Point-of-care testing for *Helicobacter pylori* infection

Horizon Scan Report 0048
April 2017

Clinical Question:

In adults attending primary care with upper gastrointestinal symptoms, what is the accuracy and utility of point-of-care testing to detect *Helicobacter pylori* infection?

Background

Helicobacter pylori (HP) is a spiral-shaped gram-negative bacterium with unipolar sheathed flagellae often tipped with a distinctive bulb. HP colonises the gastric mucosa of humans and some primates as its shape allows rapid movement in the mucus layer overlying the gastric epithelial cells (1). HP is transmitted human to human, most often to children from close family members in early life, although conflicting reports of transmission via contaminated food and water also exist (1, 2). The main risk factor for HP infection is low socioeconomic status in childhood (2).

The global prevalence of human HP infection is falling, although this reduction has been observed mostly in developed nations (1). One third of adults are infected in northern Europe and America, more than half are infected in south and east Europe, South America, and Asia, and over two-thirds of Africans (2). It follows that HP prevalence is higher in first and second generation immigrants from developing to developed nations.

HP colonisation is usually asymptomatic but always leads to a chronic active gastritis which may lead to peptic ulceration, atrophic gastritis, and intestinal metaplasia (1, 3, 4). HP colonisation is associated with a range of clinical presentations: dyspepsia, peptic ulcer disease, and gastric cancer (3). First-line therapy for HP eradication comprises a combination of acid suppression therapy and two antibiotics (4). HP eradication results in significant improvement of gastritis and gastric atrophy but not of intestinal metaplasia (4).

Current Practice

There are a number of test types to diagnose HP infection available in clinical practice. They can be subdivided into invasive and non-invasive tests. Each test type requires a different sampling procedure, and has related benefits and drawbacks. The tests are summarised in Table 1

Table 1: Invasive and non-invasive tests to diagnose *Helicobacter pylori* infection.

Test	Example testing procedure	Confirms current infection	Accuracy		Benefits	Drawbacks
			Sensitivity	Specificity		
Non-invasive						
IgG serology	Venous blood sent to laboratory for Immunoglobin-G antibody testing.	No	75-85%	79-90%	-Non-invasive. -Rapid. -Widely available. -Inexpensive.	-A positive test may represent past infection. -Delay for result.
^{13}C-Urea Breath test	Breath collected before and 15-30mins after drinking a ^{13}C-urea substrate solution. HP urease hydrolyses ^{13}C-urea. Breakdown products absorbed into circulation. Exhaled as $^{13}CO_2$. Detected by either: (1) isotope ratio mass spectrometry (IRMS); (2) non-dispersive isotope-selective infrared spectroscopy (NDIRS); (3) laser-assisted ratio analyser (LARA).	Yes	>95%	>95%	-Non-invasive. -High accuracy before and after treatment. -IRMS widely available and can analyse multiple samples. -Rapid NDIRS or LARA result.	-IRMS requires complex laboratory equipment. -NDIRS and LARA analysis not widely available -Breath collection kits only available on prescription in some settings.
Monoclonal stool antigen	Stool sample either (1) sent to the laboratory for HP antigen detection using a monoclonal enzyme immunoassay test or (2) HP detected using a rapid point-of-care qualitative immunochromatographic test.	Yes	>95%	>95%	-Non-invasive. -Accurate before and after treatment. -Widely available. -Rapid qualitative result.	-Rapid tests less accurate. -Patient reluctance to give stool samples. -Delay in laboratory result.
Invasive						
Histology (H) +/- Immunohistochemistry (I)	Gastric biopsy taken during endoscopy. HP identified using staining in the laboratory. Immunohistochemistry increases accuracy if bacteria not visible but HP presence likely.	Yes	60-86% (H) >97% (I)	>98% (H) 100% (I)	-Also detects inflammation, atrophy, metaplasia, and malignancy	-Invasive. -Expensive. -Time-consuming
Rapid urease test	Gastric biopsy taken during endoscopy placed in gel containing urea substrate. If HP present urease will hydrolyze urea to create ammonia and CO_2. Change in pH is detected.	Yes	80-95%	97-99%	-Relatively rapid and simple once gastric biopsy retrieved at endoscopy.	-Invasive. -Requires high bacterial load. -Greatest accuracy from two biopsies.
HP Culture	Gastric biopsy taken during endoscopy and cultured in an incubator for several days in the laboratory.	No	60%	100%	-Added assessment of antibiotic sensitivity & resistance.	-Invasive. -Expensive. -Complex -Time-consuming.

