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Helicobacter pylori and Gastroduodenal Diseases: Advances in Diagnostic Strategies and Clinical Implications

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ABSTRACT

Background: Helicobacter pylori causes a substantial global burden of gastroduodenal disease, including peptic ulcer, gastric MALT lymphoma, and adenocarcinoma. Accurate, context-specific diagnosis is essential to guide eradication therapy, reduce complications, and enable cancer prevention, yet test performance varies with bacterial distribution, medication exposure, bleeding, and prior surgery. Objective: To synthesize contemporary diagnostic strategies for H. pylori, integrate evidence from guidelines and primary studies, and appraise emerging tools—artificial intelligence (AI)–assisted endoscopy and proteomics—for their clinical utility and implementation. Methods: We conducted a narrative review of English-language literature (2000–2025) across PubMed, Scopus, and Web of Science, supplemented by guideline statements (Maastricht, ACG/CAG, Japanese) and reference snowballing. Evidence was organized by invasive versus non-invasive modalities, clinical scenarios (dyspepsia, bleeding, pediatrics, post-gastrectomy, test-of-cure), and translational technologies (AI, proteomics). Results: Urea breath test and monoclonal stool antigen assays consistently demonstrated ≥90% accuracy for initial diagnosis and post-treatment confirmation, contingent on appropriate medication washout. Biopsy-based histology, rapid urease testing, culture, and molecular assays offered complementary information—particularly for histopathology and resistance profiling—but were impacted by sampling and pre-analytical factors. AI systems improved endoscopic recognition and biopsy targeting, while proteomic studies identified candidate biomarkers (e.g., HSPs, annexins, ENO1, GKN1) with diagnostic and prognostic potential; however, external validation and workflow standardization remain limiting. Conclusion: Optimal H. pylori diagnosis requires individualized test selection and, where appropriate, combined strategies. AI and proteomics are poised to augment established pathways, enabling precision, resistance-aware care and earlier cancer prevention once validated and operationalized. Keywords: Helicobacter pylori; urea breath test; stool antigen; endoscopy; histopathology; rapid urease test; culture; PCR; antibiotic resistance; artificial intelligence; proteomics; biomarkers; gastric cancer; dyspepsia; precision medicine

Keywords
Antimicrobial resistance, phytochemicals, efflux pump inhibitors, synergistic therapy, plant-derived antimicrobials, alternative therapeutics.

INTRODUCTION

Helicobacter pylori is a microaerophilic, spiral-shaped, gram-negative bacterium that chronically colonizes the human stomach and is implicated in a spectrum of gastroduodenal disorders, including non-atrophic and atrophic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma (1–3). Global prevalence remains high—particularly in low- and middle-income countries—sustaining a substantial burden of dyspepsia, ulcer complications, and cancer risk at the population level (4,5). Eradication of *H. pylori* reduces ulcer recurrence and is associated with a lower subsequent risk of gastric cancer, underscoring the importance of accurate detection and timely treatment (6–8). Selecting the right diagnostic test for the right patient—and at the right time—remains a practical challenge. Available options span **non-invasive** methods such as the ^13C urea breath test (UBT), monoclonal stool antigen testing (SAT), and serology, and **invasive** approaches including endoscopy with targeted biopsies for histopathology, rapid urease testing (RUT), culture with susceptibility testing, and biopsy-based molecular assays (qPCR/NGS) (9–12). Test performance is influenced by multiple, often under-appreciated, factors: patchy bacterial distribution leading to sampling error; recent exposure to proton-pump inhibitors, antibiotics, bismuth, or H2-receptor antagonists; active upper gastrointestinal bleeding; and prior gastric surgery—all of which can shift sensitivity and specificity in predictable ways (13–16). In parallel, rising macrolide and fluoroquinolone resistance is reshaping diagnostic priorities toward assays that can also inform therapy selection (17,18).

Concurrently, **advances in imaging and computational methods** are beginning to refine endoscopic decision-making. Artificial intelligence (AI) systems trained on endoscopic images show promise for lesion detection and biopsy targeting, potentially reducing operator variability and improving the recognition of patterns associated with *H. pylori* gastritis and early neoplasia (19–21). In **translational diagnostics**, proteomics offers complementary opportunities: discovery of circulating or stool protein signatures linked to *H. pylori*–associated pathology and gastric

carcinogenesis, which could augment or, in defined contexts, partially substitute for current tests once robustly validated (22–24). However, issues of pre-analytical variability, cohort heterogeneity, and limited external validation have thus far constrained routine adoption (25,26).

