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A Narrative Review of Diagnostic Methods for *Helicobacter pylori*: Comparative Performance of Invasive, Non-Invasive, and Molecular Tests

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Abstract

Background: *Helicobacter pylori* is one of the most prevalent bacterial pathogens worldwide and is associated with chronic gastritis, peptic ulcer disease and gastric cancer. Accurate diagnosis is essential for timely treatment, successful eradication and prevention of disease progression and associated complications. **Aim:** This review evaluates the effectiveness of the major diagnostic methods used for the detection of *H. pylori* by comparing their sensitivity, specificity, diagnostic accuracy, clinical utility and limitations across different healthcare settings. It also examines factors influencing diagnostic performance and discusses appropriate diagnostic strategies for different clinical context. **Methods:** The narrative review summarizes studies published between 2020 and 2024 that were retrieved from PubMed, Scopus, Google scholar, Web of science and other various pages. Literature was identified using the key words *Helicobacter pylori*, diagnostic methods, urea breath test, stool and Polymerase chain reaction (PCR). Relevant clinical guidelines, systematic reviews, meta-analyses and representative original studies were selected to provide an overview of current diagnostic approaches and emerging trends. **Results:** Comparative analysis showed that the urea breath test (UBT) demonstrated the highest overall diagnostic accuracy for detecting active *Helicobacter pylori* infection, while the monoclonal stool antigen test (SAT) provided comparable performance with greater cost-effectiveness and practicality in resource-limited settings. Histology was generally more sensitive than culture and rapid urease testing (RUT), particularly in patients with low bacterial density, whereas culture remained indispensable for antimicrobial susceptibility testing. Molecular methods, especially polymerase chain reaction (PCR), exhibited high di-

agnostic sensitivity and enabled the detection of antimicrobial resistance-associated mutations, although their use is constrained by cost and laboratory infrastructure. **Conclusion:** No diagnostic accuracy across all methods was influenced by medication exposure, particularly proton pump inhibitors, antibiotics, and bismuth, as well as biopsy sampling, bacterial load, and clinical conditions. Overall, the evidence indicates that the optimal diagnostic approach should be selected according to the patient's clinical presentation, medication exposure, and available healthcare resources.

Keywords

Helicobacter pylori, Diagnosis, Invasive Tests, Non-Invasive Test, Urea Breath Test, Molecular Diagnostics, Stool Antigen Test

1. Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative spiral-shaped bacterium that has a tendency of colonizing the gastric mucosa, it remains one of the most prevalent chronic bacterial infections globally. Since its initial identification by Marshall and Warren in year 1982, *H. pylori* has been recognized as the prominent major cause of peptic ulcer disease, gastric adenocarcinoma, chronic gastritis and gastric mucosa associated lymphoid tissue lymphoma. Thus, the World Health Organization's International Agency for Research on Cancer (IARC) has classified *H. pylori* as Group I carcinogen because of its strong association with gastric cancer [1] [2].

Globally, the extensiveness of *H. pylori* infection is estimated to affect almost half of the world's population, although substantial geographical variation exists. Its infection rate spread is highly influenced by the socioeconomic status [3], health infrastructure and sanitation hygiene. Hence this implication reveals high infection rates in the low- and middle-income regions such as Parts of Africa, Asia and Latin America where there is poor sanitation, overcrowding and limited health care access. In contrast to that, the prevalence declines gradually in most of the high-income countries due to the fact that they are characterized with improved hygiene, health infrastructure and living conditions [4]-[7].

For several reasons, accurate diagnosis of *H. pylori* is extremely essential. Firstly, early detection of *H. pylori* enables timely eradication therapy and thereby minimizing the risk of complications such as gastric malignancy and peptic ulcers disease. Secondly, reliable diagnostic testing is necessary when confirming the eradication after being subjected to treatment and thirdly, due to increased antimicrobial resistance has led to the need for diagnostic strategies that are capable of guiding susceptibility-based therapy [1].