Invasive testing.

The invasive tests require gastric biopsy taken at upper gastrointestinal endoscopy. Meta-analysis of six randomised controlled trials (RCTs) including patients with uncomplicated dyspepsia showed a reduced risk of remaining symptomatic (Relative Risk 0.95, 95% CI 92-99%) for endoscope-and-treat policies over (non-invasive) test-and-treat strategies (5). However, the economic analysis showed a cost-saving of $389 per patient for the test-and -treat policy by reducing the number of endoscopies performed. Consequently, a test-and-treat strategy is preferred for patients without alarm symptoms (4). However, in patients with alarm symptoms (weight loss, dysphagia, gastrointestinal bleeding, an abdominal mass, or iron deficiency anaemia) endoscopy testing is required to confidently rule out gastric cancer and other significant oesophageal and gastric pathology (4). Furthermore, in countries with low HP prevalence (<10%) low quality evidence recommends endoscopic evaluation to reduce the number of false positives from non-invasive tests (4).

The invasive tests for HP include histology, immunohistochemistry, rapid urease testing, and HP culture. Despite some GPs preferring invasive testing, none of the invasive tests are candidates for point-of-care (POC) use in primary care because of their reliance of endoscopy (6). Histology, immunohistochemistry, and HP culture are time consuming, complex, and resource intensive procedures requiring laboratory equipment and specially trained staff. When endoscopy is indicated, the rapid urease test is recommended to diagnose HP as it provides relatively quick and accurate results by detecting the change in pH caused by the production of CO_2 and ammonia from the breakdown of urea (7). The rapid urease test requires a minimum of two gastric biopsies (from the gastric corpus and atrum) and a high bacterial load to ensure optimal accuracy. Polymerase Chain Reaction (PCR) testing of gastric biopsy specimens has demonstrated extremely high accuracy in the research setting, with the added benefit of identifying clarithromycin resistant HP, but at present is too expensive a test for use in routine clinical practice (7).

Non-invasive testing.

The non-invasive tests include Immunoglobulin-G (IgG) based serology, the Urea Breath Test (UBT), and the Stool Antigen Test (SAT). Antibody based saliva and urine tests are available but have shown limited sensitivity and specificity and are not recommended for use (7, 8).

Immunoglobin-G based HP serology.

Of the non-invasive tests, the simplest and most commonly used in primary care is the IgG blood test (6). At present standard practice is for the blood sample to be sent to the laboratory for analysis and reported back to the surgery. POC blood tests are feasible and exist for use in primary care. However the utility of the IgG method is limited as it cannot differentiate between current and past infection (it identifies the presence of antibodies which develop in the response to HP infection that may persist for over a year after successful eradication) (7). To avoid unnecessary treatment, a positive result requires secondary verification by a test that can identify active infection (4). Similarly, HP serology should not be used to confirm eradication. There are a limited number of clinical scenarios in which low gastric HP load reduces the accuracy of the breath and stool tests. In these scenarios the blood test may be a more reliable alternative: gastrointestinal bleeding, atrophic gastritis, gastric MALT lymphoma, and gastric carcinoma (4).

Qualitative studies report that the majority of patients would happily provide a breath or stool sample if the results were more accurate than serology (9). Neither the breath nor stool test can be performed within 2 weeks of treatment to reduce gastric acid secretion (Proton Pump Inhibitor therapy) nor within 4 weeks of antibiotic treatment as both of those treatments increase the risk of false negatives (4).

^{13}C-Urea Breath Testing.

