TITLE: Stool Antigen Tests for *Helicobacter pylori* Infection: A Review of Clinical and Cost-Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES

Helicobacter pylori (*H. pylori*) is Gram negative bacillus that colonizes the mucus layer of the human stomach and the upper part of small intestine (duodenum).[1,2] It is the principal cause of peptic ulcer disease and the main risk of gastric cancer.[2] Most infected individuals (> 70%) are asymptomatic.[2] The rates of *H. pylori* infection increase with age. In Canada, one in five people age 30 years old (about one million) is infected.[1] The rate increases to one in every two people aged 80 years or older (0.5 million).[1] About 75% of the people in First Nation communities are infected with *H. pylori*.[1] Based on origin of birth and/or area of residence, there are approximately over 4 million Canadians who are considered to be at high risk for *H. pylori* infection; total cost of testing and eradication for those people are estimated to be $350 million.[1]

H. pylori can be detected by invasive or non-invasive tests.[3] Endoscopic examination of the stomach and duodenum followed by removal of biopsy samples is an invasive procedure.[3] Tests such as histology, rapid urease testing, culture, or polymerase chain reaction (PCR) have been widely used to detect of *H. pylori* from the biopsy samples.[3] Urea breath tests, stool antigen tests, and serology are the non-invasive tests.[3]

There are two types of stool antigen tests for the diagnosis of *H. pylori* infection, one based on enzyme immunoassay (EIA) and the other based on immunochromatography (ICA).[4] Both types of tests can be operated using either monoclonal antibody or polyclonal antibodies.[4] Although both are highly sensitive and specific, the EIA-based tests appears to be more accurate than the ICA-based tests.[4,5] However, the ICA-based tests do not required specialized equipment, are easy to use, and are useful for rapid diagnosis of *H. pylori* infection.[4]

The aim of this report is to review the diagnostic accuracy, clinical effectiveness, cost-effectiveness, and guidelines of stool antigen tests for *H. pylori* infection.

RESEARCH QUESTIONS

1. What is the diagnostic accuracy and clinical effectiveness of stool antigen tests in patients with suspected *H. pylori* infections?

2. What is the cost-effectiveness of stool antigen tests in patients with suspected H. pylori infections?

3. What are the evidence-based guidelines associated with stool antigen tests in patients with suspected H. pylori infections?

KEY FINDINGS

Certain commercially available stool antigen tests with high test performance (sensitivity and specificity) provide reliable results in the diagnosis of *H. pylori* infection and in follow-up testing after eradication therapy. The use of a stool antigen test-and-treat strategy in relieving symptoms of dyspepsia or reducing the burden of gastric cancer and peptic ulceration was cost-effective. Guidelines recommend a laboratory-based validated monoclonal stool test for test-and-treat strategies and for follow-up testing after eradication therapy.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and December 3, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with suspected *Helicobacter pylori* infection
Intervention	Stool antigen tests (other names may be fecal testing for *H. pylori*, fecal testing, fecal calprotectin assay)
Comparator	Endoscopy/biopsy procedure Carbon-13 urea breath test
Outcomes	• Clinical effectiveness and diagnostic accuracy (accuracy, clinical benefit, patient harms, safety); including comparative clinical effectiveness with other procedures. • Cost-effectiveness (e.g. cost of tests, travel associated with testing), including comparative cost-effectiveness with other procedures. • Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2009, duplicate publications of the same study, or included in a selected health technology assessment or systematic review.

Critical Appraisal of Individual Studies

For the critical appraisal of studies, a numeric score was not calculated. Instead, the strength and limitations of the studies were described.

The quality of diagnostic studies was assessed using QUADAS-2.[6] Economic studies were assessed for completeness of reporting of the model, model inputs, data sources, and disaggregated results, and the sensitivity analyses conducted, based on the British Medical Journal Checklist for economic studies.[7] The Appraisal of Guidelines Research & Evaluation (AGREE II) instrument was used to evaluate the quality of the included guidelines.[8]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 239 citations. Upon screening titles and abstracts, 32 potential relevant articles were retrieved for full-text review. Four additional relevant reports were retrieved from other sources. Of the 36 potentially relevant articles, 24 reports were included in this review including 21 diagnostic studies,[9-29] two economic studies[30,31] and one guideline.[32] No health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials on the clinical effectiveness of stool antigen tests could be identified. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

The characteristics of the diagnostic studies and economic studies are summarized in Appendix 2 and 3, respectively. Appendix 4 presents the grading of recommendations and levels of evidence of the included guidelines.

Of the 21 diagnostic studies of fecal antigen in the stool, 15 studies[9-23] were for diagnosis of suspected patients with *H. pylori* infection and six studies[24-29] were for follow-up testing after patients receiving *H. pylori* eradication therapy. Most studies were prospective and included patients suffering from gastrointestinal disorders including dyspeptic symptoms, who were referred to hospital for upper gastrointestinal endoscopy examination. Two studies included hemodialysis patients.[16,26] The stool antigen tests were commercially available from different manufacturers and were of different types. These included EIA-based tests using monoclonal antibody,[9,12-17,21,23-25,27-29] EIA-based tests using polyclonal antibodies,[11,19,26,29] ICA-based tests using a monoclonal antibody,[10,13,18,20,25] and ICA-based tests using polyclonal antibodies.[13,21] For EIA based tests, the cut-off value was not reported in many studies, likely because it was present in the manufacturers' instructions. Gold standard tests varied among studies and consisted of either a single test, typically one of the invasive tests using biopsy specimens from endoscopy (culture, PCR, histopathology, or rapid urease test), or a combination of invasive tests and non-invasive tests such as the urea breath test, serology, or stool antigen test. The test performance outcomes included sensitivity, specificity, positive predictive value, negative predictive value and accuracy. For follow-up studies after *H. pylori* eradication therapy, the percentage of agreement between the stool antigen test and urea breath test was also reported, as the latter is the indicated test for follow-up.

The economic study by Schulz et al. (2014)[31] investigated which of the nine different screening and follow-up strategies would be cost effective in asymptomatic immigrants and refugees, which are high *H. pylori* prevalence populations. Screening tests included serology, stool antigen, urea breath test, and endoscopy (gastroscopy). The prevalence of *H. pylori* was assumed to be 25%, 50% or 75%. The primary outcome, which was the net cost for each cancer prevented for each strategy per 1000 people, was calculated using a decision analytic model. Costs and treatment efficacy were based on published estimates. A sensitivity analysis was performed on the most cost effective strategy in the initial analysis (stool testing with retesting of those treated). The parameters tested were cost of managing one cancer, cost of a physician visit, cost of medication for eradication, cost of managing one peptic ulcer and lifetime risk of gastric cancer. The payer perspective was taken. The time horizon of costs was the patient's life time. Costs were in 2011 US dollars. There was no discounting rate. The population included immigrants and refugees from developing countries.

The economic study by Holmes et al. (2010)[30] compared the cost-effectiveness of various, non-invasive testing strategies of *H. pylori* infection including stool antigen testing, IgG serology, IgG serology with reflex to stool antigen, urea breath testing, and IgG/IgA binary serology. The primary outcome, which was cost per symptom-free year, was calculated using a Markov simulation model. The cost per correct diagnosis was also reported as an outcome. Uncertainty of outcomes was estimated using probabilistic sensitivity analysis by changing the prevalence of *H. pylori* (5% to 40%). The societal perspective was taken. The time horizon of costs was the patient's life time. Costs were in 2009 US dollars. There was no discounting rate. The population included dyspeptic patients (< 55 years of age) with the possibility of having *H. pylori* infection, peptic ulcer(s), or both. Patients would begin to receive each of the first five tests; if positive, they would receive triple therapy (clarithromycin, amoxicillin, and lansoprazole); if negative, they would have proton pump inhibitor (PPI) therapy. If there was no relief of symptoms after initial management, or if symptoms recurred, patients would go on to receive an endoscopy with biopsy. Baseline costs of tests and treatments were based on 2009 national midpoint Medicare reimbursement rates. A probabilistic sensitivity analysis was undertaken by simulating 250 trials involving 10,000 patients each. Incremental cost-effectiveness ratios (ICERs) were calculated based on a single simulated cohort of 500,000 patients using empiric PPI trial data (i.e., no testing) as the baseline for comparison.