To date, there are several diagnostic methods available for detection of *H. pylori*, including invasive biopsy-based approaches and non-invasive based approaches. These techniques differ in diagnostic accuracy, accessibility, cost, suitability for

specific clinical scenarios and technical requirements. Invasive approaches such as rapid urease testing, histology, molecular testing, and culture provide direct evaluation of gastric tissue and may allow antimicrobial susceptibility assessment. Non-invasive methods include the stool antigen test, urea breath test, serology and more convenient widely used in primary care and post treatment monitoring [8] [9].

Recent advances in molecular diagnostics, including real-time polymerase chain reaction (PCR), next-generation sequencing (NGS) and emerging point-of-care technologies, have further expanded the diagnostic landscape. These innovations have improved the detection of low bacterial loads and resistance-associated mutations, particularly clarithromycin resistance.

The primary purpose of this narrative review is to compare invasive, non-invasive and molecular diagnostic methods for *H. pylori* infection by evaluating their sensitivity, clinical utility, specificity, advantages, limitations and applicability across different healthcare settings. The review also discusses scenario-based diagnostic selection and future directions in *H. pylori* diagnostics.

2. Classification of Diagnostic Methods

The methods of diagnosis of *H. pylori* are broadly classified into two major groups [10]; which are the invasive methods. This method involves gastric biopsy collection and upper gastrointestinal endoscopy [1] [10] and non-invasive methods. These approaches don't require endoscopy and are generally patient-friendly and convenient [11]. The selection of a diagnosis approach mainly depends on several factors, which include symptoms, patient's age, availability of endoscopy, previous treatment exposure, health resources and the need for antimicrobial susceptibility testing.

3. Invasive Diagnostic Methods

Invasive diagnostic methods are the ones that require upper gastrointestinal endoscopy, simultaneously with the collection of gastric biopsy specimens. These approaches stand out as clinically important because they provide evidence of the infection while simultaneously allowing evaluation of the gastric mucosal pathology. Invasive testing is more valuable in patients with alarming symptoms such as persistent vomiting, suspected malignancy and gastrointestinal bleeding or treatment failure [1] [10]. The following are the invasive diagnostic methods.

3.1. Histology

The histology diagnostic method involves microscopic evaluation of gastric biopsy specimens that are obtained during endoscopy. By the use of hematoxylin-eosin, Giemsa, Warthin-Starry or immunohistochemical stains tissue sections are stained to visualise *H. pylori* organisms and hence assess gastric mucosal pathology [12]-[14]. The strengths of histology are that it offers a direct visualisation of *H. pylori* organisms, and at the same time, it assesses gastritis, intestinal metaplasia, atrophy, malignancy risks and dysplasia. When sufficient biopsy sampling and

staining techniques are used, the histology method exhibits high sensitivity and specificity [14] [15]. The limitation of the histology diagnostic method is that the accuracy of diagnosis may be affected by a recent proton pump inhibitor (PPI) use, patchy bacterial distribution, gastrointestinal bleeding, antibiotic exposure and inadequate biopsy sampling. Also, histology highly demands experienced pathologists and access to endoscopic facilities [16]. Clinically, the histology diagnostic method is more useful for patients who require mucosal assessment, such as those with suspected gastric cancer, premalignant gastric lesions and peptic ulcer disease [13]. The rise of artificial intelligence has led to the development of artificial intelligence-assisted pathology, which has shown promising results in improving diagnostic consistency and reducing interobserver variability [17].

3.2. Rapid Urease Test (RUT)

The rapid urease test operates by detecting urease enzyme activity that is produced by *H. pylori* organisms. Gastric biopsy specimens are placed in a medium containing urea with a pH indicator. Therefore, the hydrolysis of urea occurs to produce ammonia, resulting in a colour change [18] [19]. The rapid urease test is inexpensive, fast, simple and widely available; its results are often obtained within hours. In some instances, false-negative results may occur in patients with low bacterial density, recent proton pump inhibitor use, recent antibiotic use, intestinal metaplasia, gastrointestinal bleeding, or atrophic gastritis. In addition, the RUT method doesn't provide any information regarding antimicrobial susceptibility or mucosal pathology. The rapid urease test is most commonly used during a routine endoscopy to confirm the infection rapidly [20]. In recent findings, microfluidic-based urease detection platforms and combined molecular confirmation approaches may improve the diagnostic sensitivity [20] [21].