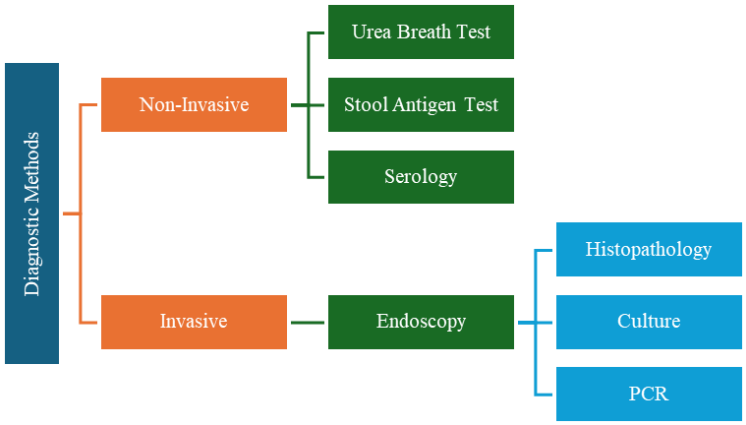

Figure 1 Diagnostic Methods Schema

This **narrative review** synthesizes contemporary diagnostic strategies for *H. pylori* across invasive and non-invasive modalities, harmonizes reported performance characteristics with real-world modifiers, and distills practical, context-specific testing recommendations relevant to dyspepsia care, peptic ulcer disease, high-risk cancer surveillance, pediatrics, and post-treatment test-of-cure (27–29). We also appraise the emerging contributions—and current limitations—of AI-assisted endoscopy and proteomics-based biomarkers, focusing on how these developments may integrate into pragmatic pathways rather than replacing established tests outright (30–32). Our goal is to provide clinicians and researchers with a concise, practice-oriented framework that supports accurate diagnosis, resistance-aware management, and judicious use of novel technologies in patients with *H. pylori*–associated gastroduodenal disease (33,34).

METHODS OF THE REVIEW

This work is structured as a narrative review that synthesizes current knowledge on diagnostic approaches for *Helicobacter pylori*–associated gastroduodenal diseases and evaluates emerging technologies such as artificial intelligence and proteomics within this context. A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science databases for English-language articles published between 2000 and 2025. Search terms included combinations of "*Helicobacter pylori*," "diagnosis," "urea breath test," "stool antigen test," "endoscopy," "rapid urease test," "molecular diagnostics," "resistance testing," "artificial intelligence," and "proteomics." Key international guidelines were also reviewed, including the Maastricht V/Florence consensus, American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG) joint recommendations, and Japanese Society for Helicobacter Research statements (35–38). References from identified papers were further screened to capture additional relevant studies. Studies were selected for inclusion based on relevance to diagnostic performance, clinical application, population screening, or technological innovation. Given the narrative nature of this review, no formal protocol was registered, and no meta-analysis or quantitative synthesis was performed. All sensitivity, specificity, and accuracy values reported herein are derived from peer-reviewed studies and guideline consensus unless otherwise noted.

PATHOPHYSIOLOGY OF *HELICOBACTER PYLORI* INFECTION

H. pylori possesses a suite of biological adaptations that allow it to survive in the harsh gastric environment and establish chronic infection, leading to a wide range of gastroduodenal pathologies (39,40). Motility mediated by 4–6 polar flagella enables the bacterium to penetrate the viscous gastric mucus layer and migrate toward less acidic niches near the epithelial surface (41). Chemotaxis further directs movement along pH gradients, allowing colonization beneath the protective mucus where the environment is more favorable for persistence (42).