The European guideline on the management of H. pylori infection was published in 2012.[32] The guidelines were developed by a panel 44 experts from 24 countries that convened in Florence in 2010. The goal of the guidelines wa to provide recommendations to health care practitioners for clinical management of *H. pylori* infection, focussing on indications, diagnostic and treatments of *H. pylori* infection with additional emphasis on disease prevention – in particular, prevention of gastric cancer. Recommendations were graded according to the strength of the recommendation and quality of the supporting evidence (Appendix 4). Consensus was defined as support by at least 70% of the experts.

Summary of Critical Appraisal

The strengths and limitations of diagnostic studies, economic studies and guidelines are summarized in Appendix 5, 6 and 7, respectively.

QUADAS-2 was used to assess the quality of the diagnostic studies. The instrument consists of four domains. Domain 1 has three questions dealing with method of patient selection. Domain 2 has two questions dealing with the conduct and interpretation of the index test(s). Domain 3 has two questions dealing with the conduct and interpretation of the standard test. Domain 4 has four questions asking if there is an appropriate time interval and interventions between index

test(s) and standard test, and whether all patients receive index test(s) and/or reference standard. Overall, for Domain 1, the risk of bias (including consecutive or random sample of patients were enrolled, and the avoiding of case-control design and inappropriate exclusions) in all studies, except three,[11,12,20] was low. The risk of bias for Domain 1 was high in one study[11] since up to 63% of patients were excluded from the study, and it was unclear in two studies[12,20] as it was unclear if the studies avoided inappropriate exclusions. For Domain 2, all studies had low risk of bias (i.e., the index test results were interpreted without knowledge of the results of the reference standard and a threshold used was pre-specified). For Domain 3, it was unclear if the reference standard test correctly classified the target condition in 10 studies,[9,10,16,22,24-29] while the risk of bias in the rest of the studies was low (i.e., the reference standard was likely to correctly classify the target condition, and the reference standard results were interpreted without the results of the index test).[11-15,17-21,23] Although in some studies[16,20,23] the stool antigen test may have been part of the reference standard panel of tests. For Domain 4, the risk of bias was high in four studies[9,11,12,25] as not all patients received index test(s) and/or the reference standard test. The timing between index test(s) and reference standard was unclear in all studies, meaning that it is possible that there were changes in condition or health status between tests.

The economic study by Schulz et al. (2014)[31] was generally well conducted and had considerable strengths in study design, data collection, and analysis and interpretation of results based on British Medical Journal Checklist for economic studies (Appendix 6). However, the discount rate and details of statistical tests were not given in this study. The study by Holmes et al. (2010)[30] had several limitations in data collection and analysis and interpretation of results including the lack of methods to value benefit, quantities of resource used, price adjustments, discount rate, the choice of variable for sensitivity analysis and details of statistic tests.

The included guideline[32] was explicit in scope and purpose, stakeholder involvement, rigour of development (except a method for guideline updating), clarity of recommendation according to AGREE II instrument (Appendix 7). Limitations of this guideline rested mainly on the applicability, for example, there was no description of facilitators and barriers to its application, and lack of advice and/or tools on how the recommendations can be put into practice.

Summary of Findings

The main findings of fecal antigen detection studies and economic studies are presented in Appendix 8 and 9, respectively. The guideline's recommendations on stool antigen tests for *H. pylori* infection are shown in Appendix 10.

A. Fecal antigen detection studies (for diagnosis)

Table 2 summarizes the test performance results of different commercially available kits used for diagnosis of *H. pylori* infection. The sensitivity and specificity values varied substantially depending on the test kit and the reference standard used, assuming errors in the handling and preparation of samples were negligible.

- Among the EIA-based tests using monoclonal antibody, the Testmate pylori antigen (TPAg EIA),[9] Premier Platinum HpSA,[13,21] and Amplified IDEIA Hp Star[23] using the corresponding reference standards had better test performance compared to other EIA-based tests. Sensitivity of those tests ranged from 90.0% to 92.4%, and specificity ranged from 91.0% to 100%.
- Among the two EIA-based tests using polyclonal antibodies, the EZ-STEP *H. pylori*[19] was the preferred test kit (sensitivity: 93.1%; specificity: 94.6%), though it is important to

note that these were compared to different reference standards and may have been subject to different sample preparation and handling.

- Among the ICA-based tests using monoclonal antibody, the Atlas *H. pylori* antigen test[10] had highest test performance (sensitivity: 91.7%; specificity: 100%).
- Both ICA-based tests using polyclonal antibodies had sensitivity and specificity over 80% (sensitivity: 81.0%, 86.7%; specificity: 88.9%, 92.0%).[13,21]

Table 2: Test Performance Results of Different Stool Antigen Test Kits Used for Diagnosis of *H. pylori* Infection

Stool antigen test kit	Reference standard	Sensitivity (%)	Specificity (%)
EIA-based (monoclonal)			
Testmate pylori antigen (TPAg EIA)[9]	Stool PCR	92.4	100
Premier Platinum HpSA[13]	Endoscopy (histopathology and rapid urease test)	92.2	94.4
Premier Platinum HpSA[21]	Endoscopy (histopathology and rapid urease test)	90.0	91.0
Amplified IDEIA Hp Star[23]	At least two of four tests (histopathology, rapid urease test, urea breath test, and fecal test) were positive	90.3	93.0
Amplified IDEIA Hp Star[12]	Two positive tests: gastric biopsy plus one of urease, breath or serology	87.2	44.0
HP Ag[13]	Endoscopy (histopathology and rapid urease test)	48.9	88.9
HP Ag[21]	Endoscopy (histopathology and rapid urease test)	77.0	91.0
Test kit from ASTRA[14]	Positive: by PCR on biopsy; Negative: by all invasive tests	87.8	75.0
HpSA[15]	Endoscopy (histopathology using hematoxylin and eosin and modified giemsa)	66.0	91.0
HpSA[16]	At least two out of three tests (urea breath test, stool antigen test and serology) were positive	100	75.0
Femtolab *H. pylori* Cnx[17]	Endoscopy (histopathology using giemsa, and hematoxylin and eosin)	72.2	66.7
EIA-based (polyclonal)			
ELISA kit Immunodianostik AG[11]	Endoscopy (histopathology using Giemsa stain)	72.2	Not determined
EZ-STEP *H. pylori*[19]	At least two of four tests (histology, rapid urease test, urea breath test, and serology) were positive	93.1	94.6
ICA-based (monoclonal)			
Atlas *H. pylori* antigen test[10]	Endoscopy (rapid urease test)	91.7	100
ImmonoCard STAT![13]	Endoscopy (histopathology and rapid urease test)	68.9	92.6
H. pylori fecal antigen[13]	Endoscopy (histopathology and rapid urease test)	78.9	87.0
Helicobacter antigen	Endoscopy (histopathology)	68.9	100

Stool antigen test kit	Reference standard	Sensitivity (%)	Specificity (%)
Quick Castle[18]			
Kits from GENERIC ASSAYS GmbH[20]	At least two of five tests (stool antigen test, urea breath test, rapid urease test, serology and histology) were positive	96.0	83.0
IHP-602 from ACON[22]	Urea breath test	88.0	87.5
ICA-based (polyclonal)			
One-step *H. pylori* antigen[13]	Endoscopy (histopathology and rapid urease test)	86.7	88.9
Kits from Vegal Farmaceutical[21]	Endoscopy (histopathology and rapid urease test)	81.0	92.0

B. Fecal antigen detection studies (for follow-up testing)

Table 3 summarizes the test performance results of different commercially available kits used for follow-up testing.