3.3. Culture

The culture diagnostic approach involves the isolation of *H. pylori* from gastric biopsy specimens using a selective medium under microaerophilic conditions [22] [23]. The culture remains the only conventional diagnostic method that allows phenotypic antimicrobial susceptibility testing. This is particularly valuable in patients with treatment failure or suspected antibiotic resistance [24]. This method is technically challenging, requires significant time, and is less sensitive compared to many other diagnostic techniques. Its effectiveness heavily depends on specimen handling, transport conditions, bacterial load, and the skill of the laboratory personnel [25] [26]. The culture is primarily used in refractory infection, resistance surveillance programs and specialized clinical or research settings [8]. In recent findings, automated culture systems and improved transport media have been developed to improve recovery and reduce turnaround times.

3.4. Polymerase Chain Reaction (PCR)

Polymerase chain reaction exhibits high specificity and sensitivity, including sam-

ples with low bacterial load. PCR combines high analytical sensitivity with the ability to detect clarithromycin-resistance mutations, but performance still depends on specimen type, primer design, and laboratory capacity [27]-[29]. The evidence here splits into diagnostic accuracy, resistance detection, and practical limitations plus newer molecular extensions. PCR generally detects *H. pylori* with high sensitivity and specificity in biopsy-based testing, and several studies report performance above 95% [27] [28]. Real-time PCR outperformed rapid urease testing in one prospective biopsy study, detecting 97.1% of infected specimens versus 82.9% for RUT [30]. Multiplex PCR assays also performed strongly, with Allplex showing 99.2% sensitivity and 100% specificity against sequencing in gastric biopsies [31]. ddPCR can detect low-density infection missed by conventional tests, including 36% of patients classified negative by standard methods in one gastric-biopsy study [32]. PCR is especially valuable because it can identify resistance-associated mutations while confirming infection, most often clarithromycin resistance linked to 23S rRNA variants [31] [33] [34]. Real-time PCR can classify clarithromycin resistance with good concordance to phenotype, including 95% concordance in LightMix testing and 87.5% accuracy for resistant genotypes in a 410-biopsy study [33] [35]. PCR can also reveal heteroresistance or minor resistant subpopulations that culture may miss. Overall, the literature supports the statement that PCR is a high-performance method for *H. pylori* detection and clarithromycin resistance profiling, particularly in biopsy samples, while also showing that cost, infrastructure, contamination control, and specimen-dependent variability limit universal use [36] [37].

4. Non-Invasive Diagnostic Methods

These are the diagnostic methods that don't involve inserting an endoscope into the body. These methods have transformed the management of *H. pylori* infection because they are safer, more acceptable to patients, and more convenient than endoscopy-based approaches. Current guidelines recommend non-invasive testing for many patients with uncomplicated dyspepsia who do not have alarm features [38] [39]. Non-invasive tests are as follows.

4.1. Urea Breath Test (UBT)

The Urea breath test detects urease activity by measuring exhaled labelled carbon dioxide after ingestion of Carbon-13 or carbon-14 labelled urea [40]. UBT is considered one of the most accurate non-invasive tests for detecting active infection and for post-eradication confirmation. Sensitivity and specificity generally exceed 90% under appropriate testing conditions [41]. Recent use of antibiotics, PPIs, or bismuth compounds may reduce the bacterial load and lead to false-negative results. The method also requires specialized equipment [11]. UBT is widely recommended for both initial diagnosis and for confirming eradication after treatment [18]. In recent findings, portable infrared spectrometry systems and simplified testing protocols have improved accessibility in resource-constrained settings

[41].