A critical feature of *H. pylori* pathogenesis is its ability to neutralize gastric acidity. The bacterium produces large quantities of urease, which hydrolyzes urea into ammonia and carbon dioxide. Ammonia acts as a buffer, raising local pH and creating a microenvironment that protects *H. pylori* from gastric acid (43). Urease activity is indispensable for colonization; knockout mutants lacking urease are unable to persist in the gastric mucosa (44). In addition, *H. pylori* expresses arginase, a binuclear manganese metalloenzyme that converts L-arginine to L-ornithine and urea. The resulting polyamines are involved in bacterial metabolism and contribute to immune evasion by competing with host inducible nitric oxide synthase, thus impairing nitric oxide-mediated antimicrobial activity (45). Adhesion to gastric epithelial cells is another key pathogenic mechanism. Outer membrane adhesins such as blood group antigen-binding adhesin (BabA) and sialic acid-binding adhesin (SabA) mediate binding to Lewis b and sialyl Lewis x antigens on the epithelial surface (46,47). BabA-mediated binding is pH-sensitive and reversible, enabling the bacterium to dynamically adapt to the changing gastric environment (48). Adhesion enhances colonization efficiency, facilitates nutrient acquisition, and anchors the bacterium close to host cells, where it can deliver virulence factors.

Once established, *H. pylori* infection triggers chronic gastritis characterized by infiltration of neutrophils, macrophages, and lymphocytes into the mucosa. Persistent inflammation contributes to epithelial damage, disruption of gastric acid regulation, and progression to more severe diseases such as peptic ulceration, gastric atrophy, intestinal metaplasia, and ultimately gastric adenocarcinoma (49–51). The bacterium's virulence factors—such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA)—further modulate host cell signaling, promote genomic instability, and potentiate oncogenic transformation (52,53). The patchy distribution of *H. pylori* within the gastric mucosa has direct implications for diagnostic accuracy. Uneven colonization increases the risk of sampling error during endoscopic biopsy and histopathological analysis (54). Moreover, the bacterium can shift into a coccoid, dormant form under antibiotic pressure or environmental stress, reducing metabolic activity and potentially yielding false-negative results in certain diagnostic tests (55). Understanding these pathophysiological adaptations is essential for interpreting diagnostic outcomes and tailoring test selection to clinical context.

DIAGNOSTIC MODALITIES FOR *HELICOBACTER PYLORI* INFECTION

Accurate diagnosis of *Helicobacter pylori* infection is central to effective clinical management, as it guides eradication therapy, enables risk stratification for gastric cancer, and informs surveillance decisions. Diagnostic approaches fall broadly into invasive and non-invasive categories,

each with distinct advantages, limitations, and indications. Invasive methods require endoscopic sampling, allowing direct visualization of the gastric mucosa and collection of biopsy specimens, while non-invasive approaches rely on breath, stool, or blood samples and are more suitable for screening and follow-up (56,57). Endoscopy remains a cornerstone in the diagnosis of *H. pylori*-associated disease. It allows direct assessment of mucosal pathology and targeted biopsy collection, which improves diagnostic yield, particularly when specimens are obtained from both the antrum and corpus to minimize sampling error due to patchy bacterial distribution (58). Visual inspection alone is insufficient, as endoscopic signs such as erythema, nodularity, or atrophy lack specificity. However, technological advances such as narrow-band imaging (NBI) and magnifying endoscopy enhance mucosal contrast and microvascular visualization, improving detection and biopsy targeting (59,60). Despite these benefits, interpretation remains operator-dependent, and diagnostic performance varies. Artificial intelligence (AI)–assisted image analysis is emerging as a promising adjunct, capable of identifying subtle mucosal changes and predicting infection status, potentially reducing observer variability and improving diagnostic accuracy (61,62).