Five studies of EIA-based tests using monoclonal antibody[24,25,27-29] found that the stool antigen tests were accurate and useful tool to determine the results of *H. pylori* eradication therapy compared to endoscopy (histopathology) and/or urea breast test. The EIA-based tests using polyclonal antibodies[26,29] had high specificity (93.3%, 97.5%), but low sensitivity (42.8%, 87.0%) for follow-up testing. The ICA-based tests using monoclonal antibody had also high performance (sensitivity: 90%, 100%; specificity: 93.6%, 94.9%) in a post-treatment setting.[25]

Table 3: Test Performance Results of Different Stool Antigen Test Kits Used for follow-up Testing after Treatment

Stool antigen test kit	Reference standard	Sensitivity (%)	Specificity (%)
EIA-based (monoclonal)			
Testmate rapid pylori antigen (Rapid TPAg)[24]	Endoscopy (histopathology)	Agreement /accuracy with urea breath test: 94.1%/96.0% Agreement /accuracy with histopathology: 94.1%/98.0%	
Amplified IDEIA Hp StAR[25]	Endoscopy (histopathology) or urea breath test	100	93.6
TPAg EIA[27]	Urea breath test	Agreement with urea breast test: 91.2%	
HpSA ELISA II[27]	Urea breath test	Agreement with urea breast test: 95.4%	
TPAg EIA[28]	Urea breath test	Agreement with urea breast test: 94.7%	
Testmate pylori antigen EIA[29]	Urea breath test	91.6	98.4
EIA-based (polyclonal)			
Premier Platinum HpSA[26]	Urea breast test	42.8	93.3
HpSA[29]		87.0	97.5
ICA-based (monoclonal)			
RAPID Hp StAR[25]	Endoscopy (histopathology) or urea breath test	100	93.6
ImmunoCard STAT! HpSA[25]	Endoscopy (histopathology) or urea breath test	90.0	94.9

C. Economic studies

Shultz et al. (2014)[31] investigated whether a screening and eradication approach would be cost effective in high prevalence populations. Stool antigen testing with repeat testing after treatment was the most cost effective approach compared to urea breath testing or endoscopy. The net cost per cancer prevented per 1000 people was US$111,800 (assuming 75% prevalence), $132,300 (50%) and $193,900 (25%). These values were considerable less than those of urea breath test and endoscopy for all assumed prevalences (Appendix 9). With 75% prevalence, stool antigen testing with repeat testing was expected to prevent 3.0 gastric cancers and 22.8 ulcers for every 1000 people managed. These values were similar to those of urea breath test and endoscopy. The test and retest after treatment strategy using stool antigen remained cost effective compared to others, even with a prevalence of 25%. It was concluded that the use of stool antigen testing in reducing the burden of gastric cancer and peptic ulceration in high prevalence populations is the most cost effective approach.

Holmes et al. (2010)[30] compared to cost-effectiveness of various non-invasive testing strategies including serology and urea breath tests. The empiric proton pump inhibitor therapy, where non-invasive testing was skipped, was used as the control. Under base case scenarios, cost-effectiveness ratios (cost per symptom free year) of the non-invasive test strategies ranged from $123 (stool antigen) to $129 (IgG/IgA combined serology), and were similar to that of empiric proton pump inhibitor therapy ($122). Sensitivity analysis showed that the results were not affected by changes in prevalence of *H. pylori* (5% to 40%). Of note, this study focussed on dyspepsia relief only and did not consider more serious illness such as gastric ulcer or cancer. It was concluded that "*the initial choice of noninvasive testing strategy does not have a significant influence on the overall cost-effectiveness of care for patients presenting with previously uninvestigated dyspepsia*."

D. Guidelines

The European guideline had three recommendation statements on stool antigen tests for *H. pylori* infection (Appendix 10).

- The test was recommended for test-and-treat strategy (Grade B, Level 2a)
- The diagnostic performance of stool antigen test is equivalent to urea breath test if the validated laboratory-based monoclonal test is used (Grade A, Level 1a)
- For follow-up testing after eradication therapy, the urea breath test or a laboratory-based validated monoclonal stool test are both recommended (Grade A, Level 1a)

Limitations

The limitations of the diagnostic accuracy studies were the heterogeneity in the type of test kits used (EIA versus ICA, and monoclonal versus polyclonal), and the potential errors in sample preparations from different laboratories. In addition, the cut-off values for EIA-based tests and the reference standards varied among studies. Some reference standards might not be reliable to correctly classify the target condition.

The main limitations of the economic studies[30,31] were the clinical assumptions including the assumed practice pattern and the probability and cost values, and the estimations of benefits of screening and treatment. The cost-effectiveness study by Holmes et al. (2010)[30] did not report the results in terms of quality-adjusted life years due to lack of data for patients with dyspepsia. It was unclear how the results of the included economic studies could be interpreted in a Canadian context.

The European guideline[32] had no significant limitations, except an update version may be needed to better reflect the current evidence. There were no Canadian guidelines identified in the literature search.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In this review, 21 reports on fecal antigen detection studies (15 on diagnosis and six on follow-up testing), two economic studies and one guideline were identified. Among EIA-based tests, three test kits (Testmate pylori antigen [TPAg EIA], Premier Platinum HpSA, and Amplified IDEIA Hp Star) using monoclonal antibody and one test kit (EZ-STEP *H. pylori*) using polyclonal antibodies appeared to have highest test performance. Among the ICA-based tests, the Atlas *H. pylori* antigen monoclonal-based test had highest test performance compared to other test kits using monoclonal antibody or those using polyclonal antibodies. The EIA-based and ICA-based tests using monoclonal antibody were comparable with endoscopy (histopathology) and/or urea breath test to determine the results of *H. pylori* eradication therapy. Evidence on clinical effectiveness regarding clinical benefit, patient harms and safety was not identified. Economic studies showed that the use of stool antigen testing in relieving symptoms of dyspepsia or reducing the burden of gastric cancer and peptic ulceration in high prevalence populations was cost-effective. A laboratory-based validated monoclonal stool test is recommended for test-and-treat strategy and for follow-up testing after eradication therapy.

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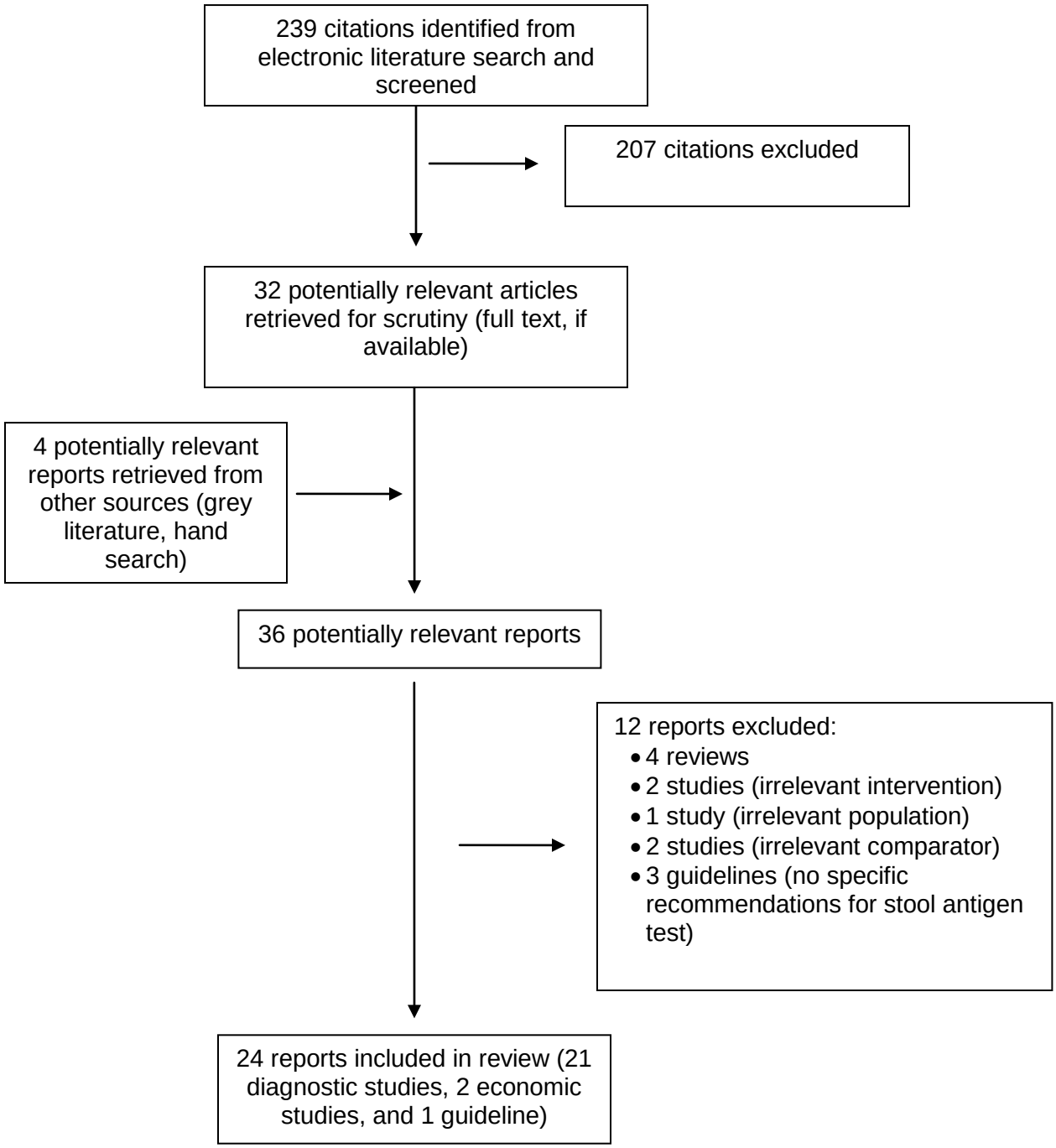
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Patient characteristics, sample Size (n)	Intervention	Comparators	Gold Standard	Outcomes
Fecal antigen detection studies (for diagnosis)					
Okuda et al. (2014)[9] Japan	Retrospective study: Stool samples from 99 adults and 52 children stored between -30 and 80°C.	EIA-based test: Monoclonal Testmate pylori antigen (TPAg EIA, Wakamoto Co.) Cut-off: 0.100	none	Stool PCR	Sensitivity, specificity, accuracy
Osman et al. (2014)[10] Malaysia	Prospective study: 59 adult dyspeptic patients	ICA-based test: Atlas *Helicobacter pylori* antigen test (Atlas medical, UK), a rapid immunoassay using monoclonal anti-*H. pylori* antibody	none	Endoscopy (rapid urease test)	Sensitivity, specificity, PPV, NPV, accuracy
Alam El-Din et al. (2013)[11] Egypt	Prospective study: 52 patients (age: NR) suffering from gastrointestinal disorders. Pathological data were available from 19 patients only	EIA-based using polyclonal antibodies (Immunodiagnostik AG, Gernamy) Cut-off: NR	Endoscopy (histopathology using Hematoxylin and Eosin stain)	Endoscopy (histopathology using giemsa stain)	Sensitivity, specificity, PPV, NPV
Chehter et al. (2013)[12] Brazil	Cross-sectional study: test results of 75 patients had clinical indication for high digestive endoscopy	EIA-based test: Monoclonal Amplified IDEIA Hp Star (DAKO Cytomation, Denmark) Cut-off: NR	Endoscopy (rapid urease test)	Two positive tests: gastric biopsy plus one of urease, breath or serology	Sensitivity, specificity
Korkmaz et al. (2013)[13] Turkey	Prospective study: 198 adult patients (75 men, 123 women; mean age (SD): 49.3 (15.0) years) with dyspeptic symptoms	EIA-based tests: Two monoclonal stool EIA tests (Premier Platinum HpSA Plus and HP Ag) Cut-off: 0.100 or greater	Three rapid ICA tests: • Two monoclonal ICA tests (ImmunoCard STAT! HpSA and *H. pylori* fecal antigen) • One polyclonal ICA	Two invasive tests (histological and rapid urease tests) were positive	Sensitivity, specificity