4.2. Stool Antigen Test (SAT)

The stool antigen test detects *H. pylori* antigens shed into the gastrointestinal tract using enzyme immunoassays or immunochromatographic assays [42]. Monoclonal antibody-based SATs demonstrate high sensitivity and specificity comparable to UBT. The method is relatively inexpensive and suitable for both adults and children [43]. Diagnostic accuracy may be reduced by improper stool handling, recent antibiotic exposure, or use of PPIs and bismuth compounds [44]. SAT is recommended for both initial diagnosis and post-treatment confirmation, particularly in settings where UBT is unavailable [44]. In recent findings, rapid immunochromatographic assays and improved monoclonal antibody platforms have enhanced test reliability [44] [45].

4.3. Serological Testing

Serological tests detect IgG antibodies to *H. pylori* in blood samples via ELISA, immunoblot or rapid immunochromatographic tests. Multiple assays can measure antibodies to many H pylori proteins (e.g., CagA, VacA, GroEL, HcpC) simultaneously in the sample [43] [46]. Serology is inexpensive, widely available, and unaffected by recent antibiotic or PPI use [43]. Antibodies may persist long after eradication, making serology unable to distinguish between active and previous infection. Consequently, specificity for active infection is relatively low [47]. Serology may still be useful in epidemiological studies or in settings where other diagnostic methods are unavailable [48]. In recent findings, research continues into antigen-specific serological markers for virulence-associated proteins such as CagA and VacA [49].

5. Comparative Performance of Diagnostic Methods

Due to the availability of various diagnosis methods that fall into invasive and non-invasive diagnosis methods, there is an importance of understanding the similarities and differences of these methods so as to create a better understanding due to their performance varying across the geographical context and clinical context. The comparative studies do allow.

1) Assessment of the Diagnosis Accuracy: Here is to determine which test is more efficient in a particular specified condition.

2) Understanding the cost efficiency: The comparison helps in the informing the healthcare policy pioneers to understand the better approach of the resources allocation.

3) Understanding the patient compliance: The comparison helps to understand the real-world feasibility and acceptability.

4) Resistance surveillance: through incorporating molecular approaches into comparison to track the resistance trends of the antibiotic.

The comparison is as follows.

5.1. Histology versus Culture

Histology generally exhibits a higher rate of sensitivity than culture, especially in cases where there is low bacterial density. However, culture remains uniquely valuable because it enables antimicrobial susceptibility testing and isolation of visible organisms [9]. Across studies, histology usually matches or exceeds culture in the detection of *H. pylori* although both methods vary due to laboratory conditions, sampling and operator expertise [50]-[53]. Histology reached 94.1% sensitivity versus 95.2 for culture in one large 2025 cohort, showing both can perform well in optimized practice [51]. Other studies found histology higher including 96.6% versus 20.7% in children and 73.3% versus 74.4% in routine workflow where both conventional methods underperformed PCR [50] [52]. **Table 1** shows the comparison of histology and culture for biopsy-based *H. pylori* detection. Therefore, the literatures suggest that histology is usually more sensitive for detection especially when organism burden is low while culture is indispensable for susceptibility testing and strain isolation hence histology is a detection plus tissue test whereas culture is a detection plus isolate test [52] [53].

Table 1. Comparison of histology and culture for biopsy-based *H. pylori* detection.

Method	Main Strength	Main Limitation	Best Use
Histology	Detects bacteria and grades gastritis	Sensitivity depends on colonization density and reader expertise	Initial biopsy-based diagnosis with mucosal assessment [52]
Culture	Enables antimicrobial susceptibility testing and strain isolation	Lower, Variable sensitivity and demanding handling requirements	Resistance guided therapy and microbiologic characterization [53]
Both together	Improves invasive workup breadth	Requires endoscopy and biopsy logistics	Causes needing diagnosis plus resistance information [52] [54]

