGD:** Every 6 months** (low quality of evidence; grade of recommendation: strong; level of agreement: 100%).			
Interval	3 to 5 years	3 years	3 years			
		Endoscopic surveillance every 3 years of patients with precancerous conditions in countries with an intermediate risk for gastric cancer is cost-effective.	Cost-effectiveness models support surveillance in CAG in populations at low to intermediate risk between 1-yearly and 3-yearly.			

*LGD, low-grade dysplasia; HGD, high-grade dysplasia

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

Cost

No local health economic studies were found on this topic. To simulate the potential costs of surveillance compared to no surveillance, we estimated the costs of endoscopy and subsequent treatments (Table Q10.3). Data on costs were based on Philippine Health Insurance's procedure case rate.[29] In scenario A, the total cost was estimated to be about PHP 153,780 for a 50-year-old patient diagnosed with a gastric premalignant lesion, subsequently underwent 6 endoscopies with biopsy conducted every 3 years and would later receive endoscopic resection for early gastric cancer. On the other hand, substantially higher costs (PHP ≥ 620,540) were estimated in a scenario where the same patient is not followed up, then diagnosed with advanced gastric cancer at 60 years old, and required surgical and chemoradiotherapy treatment.

Table Q10.3 Comparison of estimated direct costs in Philippine Pesos.

	SCENARIO A* (WITH SURVEILLANCE)	**SCENARIO B**** (NO SURVEILLANCE)
Screening endoscopy at age 50	10,540	10,540
Surveillance for gastric premalignant lesions every 3 years up to age 70 (PHP 10,540 * 6 endoscopies)	63,240	N/A
Endoscopic resection for early gastric cancer	80,000	N/A
Surgical resection for advanced gastric cancer (total gastrectomy)	N/A	70,000 (variable)
Neoadjuvant/adjuvant therapy (chemotherapy and/or radiotherapy)	N/A	540,000 to 780,000 (variable)
Subtotal	**153,780**	**620,540 to 860,540**

***** Patient underwent screening at 50 and surveillance every 3 years until age 70 when an early GC was seen and removed by endoscopic resection, rendering the patient cured without surgery and without subsequent chemotherapy and radiation therapy.
** Patient with no screening and diagnosed with advanced gastric cancer with subsequent surgery and chemotherapy/radiotherapy to achieve cure.

Cost effectiveness

No cost-effectiveness studies in the Philippines were found. Results of studies from other countries are detailed in Appendix Q10.7. In general, these studies suggest that the cost-effectiveness of surveillance endoscopy varies depending on the interval or the type of precancerous lesion.

Cost-effectiveness studies conducted in countries with low-to-intermediate gastric cancer incidence (Portugal and USA) showed that surveillance is cost-effective if done among patients at high risk for developing gastric cancer. In Portugal, a surveillance strategy every 3 years was found to be cost-effective[8] with an incremental cost effectiveness ratio (ICER) of EUR 18,336 or ~PHP 1.1 million per QALY gained, but not if conducted every 5-10 years.[30,31] On the other hand, a study conducted in the US showed surveillance is cost-effective when done annually, every 5, or even 10 years only for patients with dysplasia, but not for patients with atrophic gastritis and intestinal metaplasia.[30,32]

[8] Assuming a willingness-to-pay (WTP) threshold of EUR 36,574 euro (PHP ~2,2 million) per QALY.

Endoscopic mucosal resection (EMR) of dysplastic lesions plus endoscopic surveillance every 10 years, every 5 years, and annually exhibited an ICER of $18,600 to $39,800 per QALY gained (WTP Threshold: $50,000 /QALY), with a 89.2% to 94.7% reduction in lifetime risk of gastric cancer. An analysis on the Asian subgroup in this study also yielded a similar result, with surveillance of every 10 years, every 5 years and annually yielding an ICER of $19,700 to $36,200/QALY gained. The subjects modeled in this cohort, however, underwent EMR with surveillance. Strategies for surveillance in patients with intestinal metaplasia and gastric atrophy, however, were more costly and less effective.[30,32] Another study in the US supported the cost-effectiveness of surveillance endoscopy in patients with gastric intestinal metaplasia, but not for individuals ≥ 70 years old.[30,33]

Patient's values and preferences, equity, acceptability, feasibility

Patients' adherence to surveillance endoscopy may vary. In a qualitative study involving 20 patients with Barrett's esophagus in the US, the following factors were found to be important to consider to improve patient adherence: clear communication between physician and patient, minimizing wait time at the endoscopy center, reducing discomfort during endoscopy, and cultivating patient's trust and respect in providers and feelings of control over their disease.[34] The importance of evaluating patient's expectations and preferences were also highlighted in another study.[35] Lack of clinical signs and symptoms, fear of the screening procedure and outcome, and cost of procedure were identified as barriers to gastric screening in a meta-analysis. On the other hand, knowledge and awareness, perceived risk, age > 65, higher education and income, family history, easy access and physician recommendation are effective facilitators that drive patients to undergo gastric cancer screening.[36]

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Chapter 4. Applicability Issues, Resource Implications, and Research Gaps

RESEARCH GAPS

The guideline developers through the evidence reviewers ensured that the systematic reviews that were done to generate the evidence base were current and complete. While clinical decision-making is highly reliant on well-conducted and reproducible randomized clinical trials, several topics in the guideline had paucity of research evidence especially in terms of local evidence and cost-effectiveness. Research gaps were identified in the following topics:

1. Prevalence of gastric cancer across localities and age groups
2. Prevalence of *H. pylori* infection in the Philippines
3. Accuracy of alarm signs and symptoms as a trigger to investigate the presence of gastric cancer.
4. Accuracy of novel biomarkers and PET or AI-enhanced imaging in the local setting as adjuncts in the diagnosis of gastric cancer.
5. Accuracy of adjunctive EUS in the pre-surgical staging of early gastric cancer.
6. Effectiveness of a multidisciplinary team in terms of team composition, candidate patients and conduct of meetings.
7. Effectiveness of non-surgical options in the palliative control of bleeding in patients with advanced gastric cancer
8. Mass screening for *H. pylori* followed by eradication treatment for the prevention of gastric cancer.
9. Resistance rates and patterns of antimicrobial susceptibility of H. pylori in the local setting
10. Effectiveness of documenting H. pylori treatment eradication in the prevention of gastric cancer
11. Effectiveness of a surveillance strategy for patients with gastric premalignant conditions to decrease incidence of advanced gastric cancer and gastric cancer related morbidity and mortality.
12. Cost effectiveness studies in the local setting.

Future research on these topics will aid in the provision of a comprehensive evidence base in the future updates of this CPG.

APPLICABILITY ISSUES AND RESOURCE IMPLICATIONS

In developing the guidelines, the evidence review experts conducted a thorough literature search to provide information to consensus panelists on intervention costs, cost-effectiveness, patient preferences, equity considerations, resource implications, and alternatives. These factors were extensively discussed during consensus-building meetings. Key informants and content experts were invited to identify barriers and facilitators to implementation. Patient representatives on the consensus panel were given adequate time to articulate patient preferences. The multisectoral composition of the consensus panel allowed for in-depth identification of equity issues and discussion of the resource implications of recommendations. Due to the lack of local cost-effectiveness studies for most interventions, direct costs were determined through key informant interviews and accessing websites that publish intervention costs interventions and standard pricing (e.g., DOH and hospital websites).

The major barriers identified to implementing the guideline recommendations included:

1. Variabilities in existing facilities nationwide, contributing to unequal access to care in different localities
2. Costs of diagnostics and treatment
3. Variability in the distribution of specialists for gastric cancer care, and
4. Variations in patient preferences and values.

Efforts were made to address these barriers in formulating the recommendations, with discussions aimed at emphasizing their importance in promoting compliance and adherence to the guidelines.

Strategies to overcome these barriers include adequate dissemination of these guidelines to address knowledge gaps for the initiation of early referral systems to localities with available resources. Allocating resources to upgrade existing infrastructure for imaging, endoscopy services, and *H. pylori* confirmation laboratories is essential. Expanding service availability may potentially make the costs of diagnostics and treatment more homogenous and standardized across regions. Collaborating with professional societies involved in gastric cancer care (PSG, PSDE, PSMO, PCS and PCR) to implement specialist training programs for trainees from underserved areas will enhance specialist care provision in these localities. Information campaigns and wellness promotion efforts coordinated with primary and specialist care societies, and the Department of Health can help address variations in patient preferences and values. Lastly, the incorporation of gastric cancer into a nationwide cancer prevention program may help facilitate the implementation of these guidelines.

CPG Table 5. Barriers and Strategies for the implementation of the Gastric Cancer and *H. pylori* CPG

Barriers	Strategy	Collaborators	Timeframe for Strategy
Disparity on the availability of facilities	Strengthen linkages by creating referral systems	Primary – Specialist care (Medical Societies and DOH)	From dissemination onwards
Disparity on the availability of expertise	Institute “underserved” training prioritization in training programs	Training institutions and DOH	From dissemination onwards
Cost of Diagnostics and Treatment	Allocate funds to government hospitals	DOH	1st Year
Patient Preferences and Values	Aggressive dissemination and information campaigns, create a national cancer prevention program	DOH and all society stakeholders	1st Year

Chapter 5. Dissemination, Monitoring, Evaluation and Updating on the Guideline

DISSEMINATION

The widespread dissemination of this Clinical Practice Guideline (CPG) is vital for its success. This will require partnerships between government, non-governmental, and private institutions. Different versions of the guideline were created to fit each target user: (a) an unabridged/detailed full text, and (b) a quick reference guide or abbreviated pocket guide; and (refer to CPG Appendix 3) were submitted to the DOH National Clearinghouse for promotion and uptake to DOH activities. These are accessible through the DOH website on approved CPGs **https://doh.gov.ph/dpcb/doh-approved-cpg/,** and partner institutions. These materials will also be shared with the Philippine Health Insurance Corporation (PHIC), health maintenance organizations (HMOs), non-governmental organizations (NGOs), and medical professional societies. Additionally, the CPG will be published in indexed scientific journals to ensure accessibility to medical practitioners locally and internationally. It will also be featured in webinars, scientific conventions, and lay fora organized by collaborating societies. Specifically, the CPG can be featured during the annual Philippine Digestive Health Week held every March. Lastly, efforts will be made to integrate the CPG into medical school curricula and training programs for residents or fellows.

IMPLEMENTATION, MONITORING AND EVALUATION

For successful implementation of this Clinical Practice Guideline (CPG), a multisectoral initiative is imperative. The Department of Health (DOH) can facilitate this within government hospitals and primary care facilities by issuing department orders and policy briefs. An assigned agency will collaborate with and distribute the CPG to partner medical societies, ensuring its dissemination and endorsement for implementation across their healthcare, service, and research units. Monitoring and evaluation of compliance will be conducted through collaborative research efforts involving medical societies and the DOH.