First Author, Publication Year, Country	Patient characteristics, sample Size (n)	Intervention	Comparators	Gold Standard	Outcomes
			stool antigen test (one-step *H. pylori* antigen test)		
Pourakbari et al. (2013)[14] Iran	Prospective study: 89 patients (61 adults, 28 children) referred to hospital for diagnostic upper gastrointestinal endoscopy Mean age (SD): 44.7 (18.7) years for adults and 9.9 (2.6) years for children	EIA-based test: Monoclonal Stool antigen EIA test (ASTRA, Italy) Cut-off: NR	Endoscopy (rapid urease test, histopathology)	Positive results: confirmed by PCR on biopsy samples Negative results: confirmed by all invasive tests	Sensitivity, specificity, PPV, NPV, accuracy
Sharbatdaran et al. (2013)[15] Iran	Prospective study: 61 patients under 45 years of age with dyspeptic symptoms underwent upper endoscopy and gastric biopsy	EIA-based test: Monoclonal *H. pylori* stool antigen (HpSA) test (GA Generic Assay, Germany) Cut-off: NR	none	Endoscopy (histopathology using hematoxylin and eosin and modified giemsa)	Sensitivity, specificity, PPV, NPV
Tamadon et al. (2013)[16] Iran	Prospective study: 50 hemodialysis patients (30 men, 20 women); mean age (SD): 70 (15.8) years; hemodialysis duration (SD): 32.3 (28.3) months	EIA-based test: Monoclonal *H. pylori* stool antigen (HpSA) test (IBL kit, Germany) Cut-off: 0.100	Urea breath test	At least two out of three tests (urea breath test, stool antigen test and serology) were positive	Sensitivity, specificity, PPV, NPV
Aktepe et al. (2011)[17] Turkey	Prospective study: 132 adult dyspeptic patients receiving diagnostic endoscopy	EIA-based test: Monoclonal antigen FemtoLab *H. pylori* Cnx kits (Connex GmbH, Martinsried, Germany) Cut-off: NR	Endoscopy (culture, biopsy PCR, FISH)	Endoscopy (histopathology using giemsa and hematoxylin and eosin)	Sensitivity, specificity, PPV, NPV
Ceken et al. (2011)[18]	Prospective study: 100 dyspeptic patients	ICA-based test: Monoclonal Helicobacter	Endoscopy (rapid urease test)	Endoscopy (histopathology)	Sensitivity, specificity, PPV, NPV,

First Author, Publication Year, Country	Patient characteristics, sample Size (n)	Intervention	Comparators	Gold Standard	Outcomes
Turkey	(mean age [SD]: 47.6 [17] years) receiving diagnostic endoscopy	antigen Quick Castle test kit (GENERIC ASSAYS GmbH, Germany)			accuracy
Choi et al. (2011)[19] South Korea	Prospective study: 515 consecutive patients (288 women, mean age: 47.8 ± 9.6 years) undergoing routine health check-ups.	EIA-based test using polyclonal antibodies EZ-STEP *H. pylori* Cut-off: 0.160	Endoscopy (rapid urease test) Urea breath test	At least two of four tests (histology, rapid urease test, urea breath test, and serology) were positive	Sensitivity, specificity, PPV, NPV, accuracy
Kazemi et al. (2011)[20] Iran	Prospective study: 110 dyspeptic patients (55 women, age range: 20 to 72 years) who had indication of upper gastrointestinal endoscopy. 16 patients were excluded and 94 patients were available for analysis	ICA-based test: Monoclonal GENERIC ASSAYS GmbH, Germany)	Endoscopy (rapid urease test) Urea breath test	At least two of five tests (stool antigen test, urea breath test, rapid urease test, serology and histology) were positive	Sensitivity, specificity, PPV, NPV, accuracy
Kesli et al. (2010)[21] Turkey	Prospective study: 168 adult dyspeptic patients (52 women, mean age: 46.1 ± 14.2 years) went to hospital for routine upper gastrointestinal endoscopy	EIA-based tests: Monoclonal Premier Platinum HpSA Plus (Meridian Bioscience, Inc, cincinatti, OH) Hp Ag (Dia.Pro Diagnostic Bioprobes Srl, Milano, Italy) Cut-off: 0.100	ICA-based test: Polyclonal *H. pylori* fecal antigen test (Vegal Farmaceutical, Madrid, spain)	Endoscopy (histopathology and rapid urease test)	Sensitivity, specificity, PPV, NPV, accuracy
Silva et al. (2010)[22] Brazil	Prospective study: 98 consecutive patients, asymptomatic or dyspeptic (69 women, mean	ICA-based test: Monoclonal One step H. pylori antigen test device, IHP-602, ACON laboratories, Inc,	none	^{13}C-urea breath test	Sensitivity, specificity, PPV, NPV