5.2. Histology versus Rapid Urease Test

RUT is cheaper, faster, and simpler than histology; however, histology provides additional information on mucosal inflammation, intestinal metaplasia, atrophy, and dysplasia [11] [21]. **Table 2** shows comparison of histology and rapid urease test for *H. pylori* detection. Across studies, both tests usually show a good performance but accuracy varies widely by biopsy site, reference standard and patient population. A systematic study review conducted in 2023 concluded that neither of the test alone is a gold standard and performance varies by clinical situation [18]. Histology from antrum plus corpus reached 95.1% sensitivity and 95.1% specificity in one review table while combined site RUT reached 86.6% sensitivity and 100% specificity [18]. RUT accuracy ranged from strong in some studies, such as 94% - 95% sensitivity or accuracy to clearly weaker in others including 75% sensitivity and 32% sensitivity when compared with histology on one Saudi cohort [55]-[57]. The main reason histology and RUT differ depends on urease activity, so anything that suppresses bacteria or enzyme activity can reduce sensitivity. Histology can miss infection but it can be strengthened with special strains and can reveal mucosal pathology beyond organism detection [18] [58]. PPI use is repeat-

edly linked to false-negative RUT results, in one study 75% of false negative RUT cases had PPI exposure [59]. Histology identified additional infections missed by RUT, including 15 extra positives in 612 cases endoscopy and 33% detection increase when combined with RUT [59] [60]. Therefore, histology versus rapid urease testing in *H. pylori* detection is quite a complicated comparison because histology is usually more comprehensive and more reliable when RUT is negative or mucosal assessment matters while RUT remains fast, inexpensive option with good performance in many routine settings [39] [61] [62].

Table 2. Comparison of histology and rapid urease test for *H. pylori* detection.

Method	Main strength	Main Limitation	Typical Pattern in Studies
Histology	Detects organisms directly and shows gastritis, metaplasia and other pathology	Slower, more expensive and it requires pathology	Often treated as de facto or practical reference standard. Has high sensitivity and specificity commonly > 90% [18] [63] [64]
RUT	Fast, Low cost	Sensitivity falls with PPIs and antibiotic uses and low bacterial loads	Usually, sensitivity and specificity vary from low to very high depending on setting [63] [65]
Combined Use	Improves diagnostic yield when one test misses cases	More resources than one test alone	Review and cohort data support using at least two tests especially when suspicion remains high [18] [60] [66]

5.3. Urea Breath Test versus Stool Antigen Test

Table 3. Comparison of urea breath test and stool antigen test for *H. pylori* detection.

Method	Main Strength	Main Limitation	Best Use
Urea breath test	High overall diagnostic accuracy	More technical or less convenient	Initial diagnosis and eradication confirmation [11]
Stool Antigen Test	Lower cost and broader practically	Accuracy varies with assay and sample	Good alternative where UBT is less feasible [45] [67]
Monoclonal stool antigen	Better specificity and stronger performance	Still assay dependent	Strongest stool based option [44] [67]

Both the Urea Breath Test and the monoclonal Stool Antigen Test exhibit excellent diagnostic performance for active infection. However, the Urea Breath Test is considered more accurate than other non-invasive tests, whereas the Stool Antigen Test is the most cost-efficient and more practical in many low-resource settings [46]. **Table 3** shows comparison of *urea breath* test and stool antigen test for *H. pylori* detection. 13C urea breath test has the strongest overall evidence for higher diagnostic accuracy than stool antigen testing, with a Cochrane review finding higher diagnostic odds ratio and sensitivity at a fixed specificity although direct head to head comparison were limited [11]. Monoclonal stool antigen test can reach high accuracy and in some cohorts perform similarly to urea breath testing, especially in children or with optimized assays, but results vary by assay and setting [45] [67]-[69]. Older or some real world stool antigen tests often show lower sensitivity than urea breath testing, with several direct comparisons reporting

more false negatives for stool testing [41] [63] [70]. Urea breath testing is better supported choice when the question is which tests active *H. pylori* more accurately overall. Stool antigen testing remains a credible non-invasive alternative especially with monoclonal assay, lower resource setting and some pediatric or screening contexts [71].