Quality indicators that may signify success of the CPG can encompass both short-term and long-term outcomes. Short-term outcomes, such as changes in practice, may be determined by surveys on knowledge, attitudes, and practices (KAPs) of target users, alongside feedback on the methodological quality, applicability, and feasibility of recommendations. Stakeholder societies, such as the PCP, PAFP, PSG, PSDE, PSMO, PCS and PCR can conduct studies to gauge improvements in the quality of care and identify barriers and facilitators to implementation. Additionally, appropriate use of diagnostic tests can be measured by comparing indications and results of endoscopy or imaging tests, and increased utilization of non-invasive tests to diagnose *H. pylori* as measured in cross-sectional studies. These short-term evaluations may be recommended to stakeholder societies and the DOH during the first year of implementation and may be conducted annually until the CPG is revised. In the long term, prospective studies can measure outcomes such as decrease in gastric cancer incidence, mortality, and morbidity, with medical societies initiating these assessments starting from the third year of implementation.

UPDATING OF THE GUIDELINES

Guideline updates will be done every three years. Earlier revisions may be called for when the results of evaluation and monitoring in the implementation of the guidelines deem it necessary or, when adequate, new high-certainty evidence on screening, diagnosing, or managing gastric cancer and *H. pylori* infection become available. The recommendations provided will remain valid and applicable until new evidence on screening, diagnosing, or managing gastric cancer and *H. pylori* infection emerges. To ensure timely

updates, an agency assigned by the DOH will conduct bi-annual literature searches and review of feedback from stakeholders, the DOH, end-users, and program managers annually to identify implementation barriers and facilitators. When an update is deemed necessary, a task force will be created to initiate the entire CPG process and generate revisions for individual recommendations as interim updates or revise the entire manual as appropriate. Alternatively, an update may be warranted after three (3) years, should contingencies necessitate revisiting this Clinical Practice Guidelines on the Management of Gastric Cancer and *H. pylori* infection.

CPG Table 6. Timelines for the Dissemination, Implementation, Monitoring and Updating of the CPG

ACTIVITIES		STAKEHOLDERS	FREQUENCY	TIMELINE
Dissemination		DOH, NGOs and partner societies	Monthly	2024-2025
Monitoring	**Short-term studies** ● **KAPs** ● **Quality of care studies** ● **Cost-utility studies**	DOH, NGOs and partner societies	Annually	2024-2026
	Long-term studies ● **Prevalence** ● **Mortality and morbidity studies**		Periodically	2026-onwards
Updating	Literature searches	CPG Task Force	Bi-annual	2024-2026
	Review of feedback		Annually	

Chapter 6. CPG APPENDICES

CPG Appendix 1. DECLARATION OF CONFLICTS OF INTEREST (DCOI)

NAME	COI RATING	REMARKS
Steering Committee (SC)		
De Guzman, Roberto Jr.	D (Financial COI)	Part 3A. Financial Aid for Research, Programs, and Projects (Honorarium as Speaker for your omeprazole (Risek, Getz) and rabeprazole (Parietr, Hi Eisai; Rabeloc, Biocare) Management: (D) Financial COI. Assignment of a Co-Chair who has no financial COI
Galicia, Rommel	Allowed - Participation with no constraints	
King, Rich Ericson C.	A	
Manlagñit, Maria Crescenta	B	Personnel from the agency funding the guidelines
Mendoza, Roumilla F.	D (Financial COI)	Part 3a. Educational Activities Lecturer for *Lactobacillus reuteri* (Flotera) for 2022, 3 sessions only. Pediatrica B1a Roumilla Mendoza:Juliel Sio-Aguilar, The Validity of H. pylori immunochromatographic stool antigen test and campylobacter urease test in the diagnosis of H. pylori infection among pediatric patients. Vol. 57 No. 1 Jan-March 2008 Management: (D) Financial COI. Assignment of a Co-Chair who has no financial COI.
Rada-Llenares, Clarin M.	Allowed - Participation with no constraints	
Sarmiento, Ray I.	D (Financial COI)	Part 3a. Educational Activities Boston Scientific - SEALS Live Olympus - SEALS Live
Technical Adviser		
Yasay, Eric B.	Allowed - Participation with no constraints	
Technical Coordinator		
Bayona, Howell Henrian G.	Allowed - Participation with no constraints	
Technical Writer		
Domingo, Alrenzo Ludwig B.	Allowed - Participation with no constraints	

NAME	COI RATING	REMARKS
Consensus Panel Meeting Facilitator		
Tamondong-Lachica, Diana R.	Allowed - Participation with no constraints	
Evidence Review Experts (ERE)		
Bellido, Sarah Jean	Allowed - Participation with no constraints	
Coronel, Inah Jane	Broadcast (Financial COI)	4a. Investments and other Financial Interest Prime Doctors Hospital Management: Partnered with another reviewer who is unconflicted
Elepaño, Anton	Allowed - Participation with no constraints	
Fontanilla, Karlo Ivan Miguel	Allowed - Participation with no constraints	
Lontok, Marie Antoinette	D (Financial COI)	Part 3A. Financial Aid for Research, Programs, and Projects (Lectures - Esomeprazole – Natrapharm) Management: Partnered with another reviewer who is unconflicted
Raymundo, Nikko Theodore	Allowed - Participation with no constraints	
Tamayo, Diane	D (Financial COI)	Part 3A. Financial Aid for Research, Programs, and Projects Management: Partnered with another reviewer who is unconflicted
Torres, John Mark K.	Allowed - Participation with no constraints	
Torres, Joshua Josef R.	Allowed - Participation with no constraints	
Velasco, Rogelio	Allowed - Participation with no constraints	
Consensus Panelists (CP)		
Anacta, Maria Kristina	Allowed - Participation with no constraints	
Buliyat, Mary Gay	Allowed - Participation with no constraints	
Cañones, Arlyn	Allowed - Participation with no constraints	