The ^{13}C-UBT detects current infection and can confirm the eradication of HP (7). There are three analytic techniques available. Firstly, and most commonly, breath samples are analysed using isotope ratio mass spectrometry (IRMS) in a laboratory using an expensive gas chromatograph reliant on helium (7). Multiple samples can be run simultaneously and the results are reported back to the requestor. This is the only approach licensed for use in the UK: GPs give their patient an FP10 prescription for the Institut fur biomedizinsche Analytik und NMR Imaging (IFNAI) HP test, the patient collects the test from a pharmacy, returns for a subsequent extended appointment to give their sample by breathing into test tubes through a straw (10, 11).

The second analytic technique is Non-Dispersive Isotope selective Infrared Spectroscopy (NDIRS), a much cheaper and less time consuming method than IRMS that can be used at the point of care in settings which deal with a lower volume of samples (7). NDIRS is not widely available and requires larger breath sampling bags to be connected directly to the NDIRS device but results are rapid.

Thirdly, Laser Assisted Ratio Analysis (LARA) is a newer technique using CO_2 lasers to produce an optogalvanic effect to allow measurement of the ratio of $^{13}CO_2$ and $^{12}CO_2$. LARA is much more expensive than NDIRS but cheaper and quicker than IRMS making it more appropriate for the laboratory setting but of limited value at present as a POC device (12).

Of note, a range of ^{14}C-Urea breath tests are available, but are not considered further here as they expose the patient to a low-dose of radiation and are not advised for use in children and pregnant women (7). In addition, a portable mass spectrometer has also been developed but testing has only been reported in 45 patients at present (13)

Stool Antigen Testing.

Stool antigen test (SAT) is the other non-invasive method which has been shown to have high accuracy (14). The stool antigen tests can detect current infection and confirm HP eradication. Some primary care staff prefer stool tests to breath tests as they impact less on practice budget and time (15). However, patient compliance with stool testing can be problematic: 48% vs. 86% for breath testing and serology (16). There are two types of SATs: quantitative enzyme immunoassay (EIA) which are analysed in the laboratory setting, and qualitative immunochromatography assays (ICA) which are commonly used as a rapid test at home or in clinic (7). Both test types use polyclonal or monoclonal antibodies. In general, monoclonal antibody-based SATs are more accurate than polyclonal antibody-based SATs, whilst EIA-based stool tests and ^{13}C UBTs tests are more reliable and reproducible than ICA-based SATs (17, 18). Despite some reports of sensitivity and specificity comparable to EIA tests, numerous reports about the wide range of ICA-based SATs show much lower accuracy, so at present the use of rapid ICA SATs is not recommended (18-22).

Advantages over Existing Technology

NDIRS ^{13}C-UBTs and the qualitative ICA-SATs have the greatest potential for primary care POC use: they are non-invasive, relatively inexpensive, give rapid results, diagnose active HP infection, confirm HP eradication, and can be used outside of the laboratory setting by non-specialist staff. However, at present the ICA-SATs do not consistently demonstrate high enough accuracy to be considered further in this report (18). Therefore, the NDIRS ^{13}C-UBT is the focus of the remainder of this report.

Details of Technology:

Non-Dispersive Isotope selective InfraRed Spectroscopy (NDIRS) was first used to diagnose HP in 1996 (23). The most common procedure is for the patient to: (1) breathe into a sample collection bag to provide a "baseline" sample; (2) ingest a ^{13}C-Urea containing substrate as a drink or as a capsule together with a second substance to slow gastric motility (such as citric acid); (3) give a second "reference" breath sample 10-30 minutes later. Following ingestion, the ^{13}C-Urea substrate ($2H_2N(^{13}CO)NH_2 + 2H_20$) is hydrolysed in the stomach by the HP urease enzyme. The breakdown products ($4NH_3 + 2^{13}CO_2$) are then absorbed into the circulation. $^{13}CO_2$ is transported as bicarbonate in the blood to the lungs, and exhaled as $^{13}CO_2$.