5.4. Urea Breath Test versus Serology

Table 4. Comparison of urea breath test and serology for *H. pylori* detection.

Test	Main Strength	Main Limitation	Best use
Urea Breath Test	Strongest overall for active infection with large reviews showing high sensitivity and specificity [11] [73] [74]	Accuracy falls after recent use of PPIs, antibiotics or bismuth and also the access can be limited by equipment, cost and protocol requirements [74] [77] [78]	Best when the goal is diagnosing current or confirming post treatment rededication without endoscopy [41] [77]
Serology	Cheap, widely available and can work well as initial rule out test in some lower prevalence settings [72] [75]	Cannot distinguish current from past infections and is unreliable for confirming cure after treatment [24] [41] [76] [79]	Best as screening step or reflex entry test when UBT is limited then followed by a test for active infection if positive [72] [75]
Combined use	Improves diagnostic confidence by combining a sensitive screening step with a more specific test for active infection and can minimize diagnostic errors [72] [75]	Evidence for combined is mostly algorithmic not from many direct head to head trials of fixed combinations [11]	Best when a service wants a low cost screen plus confirmation [72] [75]

The Urea Breath Test exhibits higher specificity for active infection than serology. However, unlike serology, the Urea Breath Test is suitable for post-eradication confirmation [72]. **Table 4** shows a comparison of *urea breath test* and *serology* for *H. pylori* detection. Indirect comparison and meta analyses UBT has the stronger overall evidence base for current infection while serology remains useful when access, cost or prior medication matter [10] [11] [73]. UBT outperforms serology for detecting active *H. pylori* in the largest comparative synthesis, across 101 studies 13C-UBT had an estimated sensitivity of 94% at fixed specificity versus 84% for serology with fewer negatives [11]. Serology still has screening value in some lower prevalence settings because sensitivity can be high and negative value can be strong, but positive results do not distinguish current from past infection [41] [73] [74]. Not every dataset favors UBT on sensitivity alone. A 2020 health system analysis using histopathology as reference found serology sensitivity 0.94 versus 0.64 for UBT then proposed serology first reflex algorithms to reduce diagnostic error in that population [72]. A 2024 population level comparison also found serology sensitivity of 96.5% and NPV of 98.4% versus UBT supporting serology as initial rule out test in lower prevalence settings [75]. But serology remains limited by what it measures, it often reflects prior exposure rather than active infection and agreement with UBT worsens after eradication therapy [10], [76]. Urea breath test versus serology therefore favors UBT for diagnosing current *H. pylori* infection and for post treatment follow up while serology still has a narrower role as

low cost, accessible screening or rule out test in selected populations.

5.5. Stool Antigen Test versus Serology

The Stool Antigen Test is more efficient than serology for both post-treatment and active infection. In pediatric populations, the Stool Antigen Test is preferred for its strong diagnostic performance and practicality. Stool antigen test is cheaper and often easier for primary care, children and lower resource settings, its performance depends more on sample handling, antigen stability and bacterial load [24], [44] [45]. While UBT is widely treated as preferred non-invasive test but needs fasting, patient time and specialized equipment [11] [80]. Older biopsy based follow up data favored UBT after eradication therapy, overall 97% for 13C-UBT versus 88% for HpSA with more false positives for stool antigen testing [81]. More recent studies show this gap is not universal. UBT and stool antigen testing had 87% agreement in one Jordan eradication cohort, 96% concordance in an Italian monoclonal stool test study and complete agreement with biopsy test in small Japanese pediatric follow up sample [41] [68] [70]. For Urea Breath Test versus Stool antigen test, the overall literature leans towards UBT for the most reliable diagnosis of active infection and for eradication confirmation but the difference narrows substantially when stool testing uses well validated monoclonal assay and local logistics favor stool-based testing.