NAME	COI RATING	REMARKS
Dizon, Ma. Charina	Allowed - Participation with no constraints	
Galera, Rosemarie	Allowed - Participation with no constraints	
Go, Grace	Allowed - Participation with no constraints	
Lamsin, Marimel	Allowed - Participation with no constraints	
Maralit, Ruter M.	Allowed - Participation with no constraints	
Padua-Zamora, April	Allowed - Participation with no constraints	
Payawal, Diana	D (Financial COI)	Authorship related to CPG
Roa, Kathryn Uy	Broadcast	4a. Manageable with constraints; Shares with Davao Doctors, requirement for practice in the hospital 4b. Dr. Kristoffer Roland Roa - 75 shares at DDH, founding member United Davao Specialists Medical Center
Romano, Rommel	Allowed - Participation with no constraints	

CPG Appendix 2. EXTERNAL REVIEW SCORES

DOMAIN	Items		R1	R2	Score
A. Scope and Purpose/Clinical Applicability Max: 84 Min: 12	1.Evidence	Overall Quality of Evidence	6	6	Raw Score: 72 **Domain Score: 83.3%**
		Suitability for Use	6	6	
	2. Applicability to Target Users	Overall Quality of Evidence	6	6	
		Suitability for Use	6	6	
	3. Applicability to Patients/Populations	Overall Quality of Evidence	6	6	
		Suitability for Use	6	6	
B. Scope and Purpose/Clinical Applicability Max: 112 Min: 16	4. Values and Preferences of Target Users	Overall Quality of Evidence	6	6	Raw Score: 97 **Domain Score: 84.3%**
		Suitability for Use	6	6	
	5. Values and Preferences of Patients/Populations	Overall Quality of Evidence	6	7	
		Suitability for Use	6	6	
	6. Values and Preferences of Policy/Decision-makers	Overall Quality of Evidence	6	6	
		Suitability for Use	6	6	
	7. Values and Preferences of Guideline Developers	Overall Quality of Evidence	6	6	
		Suitability for Use	6	6	
C. Implementability Max: 56 Min: 8	8. Purpose	Overall Quality of Evidence	6	5	Raw Score: 44 **Domain Score: 91.7%**
		Suitability for Use	6	5	
	9. Local Application and Adoption	Overall Quality of Evidence	6	5	
		Suitability for Use	6	5	

**Maximum possible score per item = 7; Minimum possible score per item = 1*

$$Overall\ Score = \frac{Obtained\ Score\ -\ Minimum\ possible\ score}{Maximum\ possible\ score\ -\ Minimum\ possible\ score}$$

wherein,

$Maximum\ possible\ score\ =\ 7(highest\ quality)\ x\ 2(no.of\ appraisers)\ x\ number\ of\ items$

$Minimum\ possible\ score\ =\ 1(lowest\ quality)\ x\ 2(no.of\ appraisers)\ x\ number\ of\ items$

The specific remarks of each reviewer (verbatim) for each item are as follows:

Item	Remarks
1. Evidence	● It serves as as guide for primary care physicians ● This CPG assessed up-to-date and relevant published evidence. Risk of bias, consistency or results, directness of evidence, precision of results, magnitude of the benefits and harms, publication were thoroughly addressed.
2. Applicability to Target Users	● The guideline is applicable to target users in all specialties and serves as a guide ● This CPG addressed an important clinical problem relevant to (my) practice. There was an alignment between my scope of practice and the target population/patients. It addressed all the relevant clinical questions pertinent to the clinical/health issue
3. Applicability to Patients/Populations	● The above criteria is relevant to all populations across all ages and considers other comorbidities that would influence the overall assessment of the patient. ● This CPG included all relevant outcomes for the target patients/populations.
4. Values and Preferences of Target Users	● Values and preferences of target users, specifically invasive and noninvasive tests for *H. pylori* have been addressed. Furthermore, tests available in different localities were included and addressed in this CPG (i.e. EUS, CT, FDG-PET CT).
5. Values and Preferences of Patients/Populations	● The above criteria highly consider the patients' factors which could influence the assessment and the decision on the management of the patient ● Patients' values and preferences, accessibility, equity, and feasibility were addressed in this CPG.
6. Values and Preferences of Policy/Decision-makers	Consideration for the values and preferences of policy/decision- makers was adequately discussed in pages 18-19.
7. Values and Preferences of Guideline Developers	Values and preferences of guideline developers were adequately discussed
8. Purpose	● The guideline is very helpful for primary practitioners like family physicians in the overall assessment of the patient and helps in the decision on which patients need referral to a specialist and discuss options that could influence the overall management of the patient. ● The recommendations of this CPG aligned with implementation goals.
9. Local Application and Adoption	● The guideline is highly applicable and ideal, however, this would highly depend on the availability of the options and the socio-demographic profile and resources of the patient ● The local application and adoption of this CPG were implied rather than explicitly stated.

All reviewers recommend the guideline recommendations for use in the appropriate and local context with no suggested modifications.

CPG Appendix 3. QUICK REFERENCE GUIDE
**see separate file for actual document*

Executive Summary

This clinical practice guideline for the Management of Gastric Cancer and *Helicobacter pylori* infection in the Philippines is a collaborative effort between the Department of Health, the National Institutes of Health - Institute of Clinical Epidemiology, Bicol Medical Center, and the Philippine Society of Digestive Endoscopy.