First Author, Publication Year, Country	Patient characteristics, sample Size (n)	Intervention	Comparators	Gold Standard	Outcomes
	age: 45.8 ± 14.6 years)	San Diego, USA; Prime diagnostics, Sao Paulo, Brazil			
Calvet et al. (2009)[23] Spain	Prospective study: 199 dyspeptic patients (107 women, mean age: 48.2 ± 14.2 years), had endoscopic examination	EIA-based test: Monoclonal EIA (Amplified IDEIA Hp StAR [Thermo Fisher Scientific]) Cut-off: 0.150	Endoscopy (histology, rapid urease test) Urea breath test	At least two of four tests (histopathology, rapid urease test, urea breath test, and fecal test) were positive	Sensitivity, specificity, PPV, NPV
Fecal antigen detection studies (for follow-up testing)					
Shimoyama et al. (2011)[24] Japan	Prospective study: 102 consecutive patients (48 women, mean age: 60.0 years) received H. pylori eradication therapy	EIA-based test: Monoclonal EIA Testmate rapid pylori antigen (Rapid TPAg; Wakamoto Pharmacrutical Co., Ltd, Kanagawa, Japan) Cut-off: NR	Urea breath test	Endoscopy (histopathology)	Agreement, accuracy
Calvet et al. (2010)[25] Spain	Prospective study: 88 patients (26 women, mean age: 58.3 ± 17.7 years) had at least 8 weeks *H. pylori* treatment	EIA-based test: Monoclonal Amplified IDEIA Hp StAR Cut-off: 0.150	ICA-based tests (monoclonal): • *RAPID* Hp StAR • ImmunoCard STAT! HpSA	Endoscopy (histopathology) or urea breath test	Sensitivity, specificity, PPV, NPV
Falaknazi et al. (2010)[26] Iran	Cross-sectional study: 87 hemodialysis patients (21 women, mean age: 59 years) who had H. pylori infection and had at least 8 weeks *H. pylori* treatment	EIA-based test using polyclonal antibodies: Premier Platinum HpSA (Astra SRL, Via Ciro Menotti, Milano, Italy) Cut-off: 0.12	none	Gold for diagnosis At least two of three tests (serology, urea breath test, and fecal test) were positive Gold for follow-up testing Urea breath test	Sensitivity, specificity, PPV, NPV
Shimoyama et al. (2010)[27] Japan	Prospective study: 239 adult patients (115 women, mean age: 53.8 years)	EIA-based tests: Monoclonal • TPAg EIA • HpSA ELISA II	none	Urea breath test	Agreement between two tests Agreement to urea

First Author, Publication Year, Country	Patient characteristics, sample Size (n)	Intervention	Comparators	Gold Standard	Outcomes
	received H. pylori eradication therapy for 5 to 8 weeks.	Cut-off: NR			breath test
Shimoyama et al. (2009)[28] Japan	Prospective study: 94 patients received H. pylori eradication therapy for 6 to 8 weeks.	EIA-based test: TPAg EIA (monoclonal) Cut-off: NR	none	Urea breath test	Agreement to urea breath test
Degichi et al. (2009)[29] Japan	Prospective study: 150 patients received H. pylori eradication therapy for 4 to 8 weeks.	EIA-based test: Testmate H. pylori antigen EIA (monoclonal) Cut-off: 0.100	EIA-based test: HpSA (polyclonal) Cut-off: <0.100 negative, >0.120 positive, 0.100 to 0.119 equivocal	Urea breath test	Sensitivity, specificity

EIA = enzyme immunoassay; FISH = fluorescence *in situ* hybridization; ICA = immunochromatographic assay; NPV = negative predictive value; NR = not reported; PCR = polymerase chain reaction; PPV = positive predictive value; SD = standard deviation

APPENDIX 3: Characteristics of Economic Studies

First Author, Publication Year, Country	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Intervention, comparator	Cost included
Schulz et al. (2014)[31] Australia	CMA – decision analytic model 1° outcome: net cost per cancer prevented per 1000 people Sensitivity analysis on stool testing with retesting of those treated	Payer Lifetime US$ No discounting	Immigrants and refugees from high prevalence developing countries	Interventions: Nine different screening and follow-up strategies Comparators: Treat all without screening	Costs of testing, and costs of adverse events associated with *H. pylori* Other costs: cost of managing one cancer, cost of a physician visit, cost of medication for eradication, cost of managing one peptic ulcer and lifetime risk of gastric cancer
Holmes et al. (2010)[30] USA	Cost-effectiveness 1° outcome: Cost (US$) per symptom-free year Markov model Probabilistic sensitivity analysis (changes in *H. pylori* prevalence)	Societal Lifetime US$ No discounting	Dyspeptic patients with probability having H. pylori infection, peptic ulcer(s), or both Only patients younger than 55 years	IgG/IgA IgG Stool antigen IgG with reflex to Stool antigen Urea breath test PPI therapy [Begin with each of the first five tests; if positive, do triple therapy; if negative , do PPI therapy] [if there is no relief of symptoms after initial management, or if symptoms recur, patients will go on to receive an endoscopy with biopsy]	Baseline costs of tests and treatments were based on 2009 national midpoint Medicare reimbursement rates.

CMA = cost minimization analysis; IgA = immunoglobulin; IgG = immunoglobulin G; PPI = proton pump inhibitor

APPENDIX 4: Grading of Recommendations and Levels of Evidence

<table>
<tr><th>Guideline Society or Institute</th><th>Recommendation</th><th>Level of Evidence</th></tr>
<tr><td>European Helicobacter Study Group (2012)[32]</td><td colspan="2">
<table>
<tr><th>Grade of recommendation</th><th>Evidence level</th><th></th><th>Type of study</th></tr>
<tr><td>A</td><td>1</td><td>1a</td><td>Systematic review of RCT of good methodological quality and with homogeneity</td></tr>
<tr><td></td><td></td><td>1b</td><td>Individual RCT with narrow CI</td></tr>
<tr><td></td><td></td><td>1c</td><td>Individual RCT with risk of bias</td></tr>
<tr><td>B</td><td>2</td><td>2a</td><td>Systematic review of cohort studies (with homogeneity)</td></tr>
<tr><td></td><td></td><td>2b</td><td>Individual cohort study (including low quality RCT, e.g. <80% follow-up)</td></tr>
<tr><td></td><td></td><td>2c</td><td>Non-controlled cohort studies/ecological studies</td></tr>
<tr><td></td><td>3</td><td>3a</td><td>Systematic review of case control-studies (with homogeneity)</td></tr>
<tr><td></td><td></td><td>3b</td><td>Individual case-control study</td></tr>
<tr><td>C</td><td>4</td><td></td><td>Case series/poor quality cohort or case-control studies</td></tr>
<tr><td>D</td><td>5</td><td></td><td>Expert opinion without critical appraisal or based on physiology, bench research or ‘first principles’</td></tr>
</table>
</td></tr>
<tr><td colspan="3">CI = confidence interval; RCT = randomized controlled trial</td></tr>
</table>

APPENDIX 5: Summary of Study Strengths and Limitations – Diagnostic studies

First Author, Publication Year, Country	Strengths and Limitations
Fecal antigen detection studies (for diagnosis)	
Okuda et al. (2014)[9] Japan	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: high [not all patients received a reference standard]
Osman et al. (2014)[10] Malaysia	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Alam El-Din et al. (2013)[11] Egypt	Domain 1: Patient selection • Risk of bias: high [63% patients were excluded from the study] • Concerns regarding applicability: high [63% patients were excluded from the study] Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: high [63% patients did not have pathologic data]
Chehter et al. (2013)[12] Brazil	Domain 1: Patient selection • Risk of bias: unclear [if the study avoided inappropriate exclusions] • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low

First Author, Publication Year, Country	Strengths and Limitations
	Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: high [not all patients received index test and/or reference standard]
Korkmaz et al. (2013)[13] Turkey	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Pourakbari et al. (2013)[14] Iran	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Sharbatdaran et al. (2013)[15] Iran	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Tamadon et al. (2013)[16] Iran	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low

First Author, Publication Year, Country	Strengths and Limitations
	• Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Aktepe et al. (2011)[17] Turkey	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Ceken et al. (2011)[18] Turkey	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Choi et al. (2011)[19] South Korea	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Kazemi et al. (2011)[20] Iran	Domain 1: Patient selection • Risk of bias: unclear [16% patients were excluded] • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low

First Author, Publication Year, Country	Strengths and Limitations
	• Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Kesli et al. (2010)[21] Turkey	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Silva et al. (2010)[22] Brazil	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Calvet et al. (2009)[23] Spain	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: low • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Fecal antigen detection studies (for follow-up testing)	
Shimoyama et al. (2011)[24] Japan	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low

First Author, Publication Year, Country	Strengths and Limitations
	Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: unclear [not all patients received reference standard]
Calvet et al. (2010)[25] Spain	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: high [not all patients received reference standard]
Falaknazi et al. (2010)[26] Iran	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Shimoyama et al. (2010)[27] Japan	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Shimoyama et al. (2009)[28]	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low

First Author, Publication Year, Country	Strengths and Limitations
Japan	Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low
Degichi et al. (2009)[29] Japan	Domain 1: Patient selection • Risk of bias: low • Concerns regarding applicability: low Domain 2: Index test(s) • Risk of bias: low • Concerns regarding applicability: low Domain 3: Reference standard • Risk of Bias: unclear [if correctly classify the target condition] • Concerns regarding applicability: low Domain 4: Flow and timing • Risk of bias: low