$^{12}CO_2$ and $^{13}CO_2$ each have individual rotation-vibration bands in the infrared range of electromagnetic spectrum (between 2.5 and 8 μm). The NDIRS device calculates the change in the $\Delta^{13}CO_2$ value (‰) by comparing the $^{13}CO_2$ /$^{12}CO_2$ ratio in the "baseline" sample and the "reference" sample (Δ = 1000 x (^{13}C/^{12}Cbaseline sample - ^{13}C/^{12}Creference) / ^{13}C/^{12}Creference). A variety of ‰ thresholds to signify HP infection have been recommended by manufacturers in relation to the range of devices tested over time.

We identified three main manufacturing groups currently producing ^{13}C-UBT technology for POC use and potential application in primary care: Kibion, Otsuka, and Fischer ANalysen Instrumente. Understanding each manufacturers development helps us to group studies reporting similar technology. Kibion was founded in 2005, as a subsidiary of the Swedish pharmaceutical company Orexo AB. In 2011 Orexo acquired the German company Wagner Analysen Technik GmbH, who manufactured the IRIS™ diagnostic breath test analyser. Kibion's German subsidiary, Kibion GmbH, is based in Bremen (24). Meretek Diagnostics, Inc. was founded in 1993 and is based in Lafayette, Colorado. It changed its name to Meretek Diagnostics Group of Otsuka America Pharmaceutical, Inc. in October, 2007 and now operates as a subsidiary of Otsuka America Pharmaceutical, Inc (25). Fischer ANalysen Instrumente (FAN) are based in Fischer Leipzig, Germany where they manufacture and distribute ^{13}C and H_2 breath test devices (26).

We identified seven devices: IRIS Dynamic Base and IRIS Dynamic Pro by Kibion; UBiT IR300 and POCone by Otsuka; and FANhp, FANci2, and HeliFANplus by FAN. The dimensions, weight, breath collection, substrate requirements, number of pairs of sample bags analysed at one time, analysis and warm up time, external dependencies and approvals for these devices are summarised in Table 2.

Table 2: Characteristics of Non-Dispersive Isotope selective InfraRed Spectroscopes with potential for primary care POC use.

Manufacturer *Model*	Dimensions (cm)	*Weight (kg)*	Breath collection	^{13}C Urea substrate (mg)	Sample pairs (n)	Analysis time (min)	Warm up time (mins)	External equipment?	Approvals
Kibion									
IRIS Dynamic Base	28 x 32 x 38	*13*	120mls bag	Diabect tablet: 50mg	2	2	720	No	CE
IRIS Dynamic Pro	50 x 32 x 38	*11*	120mls bag	Diabect tablet: 50mg	8	2	720	*IRIS Dynamic base*	CE
Otsuka									
UBiT IR300	31 x 62 x 31	*22.5*	BreathTek bag	BreathTek Pranactin-Citric: 75 mg	1	5-6	40-80	No	FDA
POCone	22 x 27 x 36	*10*	BreathTek bag	BreathTek Pranactin-Citric: 75 mg	1	2	10	No	FDA CLIA
Fischer ANalysen Instrumente (FAN)									
FANhp	20 x 45 x 24	*9*	0.3l FAN bag	Not specified	1	5	10	No	CE
FANci2	41 x 44 x 24	*23*	0.3l FAN bag	Not specified	8	2	240	USB to Laptop/PC with FANci software	CE
HeliFAN plus	35 x 21 x 24	*9*	0.3l FAN bag	Not specified	4	2	480		CE

Importance:

Approximately 5% of uninvestigated dyspepsia is caused by HP infection (27). The British Society of Gastroenterology (BSG) defines dyspepsia as a group of symptoms of the upper GI tract lasting for 4 weeks or more, including upper abdominal pain or discomfort, heartburn, gastric reflux, nausea or vomiting (28). Eradication therapy using a test-and-treat strategy is thought to improve symptoms by a combination of the healing of undiagnosed peptic ulcer and small improvements in the symptoms in uninvestigated dyspepsia (4). In patients with functional dyspepsia (epigastric pain with normal endoscopy) a meta-analysis of RCTs comparing HP eradication to placebo showed the NNT to cure one case of dyspepsia with eradication therapy was 13 (95% CI 9 to 19) (3).