The CPG systematically synthesizes evidence to standardize practices in certain priority topics regarding the screening, diagnosis, management, and surveillance of gastric cancer and *Helicobacter pylori* infection in the country. Equal emphasis is placed on addressing *H. pylori* infection, given its significant role as a major risk factor for the development of gastric cancer.

The guideline development process adhered to the widely accepted Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, including GRADE Adolopment—a systematic process adapting evidence summaries—and the GRADE Evidence to Decision (EtD2) framework. This involved:

1. Identifying critical questions and outcomes
2. Retrieving current evidence
3. Assessing and synthesizing the evidence base
4. Formulating draft recommendations
5. Convening a multi-sectoral stakeholder panel to discuss values, preferences, and assess recommendation strength
6. Planning for dissemination, implementation, impact evaluation, and updates.

The CPG offers eighteen (18) recommendations and five (5) good practice statements derived from assessing the best available evidence on ten (10) prioritized clinical questions related to screening, diagnosis, management, and surveillance of gastric cancer and *H.pylori* infection. The recommendations in this CPG will remain valid and will be updated every three years or when new evidence emerges.

Target Population

This CPG is designed for individuals diagnosed with gastric cancer and for both children and adults infected with *H. pylori* bacteria. Some guideline questions target populations suspected to have gastric cancer, high-risk individuals, as well as the asymptomatic general population.

Intended Users

These recommendations are designed for use by healthcare practitioners of all levels of care. They can also be used by policymakers and allied health professionals who treat patients with gastric cancer and *H. pylori*.

Guideline Questions

#	Topic	Guideline Question	Type
1	Gastric cancer screening using alarm signs in patients with dyspepsia	GQ: Should we use alarm signs and symptoms for the early diagnosis of gastric cancer among patients with dyspepsia? RQ: Among patients with dyspepsia, how accurate are alarm signs and symptoms for the early diagnosis of gastric cancer?	Diagnosis
2	Non-invasive tests for diagnosing gastric cancer	GQ: Should we do non-invasive tests to diagnose gastric cancer? RQ: Among patients with alarm signs and symptoms, how accurate are non-invasive tests (imaging and biochemical tests) compared to biopsy/histopathology in diagnosing gastric cancer?	Diagnosis
3	Conventional CT vs. CT + EUS/PET for pre-operative staging of gastric cancer	GQ: Should we use FDG-PET CT or endoscopic ultrasound (EUS) on top of contrast CT to guide pre-operative staging in patients with gastric cancer? RQ: Among patients diagnosed with gastric cancer, how safe, accurate, and effective is contrast CT alone compared to contrast CT with adjunctive diagnostic modalities (EUS, FDG-PET-CT) in pre-operative staging?	Diagnosis
4	Multidisciplinary team approach for managing patients with gastric cancer	GQ: Should we use a multidisciplinary team approach for patients with gastric cancer? RQ: Among patients with gastric cancer, how effective is a multidisciplinary team approach in improving gastric-cancer related outcomes?	Treatment
5	Non-surgical hemostatic interventions for bleeding	GQ: Should we use non-surgical hemostatic interventions in patients with unresectable gastric cancer with tumoral bleeding? RQ: Among patients with unresectable gastric cancer presenting with tumoral bleeding, how effective are non-surgical hemostatic interventions in improving survival and bleeding control?	Treatment
6	Mass screening for H pylori in asymptomatic general population	GQ: Should we do mass or targeted screening for *H. pylori* infection in asymptomatic individuals? RQ: Among asymptomatic individuals, how safe, accurate, and effective is mass screening compared to targeted screening for detecting *H. pylori* infection and decreasing *H. pylori*-related morbidity and gastric cancer incidence?	Diagnosis
7	Non-invasive tests for H pylori diagnosis	GQ: Should we use non-invasive tests to diagnose active *H. pylori* infection in patients with dyspepsia? RQ: Among patients with dyspepsia, how accurate, safe, and effective are non-invasive tests in diagnosing active H pylori infection?	Diagnosis
8	Standard antibiotic therapy vs. other antibiotic therapy	GQ: Should we use the 14-day triple therapy in patients with *H. pylori* infection? RQ: Among patients with H pylori infection, how effective and safe is 14-day triple therapy compared to novel drug combinations in patients with *H. pylori* infection?	Treatment
9	Post-treatment surveillance for H pylori	GQ: Should we use confirmatory tests to decrease incidence of gastric cancer in patients who completed eradication treatment? RQ: Among patients who completed eradication treatment for *H. pylori*, how effective is confirmatory testing compared to no testing in decreasing incidence of gastric cancer, *H. pylori* related morbidity, and drug resistance rates?	Diagnosis, Prognosis
10	Routine surveillance EGD for gastric cancer prevention	GQ: Should we do monitoring and surveillance of precancerous lesions? RQ: Among patients diagnosed with premalignant gastric lesions, how effective is periodic monitoring using EGD in decreasing gastric cancer-related mortality and morbidity?	Diagnosis, Prognosis

Certainty of Evidence

Each recommendation was formulated with an accompanying certainty of evidence rating. The certainty of evidence reflects the assessment of the CPG developers regarding the level of confidence in the stated effects of the intervention/diagnostic test. An initial high rating was assigned to randomized controlled trials (RCTs), while observational studies were rated low. This initial rating for RCTs has been subject to downgrade based on factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. Observational studies, on the other hand, have received upgraded certainty of evidence when a large effect, dose-response relationship, and/or a significant effect despite confounding effects were observed.