Histopathological analysis of gastric biopsy specimens remains the gold standard for diagnosing *H. pylori* infection and associated mucosal alterations, including gastritis, intestinal metaplasia, dysplasia, and neoplasia (63). Sensitivity typically ranges from 69% to 93%, and specificity approaches 87% to 100%, depending on sample quality, bacterial density, and staining techniques (64,65). Special stains such as Warthin–Starry, modified Giemsa, or immunohistochemistry are recommended when bacterial density is low or infection is focal. Pre-analytical factors strongly influence test accuracy; therefore, antibiotics and bismuth should be discontinued at least four weeks before biopsy and proton pump inhibitors at least two weeks prior to avoid false negatives (66). The rapid urease test (RUT) is another widely used invasive diagnostic tool. It detects urease activity in biopsy specimens by measuring pH changes as urea is converted to ammonia and carbon dioxide. The test is inexpensive, rapid, and highly specific (90–100%), with sensitivity ranging from 80% to 95% depending on bacterial load, biopsy site, and recent medication exposure (67,68). False-negative results are possible when bacterial density is low, in the presence of gastrointestinal bleeding, or following recent antibiotic therapy. Commercial kits such as CLOtest®, PyloriTek®, and Pronto Dry® are commonly used in clinical practice, but all require adequate organism load (about 10^4 organisms) for reliable detection (69). Culture of *H. pylori* from gastric biopsies is the only technique that allows direct antibiotic susceptibility testing, providing essential information for resistance-guided therapy. Although its specificity approaches 100%, sensitivity varies from 70% to 90%, depending on specimen handling, transport conditions, and laboratory expertise (70,71). Because culture is technically demanding, expensive, and time-consuming, it is often reserved for cases of treatment failure or when antimicrobial resistance is suspected. Molecular diagnostic methods such as polymerase chain reaction (PCR) and next-generation sequencing (NGS) have added precision to biopsy-based testing. These assays detect bacterial DNA with sensitivity exceeding 90% and can identify virulence genes (*cagA*, *vacA*) and resistance-associated mutations (72,73). Despite their accuracy, molecular tests require specialized infrastructure and expertise and are limited by cost and sampling variability.

Non-invasive methods play an increasingly central role in both initial diagnosis and post-treatment evaluation. The ^13C or ^14C urea breath test (UBT) is among the most accurate non-invasive options, with sensitivity and specificity exceeding 90% in most studies (74). It is simple, safe, and suitable for use across all age groups, including pregnant women, though accuracy is slightly reduced in children under six due to limited cooperation (75). UBT should be performed at least four weeks after antibiotic or bismuth therapy and two weeks after proton pump inhibitors to avoid false-negative results (76). The stool antigen test (SAT) detects *H. pylori* antigens directly in fecal samples and is equally valuable for diagnosis and confirmation of eradication. Monoclonal ELISA-based assays achieve sensitivity and specificity above 90%, while rapid immunochromatographic formats show slightly lower accuracy (77). Test performance is reduced by watery stools, improper sample storage, or premature testing within four weeks of therapy completion (78). Serological testing for anti-*H. pylori* IgG antibodies remains one of the most widely available and cost-effective diagnostic methods. It is unaffected by recent medication use and is therefore useful for initial screening, particularly in high-prevalence settings (79). However, its inability to distinguish active from past infection limits its utility, and sensitivity and specificity typically range from 75% to 85% and 80% to 90%, respectively (80). Because antibody levels may remain elevated long after eradication, serology is not suitable for post-treatment confirmation. Non-invasive molecular assays performed on stool or saliva offer high sensitivity (90–95%) and can simultaneously detect resistance-associated mutations, but they are limited by cost and by the persistence of non-viable bacterial DNA, which can yield false positives for up to 8–12 weeks following therapy (81,82).

SELECTING THE APPROPRIATE DIAGNOSTIC STRATEGY

The selection of an appropriate diagnostic test depends on patient characteristics, clinical presentation, test availability, and pre-test probability of infection. Guidelines consistently recommend a tailored approach rather than a one-size-fits-all strategy (83). In patients under 60 years of age with uncomplicated dyspepsia and no alarm features, non-invasive testing with either UBT or a monoclonal stool antigen test is preferred (84). In contrast, individuals at higher risk—those aged 60 or older, with a family history of gastric cancer, or living in high-incidence regions—should undergo endoscopy with biopsy-based diagnostic methods as the first-line approach (85). Clinical context can significantly influence diagnostic performance. In cases of acute upper gastrointestinal bleeding, for instance, invasive tests such as RUT, culture, and histology may yield false-negative results, and testing is best deferred until bleeding has resolved (86). Among these, histology remains the most reliable during active bleeding. In patients who have undergone partial gastrectomy, the stool antigen test is the most accurate option, while UBT and RUT are less reliable due to altered gastric anatomy and reduced bacterial density (87). For pediatric patients, UBT or stool antigen testing is recommended for those over 10 years old, while stool-based assays are preferred in younger children because of better compliance and reliable performance (88). Post-treatment testing presents additional considerations. Non-invasive testing using UBT or SAT should be performed no sooner than four weeks after completion of eradication therapy to confirm bacterial clearance (89). Serological tests should be avoided in this setting, as antibody titres may remain elevated long after successful eradication. Combining complementary tests, such as RUT with histology or UBT with stool antigen detection, can increase diagnostic sensitivity and specificity, especially in complex clinical scenarios or when initial results are inconclusive (90).