APPENDIX 6: Summary of Study Strengths and Limitations – Economic studies

First Author, Publication Year	Strengths	Limitations
Schulz et al. (2014)[31]	Study design • The research question is stated • The economic importance of the research question is stated • The rationale for choosing alternative programmes or interventions compared is stated • The form of economic evaluation used is stated • The choice of form of economic evaluation used is stated Data collection • The source(s) of effectiveness estimates used are stated • The primary outcome measure(s) for the economic evaluation are clearly stated • Methods to value benefit are stated • Quantities of resource use are not reported separately from their unit costs • Methods for the estimation of quantities and unit costs are described • Currency and price data are recorded • Details of currency of price adjustments for inflation or currency conversion are given • Details of any model use are given • The choice of model used and the key parameters on which it is based are justified Analysis and interpretation of results • Time horizon of costs and benefits is stated • The approach to sensitivity analysis is given • The choice of variables for sensitivity analysis is justified • Incremental analysis is reported • Major outcomes are reported in a disaggregated as well as aggregated form • The answer of the study is given • Conclusions follow from data reported	Analysis and interpretation of results • The discount rate is not stated • Details of statistical tests are not given

First Author, Publication Year	Strengths	Limitations
Holmes et al. (2010)[30]	Study design • The research question is stated • The economic importance of the research question is stated • The rationale for choosing alternative programmes or interventions compared is stated • The form of economic evaluation used is stated • The choice of form of economic evaluation used is stated Data collection • The source(s) of effectiveness estimates used are stated • The primary outcome measure(s) for the economic evaluation are clearly stated • Methods for the estimation of quantities and unit costs are described • Currency and price data are recorded • Details of any model use are given Analysis and interpretation of results • Time horizon of costs and benefits is stated • The approach to sensitivity analysis is given • Incremental analysis is reported • Major outcomes are reported in a disaggregated as well as aggregated form • The answer of the study is given • Conclusions follow from data reported	Data collection • Methods to value benefit are not stated • Quantities of resource use are not reported separately from their unit costs • Details of currency of price adjustments for inflation or currency conversion are not given • The choice of model used and the key parameters on which it is based are not justified Analysis and interpretation of results • The discount rate is not stated • The choice of variables for sensitivity analysis is not justified • Details of statistical tests are not given

APPENDIX 7: Summary of Study Strengths and Limitations – Guidelines

First Author, Publication Year	Strengths	Limitations
European Helicobacter Study Group (2012)[32]	Scope and purpose • Objectives and target patients population were explicit • The health question covered by the guidelines is specifically described • The population to whom the guidelines is meant to apply is specifically described Stakeholder involvement • The guideline development group includes individuals from all relevant professional groups • The views and preferences of the target population have been sought • The target users of the guideline are clearly defined Rigour of development • Systematic methods were used to search for evidence • The criteria for selecting the evidence are clearly described • The strengths and limitations of the body of evidence are clearly described • The methods of formulating the recommendations are clearly described • The health benefits, side effects, and risks have been considered in formulating the recommendations • There is an explicit link between the recommendations and the supporting evidence • The guideline has been externally reviewed by experts prior to its publication Applicability • The guideline presents monitoring and/or auditing criteria Clarity of recommendation • The recommendations are specific and unambiguous • The different options for management of the condition or health issue are clearly presented • Key recommendations are easily identified Editorial independence • Competing interests of guideline development group members have been recorded and addressed	Rigour of development • A procedure for updating the guideline is not provided Applicability • The guideline does not describe facilitators and barriers to its application • The guidelines does not provide advice and/or tools on how the recommendations can be put into practice • The potential resource implications of applying the recommendations have not been considered Editorial independence • It is unclear if the views of the funding body have influenced the content of the guideline

APPENDIX 8: Main Study Findings and Authors' Conclusions – Clinical

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	Comparators
Diagnostic accuracy studies (for diagnosis)						
Okuda et al. (2014)[9] Japan	EIA-based test: Monoclonal Testmate pylori antigen (TPAg EIA, Wakamoto Co.)	0.100	none	Stool PCR	Adults: Sensitivity: 92.4% Specificity: 100% Accuracy: 94.9% Children: Sensitivity: 82.7% Specificity: 100% Accuracy: 90.4%	none
Authors' conclusions: "*A stool antigen test (TPAg) using mAb for native catalase is useful for diagnosis of H. pylori in children and adults. Additionally, this test has particularly high specificity.*"						
Osman et al. (2014)[10] Malaysia	ICA-based test: Atlas *Helicobacter pylori* antigen test (Atlas medical, UK), a rapid immunoassay using monoclonal anti-*H. pylori* antibody	NR	none	Endoscopy (rapid urease test)	Sensitivity: 91.7% Specificity: 100% PPV: 100% NPV: 94.6% Accuracy: 96.6%	none
Authors' conclusions: "*The Atlas H. pylori antigen test is a new non-invasive method which is simple to perform and avails reliable results in a few minutes."*						
Alam El-Din et al. (2013)[11] Egypt	EIA-based using polyclonal antibodies (Immunodiagnostik AG, Gernamy)	Cut-off: NR	Endoscopy (histopathology using Hematoxylin and Eosin stain)	Endoscopy (histopathology using Giemsa stain)	Sensitivity: 72.2% Specificity: -- PPV: 92.9 NPV: -- (specificity and NPV could not be calculated – no true-negative cases)	Histopathology Sensitivity: 88.9% Specificity: 100% PPV: 100% NPV: 33.3%
Authors' conclusions: "*Among the non-invasive methods for diagnosis of H. pylori infection, the 3 methods used in this study recorded promising results, including good sensitivity*"						

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	Comparators
Chehter et al. (2013)[12] Brazil	EIA-based test: Monoclonal Amplified IDEIA Hp Star (DAKO Cytomation, Denmark)	Cut-off: NR	Endoscopy (rapid urease test)	Two positive tests: gastric biopsy plus one of urease, breath or serology	Sensitivity: 87.2% Specificity: 44%	Rapid urease test Sensitivity: 65.6% Specificity: 58.8%
Authors' conclusions: "*The ROC curve showed a good correlation between the compared methods. In Brazil the standardization of the ELISA test for the detection of H. pylori in stool specimens constitutes a non-invasive diagnostic alternative."*						
Korkmaz et al. (2013)[13] Turkey	EIA-based tests: Two monoclonal stool EIA tests (Premier Platinum HpSA Plus and HP Ag)	Cut-off: 0.100 or greater for Premier Platinum HpSA Plus and HP Ag	Three rapid ICA tests: • Two monoclonal ICA tests (ImmunoCard STAT! HpSA and *H. pylori* fecal antigen) • One polyclonal ICA stool antigen test (one-step *H. pylori* antigen test)	Two invasive tests (histological and rapid urease tests) were positive	Premier Platinum HpSA Plus test Sensitivity: 92.2% Specificity: 94.4% HP Ag test Sensitivity: 48.9% Specificity: 88.9%	ImmunoCard STAT! HpSA test Sensitivity: 68.9% Specificity: 92.6% *H. pylori* fecal antigen test Sensitivity: 78.9% Specificity: 87% One-step *H. pylori* antigen test Sensitivity: 86.7% Specificity: 88.9%
Authors' conclusions: "*The Premier Platinum HpSA Plus EIA test was determined to be the most accurate stool test for diagnosis H. pylori infections in adult dyspeptic patients. The currently available ICA-based tests are fast and easy to use but provide less reliable results*."						
Pourakbari et al. (2013)[14] Iran	EIA-based test: Monoclonal Stool antigen EIA test (ASTRA, Italy)	Cut-off: NR	Endoscopy (rapid urease test, histopathology)	Positive results: confirmed by PCR on biopsy samples Negative results: confirmed by all invasive tests	Sensitivity: 87.8% Specificity: 75% PPV: 81.1% NPV: 83.3% Accuracy: 82%	Rapid urease test: Sensitivity: 95.9% Specificity: 85% PPV: 88.7% NPV: 94.4% Accuracy: 91% Histopathology: Sensitivity: 100% Specificity: 90% PPV: 92.5%