Certainty	Definition and Implications	Randomized Controlled Trials	Observational Studies
HIGH ⊕⊕⊕⊕	The group is very confident that the true effect lies close to that of the estimate of the effect (Further research is very unlikely to change confidence in the effect estimate)	No serious flaws in study quality	Extremely strong association and no major threats to validity
MODERATE ⊕⊕⊕◯	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that is substantially different. (Further research is likely to have an important impact)	Serious flaws in design or execution; quasi-experimental design	Strong consistent association and no plausible confounders
LOW ⊕⊕◯◯	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. (Further research is very likely to have an important impact)	Very serious flaws in design or execution	No serious flaws in study quality
VERY LOW ⊕◯◯◯	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. (The estimate of the effect is very uncertain)	Very serious flaws and at least one other serious threat to validity	Serious flaws in design and execution

Summary of Recommendations

No.	Recommendations	Strength of Recommendation	Certainty of Evidence	Considerations
Gastric cancer screening using alarm signs in patients with dyspepsia				
1	Among adults with dyspepsia, we suggest using alarm signs and symptoms* to identify those who may need an upper gastrointestinal endoscopy. **Includes any of the following: unintended weight loss (at least 5% of usual body weight in the preceding 6-12 months), dysphagia or odynophagia, bleeding, anemia, vomiting, abdominal mass, age ≥ 50 years old*	**Weak**	**Very Low** ⊕◯◯◯	Using alarm signs and symptoms for gastric cancer screening may be justified, as the benefits may outweigh the risks of false positive cases. Based on local data showing higher gastric cancer incidence, a cut-off age of ≥50 is suggested for screening, as screening may not be cost-effective for children and adolescents due to the low prevalence. However, there may be a potential for higher false positives in this age group, leading to a weak recommendation for those with ≥3 alarm signs. This recommendation may result in high direct medical costs associated with further testing, and its implementation would be affected by endoscopy availability and patient preference.
Non-invasive tests for diagnosing gastric cancer				
2.1	The gold standard for diagnosing gastric cancer is through biopsy, histopathology obtained through esophagogastroduodenoscopy (EGD) and/or surgery.	**Good practice statement**		Non-invasive tests are integral components of the diagnostic process for cancer, often used early on or as additional tools for diagnosis. However, it is essential to recognize that more invasive procedures, such as biopsy through surgery or endoscopy, remain the gold standard for confirmation of diagnosis due to their reliability.
2.2	Among patients with alarm signs and symptoms, we recommend against the use of non-invasive tests in place of biopsy for diagnosing gastric cancer.	**Strong**	**Very Low** ⊕◯◯◯	

No.	Recommendations	Strength of Recommendation	Certainty of Evidence	Considerations
Conventional CT (computed tomographic) vs. CT + endoscopic ultrasonography/positron emission tomography (EUS/PET) for pre-operative staging of gastric cancer				
3.1	Among patients with gastric cancer, we recommend the use of MDCT for staging gastric cancer prior to surgery.	**Strong**	**Low** ⊕⊕◯◯	MDCT, the standard diagnostic exam for staging gastric cancer, may not be widely available across the country, and there is a shortage of trained specialists to interpret the results. While MDCT scans are crucial for determining metastatic makeup, endoscopic ultrasound may offer the most benefit for early-stage gastric cancer. FDG-PET scans, although available, are not ideal due to false positives and cost considerations. Moreover, standard CT scans are generally deemed sufficient for detecting metastatic diseases. However, in cases like node-positive and intraperitoneal metastatic gastric cancer, CT scans may sometimes miss lesions. FDG-PET scans are not consistently more accurate in these instances based on the reviewed studies.
3.2	Among patients with early gastric cancer, we suggest the use of EUS as an adjunct to multidetector computed tomography (MDCT) in areas where it is available and technical expertise is present.	**Weak**	**Very Low** ⊕◯◯◯	
3.3	Among patients with gastric cancer, we do not recommend the routine use of FDG-PET/CT as an adjunct to MDCT for staging.	**Strong**	**Low** ⊕⊕◯◯	
Multidisciplinary team approach for managing patients with gastric cancer				
4	Among patients with gastric cancer, we recommend the use of a multidisciplinary team approach.	**Strong**	**Very Low** ⊕◯◯◯	Despite the very low certainty of evidence regarding its benefits, multidisciplinary team (MDT) discussions have the potential to enhance clinical decision-making, particularly for cases of advanced gastric cancer. Patients perceive this approach as advantageous for their welfare and well-being, although it may come with increased costs. Integrating MDT discussions into standardization and policy-making processes was suggested as a strategy to mitigate these costs. However, potential harms, such as overstaging, and concerns about feasibility and availability in low-resource areas must be carefully considered.