POPULATION SCREENING AND PUBLIC HEALTH PERSPECTIVES

Population-based screening for *H. pylori* has gained attention as a potential public health intervention to reduce the burden of gastric cancer, particularly in regions with high infection prevalence and cancer incidence. The International Agency for Research on Cancer and the World Health Organization have endorsed *H. pylori* detection and eradication as a strategy to prevent gastric malignancy (91). In such settings, non-invasive methods are the preferred tools for large-scale implementation because they are safer, more cost-effective, and more acceptable to the general population compared with endoscopy.

Table 1: Diagnostic Methods and Proteomic Markers in H. pylori-Associated Gastroduodenal Diseases and Gastric Cancer

Method / Category	Advantages	Disadvantages	Limitations	Key Proteins / Biomarkers	Expression or Role	References
Endoscopy	Direct morphological evaluation; biopsy capability; enhanced visualization with blue laser / linked color imaging.	Invasive procedure.	Observer variability; no objective scoring; variability in gastritis staging.	–	–	(33, 34, 42, 70, 71)
Narrow Band Imaging (NBI)	High specificity; rapid diagnosis; targeted biopsy.	Invasive; relatively low specificity.	Observer variability; no standard scoring system.	–	–	(33, 37, 39, 42)
Magnifying Endoscopy	Detects *H. pylori* via mucosal microvascular changes; effective with white-light and chromoendoscopy.	Invasive.	Operator-dependent interpretation; subjectivity; no standardization.	–	–	(33, 40–42)
AI-Assisted Endoscopy	Improves diagnostic precision; reduces operator dependence.	Emerging technology; limited availability.	Requires validation; depends on image quality and algorithm training.	–	–	(44, 45)
Rapid Urease Test (RUT)	Cost-effective; fast results; specificity ~95%.	Invasive; needs biopsy.	False negatives; sensitivity ~39.6%.	–	–	(33, 53)
Histopathology	Gold standard; specificity ~100%; identifies precancerous lesions.	Labor-intensive; requires skilled personnel.	Affected by biopsy quality, density, medications.	–	–	(72–74)
Culture	Identifies bacteria, resistance, morphology; specificity ~100%.	Time-consuming, expensive.	Requires strict transport; skilled staff; false negatives possible.	–	–	(36, 75, 76)
Urea Breath Test (UBT)	Non-invasive; high specificity; applicable for all ages; post-eradication monitoring.	Lower specificity in <6 years; false negatives.	Results influenced by diet, smoking, probiotics.	–	–	(33, 34, 40, 72, 77, 78)
Serology	Non-invasive; cost-effective; unaffected by antibiotics or PPI.	Cannot distinguish past vs. active infection.	Sensitivity ~76–80%; specificity ~79–90%; false positives in low-prevalence regions.	–	–	(33, 40, 48)
Stool Antigen Test	Non-invasive; high sensitivity (≥90%) and specificity (ELISA); home collection.	Reduced sensitivity with watery stools or poor storage.	Accuracy affected by load, bleeding, constipation.	–	–	(48, 79)
Molecular Testing (Invasive)	Detects *H. pylori* genes (*CagA*, *VacA*); sensitivity ~95%; resistance profiling (qPCR, NGS).	Costly; requires technical expertise.	Multiple samples; false positives from coccoid forms.	–	–	(31, 32, 34, 78)
Molecular Testing (Non-Invasive)	Stool/saliva PCR highly sensitive and specific; suitable for pediatrics and resistance-guided therapy.	False positives due to residual DNA.	Requires 8–12 weeks post-eradication to avoid false positives.	–	–	(33, 34)
Heat Shock Proteins (HSPs)	–	–	–	HSP27, HSP60, HSP70, HSP90, HSP105	Overexpressed in gastric cancer; linked to invasion and progression.	(99–105)
Metabolic Proteins	–	–	–	ENOA, GKN1	ENOA promotes metastasis via glycolysis; GKN1 downregulated, halts cell cycle.	(106–113)
Annexins (Membrane Proteins)	–	–	–	ANXA1–10	Differential expression influences invasion, metastasis, and survival.	(114–121)
S100 Proteins	–	–	–	S100, S100A2	Regulate cytoskeleton and invasiveness; expression correlates with metastatic potential.	(122–123)
Other Proteins	–	–	–	CALD, EPHA2, CAPG, CRIP1	Associated with invasion, metastasis, and lymph node involvement.	(101, 123–124)