6. Scenario-Based Selection of Diagnosis

The selection of the most efficient diagnostic method should be guided by patient risk factors, clinical presentation and health care resources.

6.1. Initial Diagnosis

For younger patients with uninvestigated dyspepsia and no alarm features, the literature consistently supports a test and treat strategy using non-invasive testing rather than immediate endoscopy [82] [83]. Urea breath testing and stool antigen testing are the main non-invasive options recommended for primary diagnosis, while serology is limited because it does not distinguish active from passive infections [1] [10] [84]. 13c-UBT had the highest pooled non-invasive accuracy in a Cochrane review with sensitivity 0.94 at specificity 0.9 [11]. Also Monoclonal SAT supports first line use with reviews describing high accuracy and frequent sensitivity/specificity above 90% [45] [85].

The alarming features, such as gastrointestinal bleeding, anemia, weight loss or malignancy suspected shifts evaluation to endoscopy with biopsy based testing [82] [86] [87].

6.2. Follow-Up and Pediatric Use

For post-eradication confirmation, the key principle is to use tests that detect active infection which favors UBT and stool antigen over serology [45] [84] [88]. Pediatric evidence is more nuanced: non-invasive tests are useful for confirming

eradication but routine test and treat strategies for children are not recommended because the diagnostic goal is to explain symptoms, not simply detect colonization. Testing should usually take place at least four weeks post-therapy and after stopping PPIs [89]-[91].

6.3. Refractory and Low-Resources Settings

Repeated treatment failure changes the diagnostic goal from simple detection to resistance profiling. In that setting, culture and molecular methods become especially valuable because they can guide susceptibility based therapy although they usually require biopsy access or specialized laboratories [84] [91]. In low resource setting, feasibility matters as raw accuracy, so stook antigen testing often offers the best practical compromise when endoscopy, UBT or molecular testing are hard to access [71] [82] [92]. Culture remains the reference method for susceptibility testing but needs endoscopy and dedicated laboratory support [82] [91]. Molecular assays are useful mainly for detecting antibiotic resistance, including on gastric biopsy specimens [91]. And in constrained settings, SAT is attractive because it is cheaper that UBT and still useful before and after eradication treatment [45] [71] [88].

Therefore, scenario-based *H. pylori* diagnosis is the best approach whereby the choice of the method depends on clinical risk, age and local resources. For personal diagnositic decisions the evidence should be applied by licensed clinician who can account for symptoms, medication washout and local test performance.

7. Factors Influencing Diagnostic Accuracy

Various elements can affect the reliability of *H. pylori* diagnostic tests, the evidence here splits drug interference, biopsy, specimen factors and patient related clinical conditions [50] [93]. Across reviews, guidelines and comparative studies, false negatives are the dominant concern, especially when testing is done during PPI, antibiotic, or bismuth exposure or in settings of low bacterial density.

7.1. Medication Effects

Drug exposure is the most consistently reported cause of reduced *H. pylori* test sensitivity, particularly for UBT, SAT, histology, RUT, and culture [94]-[96]. Reviews specifically link PPIs, antibiotics, and bismuth to false-negative results by lowering bacterial load. Histology is also affected by PPI exposure, and multiple sources state that PPIs should be stopped for 2 weeks before biopsy-based testing [1] [86] [97]. UBT is more vulnerable to acid suppression than SAT in several studies [98] [99]. In one medication-interference study, lansoprazole caused false-negative UBTs in 30% - 40% and bismuth in 45% - 55%; SAT false negatives were lower at 15% - 25% and 10% - 15% [96]. Although some newer SAT assays retained high sensitivity during PPI use, these data are assay-specific rather than universal [98] [99].