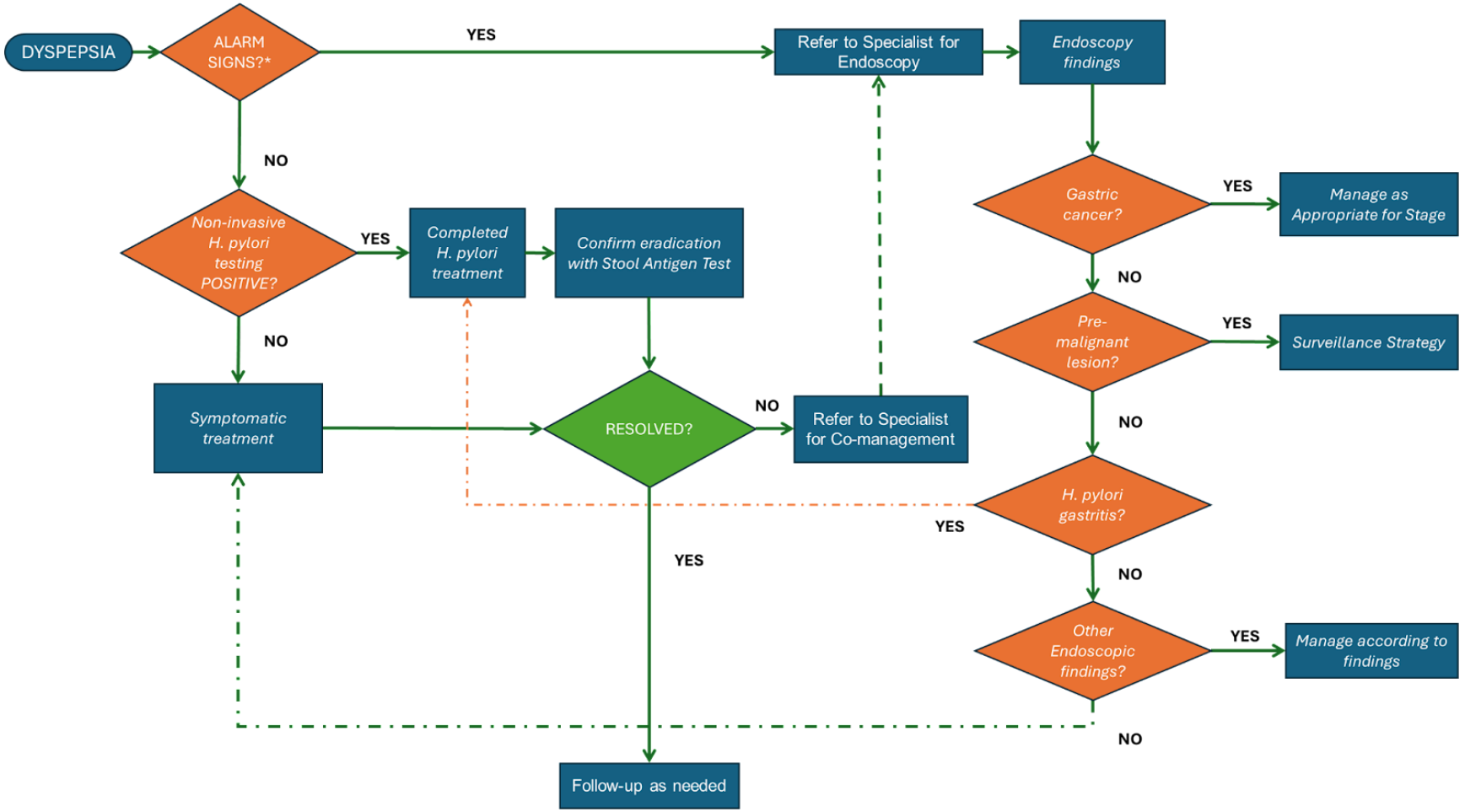
No.	Recommendations	Strength of Recommendation	Certainty of Evidence	Considerations
Non-surgical hemostatic interventions for bleeding				
5.1	Shared decision making for the palliative control of tumor bleeding by endoscopic techniques and/or radiotherapy should be discussed to the patient as deemed necessary.	**Good practice statement**		Non-surgical hemostatic interventions may have limited efficacy in patients with lower functional status (ECOG 3+). Endoscopic treatments, including clips, are considered appropriate for cases of unresectable bleeding. Concerns about potential harms from transarterial embolization (TAE), such as spleen infarction and pyloric stenosis, were highlighted. While TAE was favored by the panel, its use was subject to the condition of a low risk of bleeding impacting other organs. Hemospray was viewed as a more acceptable option for patients, while radiotherapy posed challenges due to limited accessibility outside Metro Manila and additional costs associated with transportation and logistics. A good practice statement emphasized the importance of shared decision-making between patients and healthcare providers, considering factors like cost-effectiveness, physician expertise, logistical support, and practical feasibility, rather than endorsing a specific procedure outright.
5.2	Among patients with unresectable gastric cancer with tumor bleeding, we suggest the use of hemostatic spray powder application or transarterial embolization as bridging therapy for more definitive treatment for tumor bleeding where accessible.	**Weak**	**Very Low** ⊕◯◯◯	
Screening for *H. pylori* in asymptomatic general population				
6.1	Among asymptomatic individuals, we suggest against mass screening for *H. pylori.*	**Weak**	**Very Low** ⊕◯◯◯	Mass screening for gastric cancer in the Philippines is not recommended due to a lack of local evidence regarding disease burden and risk distribution. The prevalent strains of Helicobacter pylori in the country are not proven to be carcinogenic. Implementing mass screening was considered less feasible and cost-effective without substantial incidence data to support it. Instead, individualized screening may be conducted under specific conditions, which would be more realistic and sustainable in the long term.