Among non-invasive tests, the ^13C urea breath test offers the highest diagnostic accuracy but is costly and requires specialized equipment, limiting its use in low-resource settings (92). The stool antigen test, by contrast, is less expensive, widely available, and suitable for large-scale screening programs, although antigen degradation can occur if samples are not processed promptly, potentially reducing sensitivity (93). Serological testing remains the most economical approach for initial epidemiological studies and population surveys, particularly in settings with high prevalence (94).

Japan provides a notable example of a successful national screening strategy, where school-based *H. pylori* testing and treatment programs have significantly reduced gastric cancer risk later in life (95). The cost-effectiveness of such programs depends on several variables, including infection prevalence, test costs, patient adherence to testing and treatment, and the overall healthcare infrastructure's capacity for follow-up (96). Integrating *H. pylori* screening into national cancer prevention policies, particularly in high-risk regions, may substantially reduce gastric cancer incidence and associated healthcare costs over time.

PROTEOMICS AND BIOMARKER DISCOVERY IN *H. PYLORI*-ASSOCIATED DISEASE

The emergence of proteomics has significantly advanced the understanding of *Helicobacter pylori*–related gastroduodenal disease and gastric carcinogenesis. Proteomics, the large-scale study of protein expression, structure, and interactions, enables the identification of disease-specific biomarkers that can aid in diagnosis, predict disease progression, and inform therapeutic decision-making. Because proteins are direct effectors of cellular function and reflect real-time physiological and pathological states, proteomic analysis provides deeper insights than genomics or transcriptomics alone (97,98). Furthermore, proteomics can be applied to a variety of biological samples—including serum, plasma, gastric tissue, saliva, urine, and even exhaled breath condensate—making it particularly attractive for the development of non-invasive diagnostic tools (99).