HP-positive patients have a 10 to 20% lifetime risk of developing peptic ulcer disease (29). Meta-analysis of RCTs comparing HP eradication therapy to placebo show eradication therapy to be cost effective leading to significantly lower rates of ulcer relapse compared with long term acid suppression (3). To prevent duodenal and gastric ulcer relapse, the numbers needed to treat (NNT) with HP eradication therapy are 2 and 3 respectively (3).

HP was the first infection to be classified as a grade 1 carcinogen by the World Health Organisation. 5.2% of the global cancer burden was attributable to HP infection in 2008 (more than any other infective agent including Human Papilloma Virus), totalling 46% of infection related cancers in the developed world and 29% in the less developed (30). HP is implicated in gastric cancer and gastric mucosa-associated lymphoid tissue (gMALT) lymphoma. A systematic review of nested case-control studies reported that HP infected cases were three to six times more likely to develop gastric cancer than controls (31). A systematic review of over 6000 patients from six RCTs showed that HP eradication resulted in a significant reduction in the incidence of gastric cancer compared to placebo (32). Nearly all cases of gastric MALT lymphoma are HP positive, which has seven times greater risk of developing in the presence of HP infection (1, 30).

Patient Group and Use:

Adults presenting to primary care in settings where HP prevalence is >10% (4):

- with uninvestigated dyspepsia lasting for 4 weeks with no alarm symptoms.
- with a past history of gastric ulcer or duodenal ulcer who have not previously been tested for HP, are starting or already taking NSAIDS.
- with unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura & vitamin B12 deficiency who have not previously been tested for HP.
- to confirm HP eradication following treatment.

Previous Research:

Gisbert et al conducted a narrative review of studies published before May 2004 reporting the clinical application and accuracy of the ^{13}C urea breath test for HP detection (12). Of 43 studies included, 12 reported the diagnostic accuracy of NDIRS method to detect HP infection. Sensitivity ranged from 91-100% and specificity from 74-100%. A range of HP thresholds (from 3.5-11 ‰) were used across studies, and a range of reference standards (rapid urease testing, histology, culture, ^{14}C-urea breath test, and the stool antigen test). All 12 studies investigated the utility of NDIRS for the

detection of active infection pre-eradication, and one (33) also the utility post eradication (Sn 100%, Sp 89%). A quality assessment of the included studies was not performed. Neither the NDIRS device models/manufacturers nor the location of the device were reported by the review authors.

In a systematic review, Ling extracted sensitivity and specificity values from 21 studies published between 2003 and 2012 to determine the diagnostic accuracy of the ^{13}C urea breath test against a composite reference standard (most commonly culture followed by concordance on histology and the rapid urease test) (34). Pooled sensitivity was 98.1% (95% CI, 96.3%–99.0%) and specificity was 95.1% (95% CI, 90.3%–97.6%). The summary LR+ and LR− estimates were 19.9 (95% CI, 9.9–39.9) and 0.02 (95% CI, 0.01–0.04), respectively. The AUC was 98.8% (95% CI, 97.4%–100%). Neither the analysis technique nor the location of the device were reported.

Fewana et al, more recently conducted a meta-analysis of cross-sectional studies including consecutive adult patients with dyspeptic symptoms to assess the diagnostic accuracy of the ^{13}C or ^{14}C breath tests against a reference standard of HP culture and/or histological examination (not blood or stool antigen testing) (35). The pooled sensitivity for the five studies reporting the accuracy of "infrared assisted" ^{13}C detection was 95% (95% CI, 93-96%) and the pooled specificity was 93% (91-95%) which were not significantly different from the 18 studies reporting "infrared not assisted" techniques (Sensitivity 97% [95% CI 96-98%]; Specificity 93% [95% CI 91-95%]). Although there were some ^{14}C devices included in the "infrared not assisted" group, a separate subgroup analysis comparing ^{13}C with ^{14}C devices also showed no statistically significant subgroup effect (35). The authors concluded that more widespread breath testing should be adopted given the high accuracy, but the NDIRS device model/manufacturer and setting were not reported (35).