No.	Recommendations	Strength of Recommendation	Certainty of Evidence	Considerations
Non-invasive tests for *H. pylori* diagnosis				
7.1	Among adults with dyspepsia without alarm signs and symptoms, we recommend the test-and-treat strategy in the non-invasive testing of *H pylori* infection.	**Strong**	**Low** ⊕⊕◯◯	The stool antigen test (SAT) is strongly recommended for diagnosing H. pylori infection in adults due to its accuracy, cost-effectiveness, and ease of implementation. SAT is more readily available than urea breath tests (UBT) and exhibits sensitivity comparable to other diagnostic methods. In cases where patients present with alarm signs and symptoms, conducting endoscopy and testing for H. pylori using the rapid urease test (RUT) is suggested by the consensus panel. However, patient reluctance to handle stool samples may affect the test's acceptability in routine medical practice. Although serology is the most widely available and cost-effective option, it cannot distinguish between past and current infections. Qualitative tests may remain positive for up to 3 years post-treatment, and quantitative levels may persist for 6 to 12 months after treatment. UBT may face availability challenges in hospitals, limiting its applicability to the general population. However, UBT could be beneficial for patients on anticoagulants, with low platelet counts, or at high risk of cardiac complications. It is not recommended for children due to low specificity and sensitivity, as well as challenges in compliance. Patient acceptability tends to favor UBT, with high satisfaction rates compared to endoscopy. Factors influencing UBT accuracy include the presence of *Helicobacter heilmannii,* certain infections causing false positives, and recent antibiotic or bismuth compound use leading to potential false negatives.
7.2	Among adults with dyspepsia without alarm signs and symptoms, we recommend the use of stool antigen tests to diagnose *H. pylori* infection.	**Strong**	**Low** ⊕⊕◯◯	
7.3	Among adults with dyspepsia without alarm signs and symptoms, we suggest the use of 13C or 14C Urea Breath test (UBT) to diagnose *H. pylori* infection.	**Weak**	**Low** ⊕⊕◯◯	
7.4	Among adults with dyspepsia without alarm signs and symptoms, we suggest against the use of serology to diagnose *H. pylori* infection.	**Weak**	**Low** ⊕⊕◯◯	
7.5	Among children with dyspepsia without alarm signs and symptoms, we recommend against non-invasive testing (13C/14C UBT, serology, stool antigen tests) for *H. pylori* infection.	**Strong**	**Low** ⊕⊕◯◯	

No.	Recommendations	Strength of Recommendation	Certainty of Evidence	Considerations
Standard triple antibiotic therapy for *H. pylori*				
8.1	Among adults and children with *H. pylori* infection, we suggest using the 14-day concomitant triple therapy containing clarithromycin.	**Weak**	**Very Low** ⊕◯◯◯	The 14-day triple therapy is suggested for both adults and children, in accordance with common practice. However, the panel opted to lower the strength of this recommendation due to concerns regarding the rising clarithromycin resistance observed in the country. Local data regarding the extent of this increase was unavailable, and routine testing for resistance was not commonly conducted locally, leading to an information gap. Alternative regimens may be considered for retreatment, albeit they are costlier compared to the 14-day triple therapy. While deliberating the inclusion of probiotics in recommendations for children, a decision was deferred due to insufficient clinical data supporting their use.
8.2	Among adults with *H. pylori* infection, we suggest using alternative regimens*. **14D clarithromycin-based sequential, 14D levofloxacin-based sequential, 10-14D bismuth-containing quadruple, 7D vonoprazan-containing triple therapy*	**Weak**	**Very Low** ⊕◯◯◯	
8.3	Among children with *H. pylori* infection, we suggest using alternative regimens*. **14D sequential, bismuth-based quadruple therapy*	**Weak**	**Very Low** ⊕◯◯◯	
Post-treatment surveillance of *H. pylori*				
9.1	In adults and children who completed eradication treatment for *H. pylori* infection, clinicians should consider doing tests of cure using urea breath test or stool antigen test to confirm eradication of *H. pylori*.	**Good practice statement**		A good practice statement was formulated in recognition of the potential benefits of post-treatment surveillance, notwithstanding the absence of direct evidence. The recommendation discourages re-testing for individuals with negative results but advocates for re-testing for those who initially test positive and undergo antibiotic treatment. Subsequent retesting is deemed
9.2	Biopsy-based testing for cure may be considered only if there are other indications for a repeat EGD.	**Good practice statement**		

No.	Recommendations	Strength of Recommendation	Certainty of Evidence	Considerations
9.3	Tests of cure should be done at least 4 weeks after the completion of antibiotic therapy and after proton pump inhibitor (PPI) therapy has been withheld for 1-2 weeks.	**Good practice statement**		unnecessary once a negative outcome is achieved, unless symptoms reappear. Anticipated challenges pertaining to logistics, particularly concerning costs and test availability, are expected, particularly in provincial areas. The decision to consolidate pediatric and adult statements was justified by the non-practice of test-and-treat in pediatrics due to the non-standardized urea breath test (UBT) and the absence of routine stool antigen tests in the Philippines. However, the necessity for local studies and eradication therapy was underscored.
Surveillance for precancerous lesions				
10	Among patients with gastric premalignant conditions, we suggest periodic surveillance using upper gastrointestinal endoscopy. ● **Atrophic gastritis:** within 3 years ● **Gastrointestinal metaplasia:** within 3 years ○ **Dysplasia:** endoscopic resection, if available, or annual surveillance	**Weak**	**Low** ⊕⊕◯◯	Endoscopic surveillance every 3 years is recommended considering the relatively low incidence rate of gastric cancer in the Philippines. The consensus panel underscored the importance of enhancing not only equipment but also the quality of training for individuals performing endoscopy to ensure the highest standard of surveillance. Given the rapid development of gastric cancer compared to certain other cancers, regular surveillance was emphasized for its potential to mitigate false positives in diagnosis, alleviate the risks and anxieties associated with additional tests such as biopsy, and ultimately influence the overall costs of prevention and diagnosis.

Algorithm for Recommendations 1, 7, 9, and 10



Quick Reference Figure 1. Algorithm summarizing Recommendations 1, 7, 9 and 10