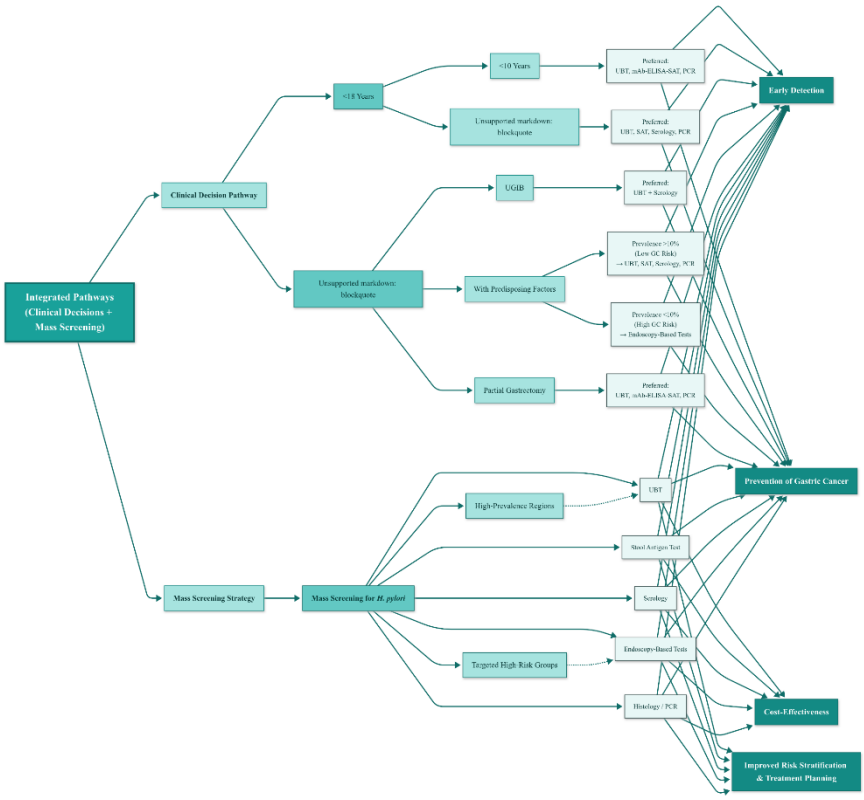

Figure 2 Figure X. Integrated Diagnostic and Screening Pathways for Helicobacter pylori and Gastroduodenal Diseases. This concept map illustrates the comprehensive approach to H. pylori detection and management by combining individualized clinical decision pathways with population-level mass screening strategies. Age, clinical presentation (e.g., upper gastrointestinal bleeding, predisposing factors, or prior gastrectomy), and regional infection prevalence guide the choice of diagnostic methods, including non-invasive tests such as the urea breath test (UBT), stool antigen testing, and serology, as well as invasive approaches like endoscopy, histopathology, and molecular assays. The integration of diagnostic algorithms with targeted screening programs in high-prevalence regions and high-risk populations enhances early detection, supports gastric cancer prevention, optimizes cost-effectiveness, and improves risk stratification and treatment planning.

In gastric cancer, which remains one of the most lethal malignancies worldwide, proteomic profiling has revealed numerous candidate biomarkers associated with tumor initiation, progression, and metastasis. Biomarkers are typically categorized into diagnostic, prognostic, and predictive classes based on their clinical utility. Diagnostic biomarkers are used to detect disease presence, prognostic biomarkers provide information about disease course and patient outcomes, and predictive biomarkers forecast therapeutic responses (100). In gastric cancer and *H. pylori*-associated pathology, several protein families have been extensively studied in these roles.

Heat shock proteins (HSPs) such as HSP27, HSP60, HSP70, HSP90, and HSP105 are frequently overexpressed in gastric cancer tissues and have been implicated in tumor survival, proliferation, and invasion (101). Their elevated levels often correlate with more aggressive disease and poor clinical outcomes, highlighting their potential as diagnostic and prognostic markers. Similarly, metabolic proteins like alpha-enolase (ENOA) are upregulated in gastric cancer and facilitate tumor growth through enhanced glycolysis and pyruvate synthesis, whereas gastrokine-1 (GKN1), a tumor-suppressor protein, is typically downregulated and inversely correlated with ENOA expression (102). Alterations in oxidative

phosphorylation and Krebs cycle enzymes have also been documented, reflecting a metabolic shift toward aerobic glycolysis, or the Warburg effect, which supports rapid tumor cell proliferation (103).

Membrane-binding proteins such as annexins (ANXA1, ANXA2, ANXA3, ANXA5, ANXA7, and ANXA10) play multifaceted roles in tumor biology, including modulation of cell motility, invasion, and angiogenesis. Overexpression of ANXA2 and ANXA3, for instance, is associated with increased metastatic potential, whereas reduced ANXA10 expression correlates with poor survival in intestinal and diffuse-type gastric cancers (104). Members of the S100 protein family are similarly significant; S100A2, for example, reduces invasive potential when upregulated, while downregulation of S100 proteins in certain contexts enhances metastatic activity (105). Other noteworthy biomarkers include prohibitin (PHB), caldesmon (CALD), EPHA2, CAPG, and CRIP1, all of which have been linked to gastric tumor biology and may serve as diagnostic or prognostic markers (106).

Despite these advances, proteomics faces several technical and biological challenges. Protein expression is highly dynamic and context-dependent, varying between cell types and disease states, which complicates standardization and reproducibility (107). Post-translational modifications add another layer of complexity, and the absence of amplification techniques equivalent to PCR in genomics limits the detection of low-abundance proteins. Pre-analytical variables, including sample collection, preparation, and storage, can also significantly influence mass spectrometry results (108). Nevertheless, continuous improvements in high-throughput proteomic technologies, bioinformatics pipelines, and validation platforms are gradually overcoming these barriers, paving the way for the integration of proteomics into clinical diagnostic workflows.