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	Comparators
						NPV: 100% Accuracy: 95%
Authors' conclusions: "*Stool antigen test can consider as a suitable non-invasive test for detection of H. pylori infection*."						
Sharbatdaran et al. (2013)[15] Iran	EIA-based test: Monoclonal *H. pylori* stool antigen (HpSA) test (GA Generic Assay, Germany)	Cut-off: NR	none	Endoscopy (histopathology using hematoxylin and eosin and modified Giemsa)	Sensitivity: 66% Specificity: 91% PPV: 93% NPV: 62%	none
Authors' conclusions: "*The HpSA test for the detection of H. pylori infection seems to be a good alternative for invasive diagnostic tests such as urea breath test, especially in our country*"						
Tamadon et al. (2013)[16] Iran	EIA-based test: Monoclonal *H. pylori* stool antigen (HpSA) test (IBL kit, Germany)	Cut-off: 0.100	Urea breath test	At least two out of three tests (urea breath test, stool antigen test and serology) were positive	Sensitivity: 100% Specificity: 75% PPV: 60.9% NPV: 100%	Urea breath test Sensitivity: 62.5% Specificity: 65.4% PPV: 62.5% NPV: 65.4%
Authors' conclusions: "…*stool antigen test has higher diagnostic values than UBT, and… more reliable than UBT in diagnosis of H. pylori infection in hemodialysis patients*"						
Aktepe et al. (2011)[17] Turkey	EIA-based test: Monoclonal antigen FemtoLab *H. pylori* Cnx kits (Connex GmbH, Martinsried, Germany)	Cut-off: NR	Endoscopy (culture, biopsy PCR, FISH)	Endoscopy (histopathology using giemsa and hematoxylin and eosin)	Sensitivity: 72.2% Specificity: 66.7% PPV: 81.3% NPV: 45.5%	Culture Sensitivity: 61.2% Specificity: 91.5% PPV: 92.9% NPV: 43.4% Biopsy PCR Sensitivity: 88.2% Specificity: 51.1% PPV: 76.5% NPV: 29.4% FISH Sensitivity: 92.9% Specificity: 95.7% PPV: 97.5% NPV: 11.8%

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	Comparators
Authors' conclusions: "*The HpSA test is a rapid, simple, and noninvasive test for monitoring therapy. FISH is an accurate, rapid, cost-effective, and easy-to-use test for H. pylori detection*."						
Ceken et al. (2011)[18] Turkey	<u>ICA-based test:</u> Monoclonal Helicobacter antigen Quick Castle test kit (GENERIC ASSAYS GmbH, Germany)	Cut-off: NR	Endoscopy (rapid urease test)	Endoscopy (histopathology)	Sensitivity: 68.9% Specificity: 100% PPV: 100% NPV: 67.2% Accuracy: 81%	<u>Rapid urease test</u> Sensitivity: 62.2% Specificity: 100% PPV: 100% NPV: 66.1% Accuracy: 80%
Authors' conclusions: "*The results obtained with biopsy urease and HpSA tests were generally similar to those obtained by histopathological examination*."						
Choi et al. (2011)[19] South Korea	<u>EIA-based using polyclonal antibodies</u> EZ-STEP *H. pylori*	Cut-off: 0.160	Endoscopy (rapid urease test) Urea breath test	At least two of four tests (histology, rapid urease test, ^{13}C-urea breath test, and serology) were positive	Sensitivity: 93.1% Specificity: 94.6% PPV: 95.1% NPV: 92.3% Accuracy: 93.8%	<u>Histology</u> Sensitivity: 89.1% Specificity: 98.8% PPV: 98.8% NPV: 88.8% Accuracy: 93.6% <u>Rapid urease test</u> Sensitivity: 91.2% Specificity: 99.6% PPV: 99.6% NPV: 90.9% Accuracy: 95.1% <u>Urea breath test</u> Sensitivity: 92.7% Specificity: 99.6% PPV: 99.6% NPV: 92.3% Accuracy: 95.9%
Authors' conclusions: "*The performance of a new stool antigen test was comparable to that of other methods in the diagnosis of H. pylori infection for the screening population, even with the presence of atropic gastritis/intestinal metaplasia*."						
Kazemi et al. (2011)[20] Iran	<u>ICA-based test:</u> Monoclonal GENERIC ASSAYS GmbH,	Cut-off: NR	Endoscopy (rapid urease test)	At least two of five tests (stool antigen test, urea breath test, rapid urease test, serology and	Sensitivity: 96% Specificity: 83% PPV: 98% NPV: 96%	<u>Histology</u> Sensitivity: 89% Specificity: 78% PPV: 93%

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	Comparators
	Germany)		Urea breath test	histology) were positive	Accuracy: 91%	NPV: 91% Accuracy: 85% Rapid urease test Sensitivity: 93% Specificity: 75% PPV: 95% NPV: 94% Accuracy: 86% Urea breath test Sensitivity: 96% Specificity: 83% PPV: 98% NPV: 96% Accuracy: 91%
Authors' conclusions: "*Stool antigen test is the most accurate test for Helicobacter pylori diagnosis before eradication of these bacteria*."						
Kesli et al. (2010)[21] Turkey	EIA-based tests: Monoclonal Premier Platinum HpSA Plus (Meridian Bioscience, Inc, cincinatti, OH) Hp Ag (Dia.Pro Diagnostic Bioprobes Srl, Milano, Italy)	Cut-off: 0.100	Lateral flow chromatography (ICA) Polyclonal *H. pylori* fecal antigen test (Vegal Farmaceutical, Madrid, spain)	Endoscopy (histopathology and rapid urease test)	Premier Platinum HpSA Plus Sensitivity: 90% Specificity: 91% PPV: 85% NPV: 94% Accuracy: 90% Hp Ag Sensitivity: 77% Specificity: 91% PPV: 83% NPV: 87% Accuracy: 86%	H.pylori fecal antigen test Sensitivity: 81% Specificity: 92% PPV: 86% NPV: 89% Accuracy: 88%
Authors' conclusions: "*One of the 2 important conclusions obtained from the study was that the Premier Platinum HpSA Plus was found to be the most accurate test for the diagnosis of H. pylori infection in adult dyspeptic patients before eradication therapy, and the other was that monoclonal and high-quality, reliable immunochromatographic assay tests are a good option especially for small hospital laboratories that do not have appropriate equipment for performing the EIA and working on few samples*."						
Silva et al. (2010)[22]	ICA-based test: Monoclonal One step H. pylori	Cut-off: NR	none	^{13}C-urea breath test	Sensitivity: 88% Specificity: 87.5% PPV: 88%	none

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	Comparators
Brazil	antigen test device, IHP-602, ACON laboratories, Inc, San Diego, USA; Prime diagnostics, Sao Paulo, Brazil				NPV: 87.5%	
Authors' conclusions: "*the lateral flow stool antigen test can be used as an alternative to breath test for H. pylori infection diagnosis especially in developing countries.*"						
Calvet et al. (2009)[23] Spain	EIA-based test: Monoclonal EIA (Amplified IDEIA Hp StAR [Thermo Fisher Scientific])	Cut-off: 0.150	Endoscopy (histology, rapid urease test) Urea breath test	At least two of four tests (histology, rapid urease test, ^{13}C-urea breath test, and fecal test) were positive	Sensitivity: 90.3% Specificity: 93% PPV: 94.4% NPV: 87.9%	Histology Sensitivity: 93.8% Specificity: 98.8% PPV: 99.1% NPV: 92.4% Rapid urease test Sensitivity: 94.7% Specificity: 100% PPV: 100% NPV: 93.5% Urea breath test Sensitivity: 90.3% Specificity: 89.5% PPV: 91.9% NPV: 87.5%
Authors' conclusions: "*Histological examination and rapid urease testing showed excellent diagnostic reliability. The stool test seems to be a good, noninvasive alternative to endoscopy-based tests. By contrast, the infrared-based UBT evaluated in our study showed a lower than expected performance, which was partially corrected when the cut-off value for the test was recalculated*."						
Fecal antigen detection studies (for follow-up testing)						
Shimoyama et al. (2011)[24] Japan	EIA-based test: Monoclonal EIA: Testmate rapid pylori antigen (Rapid TPAg; Wakamoto Pharmacrutical	Cut-off: NR	Urea breath test	Endoscopy (histopathology)	Agreement: 94.1% Accuracy: 98.0%	Agreement: 94.1% Accuracy: 96.0%