7.2. Sampling and Timing

Patchy gastric colonization lowers the sensitivity of biopsy-based tests, so inadequate site selection or too few biopsies can produce false negatives. Multiple reviews recommend sampling from both antrum and corpus, often with at least two biopsies from each site, to reduce sampling error. Test performance also depends on technical handling: culture sensitivity drops when biopsy transport is delayed or specimens are exposed to aerobic conditions. Recent eradication therapy lowers sensitivity across tests, and real-world data show reduced detection after prior treatment history. Exclusion and washout rules in diagnostic studies commonly require PPI cessation for 2 weeks and antibiotic or bismuth cessation for 4 weeks before UBT or SAT. Reading a rapid urease test too early can itself create a false negative [1] [86] [95] [100] [101].

7.3. Clinical Conditions

Low bacterial load is a central mechanism linking several patient factors to poor test performance [50] [102]. Atrophic gastritis, intestinal metaplasia, bleeding, gastric cancer, and MALT lymphoma are repeatedly associated with reduced sensitivity, especially for conventional invasive tests and for UBT/SAT in advanced gastric pathology [95] [102]. In atrophy, bacterial density can fall markedly or disappear, which lowers histology, culture, and urease-test sensitivity [1] [50]. Upper GI bleeding often reduces test sensitivity, though newer observational data show some inconsistency by population and bleed definition [94] [95] [97]. Histology and culture perform much better when bacterial load is high, with sensitivities exceeding 90% in high-load biopsies in one large workflow study. Molecular testing on biopsy appears less vulnerable to low culture yield and can improve detection plus resistance profiling [50].

Overall, the literature supports the washout rule you stated: stop PPIs for about 2 weeks and antibiotics or bismuth for about 4 weeks before testing whenever feasible [1] [95] [100]. For personal testing decisions, a licensed clinician should interpret these factors in the context of symptoms, bleeding risk, recent therapy, and the specific assay being used.

8. Emerging Technologies and Future Perspectives

Molecular diagnostics are poised to become increasingly important for detecting *H. pylori* and resistance patterns. Techniques such as real-time PCR and next-generation sequencing enable rapid identification of resistance mutations, supporting personalised treatment plans.

Platforms such as Loop-mediated isothermal amplification (LAMP) and CRISPR-based diagnostics offer promising, rapid, and simplified molecular detection, particularly useful in resource-limited settings.

Artificial intelligence in pathology and imaging could further improve diagnostic reliability and efficiency [17].

Future research directions include:

1) Standardising molecular diagnostic methods.

2) Developing affordable point-of-care tests.

3) Improving access to resistance testing.

4) Incorporating precision medicine approaches into clinical practice.

5) Boosting research efforts in underserved regions such as Sub-Saharan Africa and Latin America.

9. Conclusions

Accurate detection of *Helicobacter pylori* is crucial for effective treatment, confirmation of eradication, and prevention of complications such as gastric cancer.

Non-invasive methods such as the urea breath test and monoclonal stool antigen test are highly accurate and suitable for both initial and follow-up testing. Invasive methods such as histology, rapid urease testing, and culture are essential when endoscopy, mucosal assessment, or susceptibility testing is required.

Molecular techniques, especially PCR and next-generation sequencing, greatly enhance diagnostic precision and resistance detection but face barriers such as cost and infrastructure requirements.

No single test is perfect for all situations. Choices should be tailored to clinical indications, medication history, patient factors, resource availability, and resistance testing needs.

This review is narrative and does not include a formal quantitative analysis or quality assessment of the studies. Diagnostic performance can vary by population, testing platform, and regional antimicrobial resistance patterns.

Advances in molecular diagnostics, AI, and point-of-care devices are expected to improve the management of *H. pylori* infection in the future and facilitate more precise, accessible healthcare worldwide.

Disclosure of Financial Interests

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Author Contributions

Brenda Ngowi was responsible for the preparation and drafting of the manuscript. Dr. Hongzhang Shen provided supervision, guidance, and critical review of the manuscript. Both authors reviewed and approved the final version of the manu-

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Abbreviations

UBT	Urea Breath Test
SAT	Stool Antigen Test
RUT	Rapid Urease Test
PCR	Polymerase Chain Reaction
NGS	Next Generation Sequencing
POC	Point of care