The integration of proteomics with conventional diagnostic tests offers a promising path forward. Protein biomarkers could complement established assays such as the urea breath test or stool antigen test by improving early disease detection, refining risk stratification, and enabling individualized surveillance strategies. Moreover, as proteomic signatures become better validated, they may provide non-invasive alternatives for gastric cancer screening and help distinguish between benign *H. pylori* infection and malignant transformation.

ARTIFICIAL INTELLIGENCE IN GASTROINTESTINAL DIAGNOSTICS

Artificial intelligence (AI) has rapidly emerged as a transformative technology in modern medicine, offering solutions to long-standing diagnostic challenges in gastroenterology. With its ability to analyze vast amounts of data, recognize complex patterns, and learn from experience, AI has shown potential to augment clinical decision-making, particularly in image-based diagnostics where interpretation variability is high (109,110). In the context of *H. pylori* infection and associated gastroduodenal diseases, AI has been applied to endoscopic image analysis, disease classification, lesion detection, and risk prediction.

Deep learning algorithms trained on large datasets of endoscopic images have demonstrated high diagnostic accuracy in detecting *H. pylori*-induced gastritis, often outperforming non-expert endoscopists and matching the performance of experienced specialists (111). Convolutional neural networks (CNNs), in particular, are capable of distinguishing between *H. pylori*-positive and *H. pylori*-negative mucosa based on subtle vascular and textural patterns that are difficult to discern with the human eye (112). AI can also assist in biopsy targeting by identifying areas of mucosal abnormality most likely to yield diagnostic tissue, thereby improving sampling efficiency and diagnostic yield.

Beyond gastritis, AI has been applied to the detection of early gastric neoplasia, differentiation of premalignant lesions, and assessment of treatment response. In capsule endoscopy and colonoscopy, machine learning models have been used to automate lesion detection and classification, reducing interpretation time and improving sensitivity for clinically relevant findings (113). In addition, AI tools are being developed to predict treatment outcomes based on patient data, bacterial genotypes, and biomarker profiles, potentially enabling more personalized therapeutic approaches (114).

Despite these advances, several challenges remain before AI can be fully integrated into clinical practice. Algorithm performance is highly dependent on the quality and diversity of training data, and models trained on one population or device type may not generalize well to others. Regulatory, ethical, and data privacy considerations must also be addressed before widespread clinical adoption (115). Furthermore, AI is not intended to replace clinician expertise but rather to enhance diagnostic accuracy and efficiency. The optimal model for future practice is likely to be a hybrid approach in which AI-driven tools complement, rather than replace, expert interpretation and clinical judgment.

CONCLUSION

The diagnosis and management of *Helicobacter pylori*–associated gastroduodenal diseases remain critical components of gastroenterological practice due to their profound implications for global public health. While conventional diagnostic modalities—including endoscopy, histopathology, rapid urease testing, culture, stool antigen assays, and the urea breath test—continue to provide robust diagnostic information, each has intrinsic limitations related to invasiveness, accuracy, cost, and applicability in different patient populations. Appropriate test selection must therefore be guided by clinical context, patient characteristics, and regional disease prevalence to optimize outcomes.

Advances in diagnostic technology are reshaping this landscape. Molecular assays now enable precise detection of bacterial DNA and antimicrobial resistance mutations, supporting tailored eradication strategies. Proteomics offers the promise of biomarker-based diagnostics that may allow earlier disease detection and personalized risk assessment, while artificial intelligence is redefining the capabilities of endoscopic imaging, improving diagnostic accuracy, and supporting clinical decision-making. Although these emerging technologies are not yet ready to replace traditional methods, they are poised to augment them significantly, particularly as validation studies expand and integration into clinical workflows matures.

The future of *H. pylori* diagnostics lies in an integrated, precision-medicine approach that combines traditional assays with molecular, proteomic, and computational tools. This multidimensional strategy has the potential to improve diagnostic accuracy, facilitate early intervention, reduce gastric cancer incidence, and enhance patient outcomes worldwide. As research continues to bridge the gap between discovery and clinical application, the management of *H. pylori* infection will increasingly shift from a reactive to a proactive model, grounded in early detection, individualized therapy, and evidence-based prevention strategies.

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