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	Comparators
	Co., Ltd, Kanagawa, Japan)					
Authors' conclusions: "*Rapid TPAg is a useful diagnostic test for immediate and accurate determination of the results of H. pylori eradication therapy. The antigenicity of stool sample suspensions was preserved for 7 days in the collection devices*."						
Calvet et al. (2010)[25] Spain	EIA-based test: Monoclonal Amplified IDEIA Hp StAR	Cut-off: 0.150	ICA-based tests (monoclonal): • *RAPID* Hp StAR • ImmunoCard STAT! HpSA	Endoscopy (histopathology) or urea breath test	Sensitivity: 100% Specificity: 93.6% PPV: 66.7% NPV: 100%	*RAPID* Hp StAR Sensitivity: 100% Specificity: 93.6% PPV: 67.0% NPV: 100% ImmunoCard STAT! HpSA Sensitivity: 90% Specificity: 94.9% PPV: 69.2% NPV: 98.7%
Authors' conclusions: "*All monoclonal fecal tests in this series presented similar performance in the post-treatment setting. A negative test after treatment predicted cure of the infection. However, nearly a third of tests were false positive, showing a poor predictive yield for persistent infection*."						
Falaknazi et al. (2010)[26] Iran	EIA-based test using polyclonal antibodies: Premier Platinum HpSA (Astra SRL, Via Ciro Menotti, Milano, Italy)	Cut-off: 0.12	none	Gold for diagnosis At least two of three tests (serology, ^{13}C-urea breath test, and fecal test) were positive Gold for follow-up testing Urea breath test	Diagnosis Sensitivity: 87.1% Specificity: 93.7% PPV: 91.8% NPV: 90.0% After treatment to detect failure of eradication Sensitivity: 42.8% Specificity: 93.3% PPV: 60.0% NPV: 87.5%	none
Authors' conclusions: "*Helicobacter pylori stool antigen assay is a noninvasive reliable tool to screen H pylori infection before therapy and assess the success of eradication in patients on hemodialysis*."						
Shimoyama et al. (2010)[27] Japan	EIA-based tests: • TPAg EIA • HpSA ELISA II	Cut-off: NR	none	Urea breath test	Agreement between the two tests: 95.6% Agreement to urea	none

Study	Stool antigen test	Cut-off value	Comparators	Reference standard	Test performance	
					Stool antigen test	**Comparators**
					breath test: • TPAg EIA: 91.2% • HpSA ELISA II: 95.4%	
Authors' conclusions: "*Both TPAg EIA and HpSA ELISA II were equally useful to determine the results of eradication therapy comparing with UBT."*						
Shimoyama et al. (2009)[28] Japan	EIA-based test: TPAg EIA (monoclonal)	Cut-off: NR	none	Urea breath test	Agreement to urea breath test: 94.7%	none
Authors' conclusions: "*TPAg appears to be an accurate test for evaluating the results of H. pylori eradication therapy, and to be as efficient as ^{13}C-UBT*."						
Degichi et al. (2009)[29] Japan	EIA-based tests: • Testmate H. pylori antigen EIA (monoclonal) • HpSA (polyclonal)	Monoclonal Cut-off: 0.100 Polyclonal Cut-off: <0.100 negative, >0.120 positive, 0.100 to 0.119 equivocal	none	Urea breath test	Monoclonal (Testmate) Sensitivity: 91.6% Specificity: 98.4% Polyclonal (HpSA) Sensitivity: 87.0% Specificity: 97.5%	none
Authors' conclusions: "*The new stool antigen test using monoclonal antibody is useful for the diagnosis of H. pylori eradication 4 weeks after the end of treatment.*"						

EIA = enzyme immunoassay; FISH = fluorescence *in situ* hybridization; ICA = immunochromatographic assay; NPV = negative predictive value; NR = not reported; PCR = polymerase chain reaction; PPV = positive predictive value; SD = standard deviation

APPENDIX 9: Main Study Findings and Authors' Conclusions – Economic

<table>
<tr><th>Author, Year, Country</th><th>Main Study Findings</th></tr>
<tr><td>Schulz et al. (2014)[31]

Australia</td><td>Net cost per cancer prevented (US$) for each strategy at varying prevalence of H. pylori
<table>
<tr><th>Net cost per cancer prevented</th><th colspan="3">Prevalence</th></tr>
<tr><th>Management options</th><th>25%</th><th>50%</th><th>75%</th></tr>
<tr><td>Treat all and no screening</td><td>477800</td><td>206900</td><td>116600</td></tr>
<tr><td>Serology</td><td></td><td></td><td></td></tr>
<tr><td>No follow-up</td><td>294700</td><td>169900</td><td>128300</td></tr>
<tr><td>Stool antigen test</td><td></td><td></td><td></td></tr>
<tr><td>No follow-up</td><td>219200</td><td>142700</td><td>117100</td></tr>
<tr><td>Follow-up and retreat</td><td>193900</td><td>132300</td><td>111800</td></tr>
<tr><td>Urea breath test</td><td></td><td></td><td></td></tr>
<tr><td>No follow-up</td><td>360200</td><td>213800</td><td>165000</td></tr>
<tr><td>Follow-up and retreat</td><td>334600</td><td>216400</td><td>177000</td></tr>
<tr><td>Gastroscopy</td><td></td><td></td><td></td></tr>
<tr><td>No follow-up</td><td>972000</td><td>520600</td><td>370200</td></tr>
<tr><td>Follow-up with gastroscopy and retreat</td><td>939900</td><td>577200</td><td>456300</td></tr>
<tr><td>Follow-up with breath test and retreat</td><td>820200</td><td>460100</td><td>340100</td></tr>
<tr><td>Follow-up with stool antigen and retreat</td><td>794400</td><td>433900</td><td>313700</td></tr>
</table></td></tr>
<tr><td colspan="2">Authors' conclusions: "H. pylori screening and eradication can be effective strategy for reducing rates of gastric cancer and peptic ulcers in high prevalence populations and our data suggest that use of stool antigen testing is the most cost effective approach."</td></tr>
<tr><td>Holmes et al. (2010)[30]

USA</td><td>Cost-effectiveness ratios for each strategy
<table>
<tr><th>Strategy</th><th>Cost (US$) per symptom-free year (95% CI)</th></tr>
<tr><td>PPI therapy</td><td>122.13 (120.00 to 124.88)</td></tr>
<tr><td>Stool antigen</td><td>123.23 (120.68 to 125.58)</td></tr>
<tr><td>IgG serology</td><td>125.76 (123.18 to 128.27)</td></tr>
<tr><td>IgG serology with reflex to stool antigen</td><td>126.17 (123.43 to 128.08)</td></tr>
<tr><td>Urea breath test</td><td>128.31 (125.69 to 130.72)</td></tr>
<tr><td>IgG/IgA binary serology</td><td>129.04 (126.43 to 131.48)</td></tr>
</table>
Cost per correct diagnosis for each strategy modeled
<table>
<tr><th>Testing strategy</th><th>Average cost per correct diagnosis</th></tr>
<tr><td>Stool antigen</td><td>$2767.85</td></tr>
<tr><td>Urea breath test</td><td>$2825.24</td></tr>
<tr><td>IgG serology</td><td>$3371.91</td></tr>
<tr><td>IgG serology with reflex to stool antigen</td><td>$3373.39</td></tr>
<tr><td>IgG/IgA binary serology</td><td>$4061.91</td></tr>
</table>
None of the results were sensitive to changes in prevalence of H. pylori (5% to 40%).</td></tr>
<tr><td colspan="2">Authors' conclusions: "In this model of H. pylori diagnosis and treatment, the choice of initial noninvasive test did not have a significant impact on cost or quality outcome. This is likely attributable to the assumption of a high resource intensity practice environment. In practice settings where endoscopy is less available and/or less readily employed, these findings may not apply."</td></tr>
<tr><td colspan="2">IgA = immunoglobulin; IgG = immunoglobulin G; PPI = proton pump inhibitor</td></tr>
</table>

APPENDIX 10: Guidelines and Recommendations on stool antigen tests for *Helicobacter pylori* infection

Guideline Society, Country, Author, Year	Recommendations
European Helicobacter Study Group Malfertheiner et al. (2012)[32] 44 experts, 24 countries	• *The main non-invasive tests that can be used for the test-and-treat strategy are the UBT and monoclonal stool antigen tests. Certain validated serological tests can also be used.* (**Grade B, Level 2a**) p. 647 • *The diagnostic accuracy of the stool antigen (SAT) is equivalent to the UBT if a validated laboratory-based monoclonal test is used.* (**Grade A, Level 1a**) p. 649 • *The UBT or a laboratory-based validated monoclonal stool test are both recommended as non-invasive tests for determining the success of eradication treatment. There is no role for serology.* (**Grade A, Level 1a**) p. 653
UBT = urea breath test	