Accuracy compared to existing technology

Kibion

We retrieved five studies that reported on the accuracy of devices related to the technology in current Kibion NDIRS devices (IRIS).

1. A German study compared IRMS (Tracemass, Europa Scientific Ltd., Crewe, UK) and IRIS using breath samples from 538 asymptomatic volunteers attending the annual meeting of the German Society for Internal Medicine in 1995 (36). For the IRIS analysis breath was expired into 1200ml aluminized breath bags, eight of which could be connected to IRIS and analysed sequentially taking 90 seconds a sample. Using a threshold of 5‰, a highly linear correlation was found ($r=0.945$; $p<0.001$), the mean difference between the two methods was -1.96% ± 2.76‰. IRIS had a sensitivity of 98.3% and a specificity of 98.6% compared to IRMS (confidence intervals not reported).

2. A German prospective study of 145 patients undergoing endoscopy (indication unknown) reported the accuracy of IRIS 30 minutes after ingesting 75mg of urea and 200mls of apple juice against a composite reference standard of histology, culture, and rapid urease testing. The optimal threshold reported was 3.5‰: 52 out of 57 (87%) patients were correctly diagnosed by IRIS; sensitivity was 91.2%; specificity 90.2% (confidence intervals not reported) (37). Nine thresholds were reported in total (Table 3).

Table 3. Diagnostic accuracy of IRIS at nine thresholds in 145 patients undergoing endoscopy.

Threshold (‰)	Sensitivity (%)	Specificity (%)
2.0	91.2	84.0
2.5	91.2	86.7
3.0	91.2	86.7
3.5	91.2	89.3
4.0	87.7	92.0
4.5	85.2	93.3
5.0	78.9	96.0
5.5	78.9	96.0
6.0	78.9	97.3

3. A Brazilian study compared IRIS (using a threshold of 4.0‰) with a combined reference standard of the ^{14}C-urea breath test (using a threshold of 0.8% CO2/Kgs weight), rapid urease test and histology using samples from fifty-three patients with duodenal ulcers attending outpatients (38). Sample collection bags were sent by airmail to a central laboratory for analysis. There was 100% agreement between the results of the ^{13}C-urea breath tests and the HP status determined by the combination of the urease test, histological examination and ^{14}C-urea breath tests leading authors to state that IRIS is a low cost, easy to manage, highly sensitive and specific test for HP detection.

4. IRIS was compared with two mass spectrometers (ABCA, Europa Scientific, Crewe, UK, and Breath Mat, Finnigan, Bremen, Germany) in an Italian study of 134 fasted consecutively endoscoped dyspeptic patients suffering from non-ulcer dyspepsia (97 cases) or duodenal ulceration (37 cases) (39). Breath samples were collected in aluminumised bags 15 mins and 30 mins after ingestion of 75 mg of ^{13}C-urea dissolved in 150 ml 0.033 mol/L citric acid. A highly linear correlation (r=0.963-0.987 at 15 min and 0.977-0.985 at 30 min; p<0.0001) was found in every two-by-two comparison using a threshold of 5.0‰. The sensitivity ranged from 97–100% at both times with all devices. Specificity was slightly inferior with NDRS than with the two IRMS machines (95% vs 98–100% at 30 min), but the difference was not significant (exact p-value not reported). The authors recommended that NDIRS was a valid alternative to IRMS in patients who had fasted.

5. A Belgian study including 223 fasted patients referred for endoscopy assessed IRIS against histological examination of 4 gastric biopsy specimens (40). The authors investigated four test lengths (10, 20, 25, 30 minutes) and five thresholds (3, 3.5, 4, 4.5, 5‰) (40). They suggested using a 10-minute test with a cut-off value lying between 4 and 5‰ after ingesting 75 mg of urea and 0.1N citric acid. Sensitivity at these thresholds was 100% and specificity was 95% for the 182 patients taking no acid suppression or antibiotic medication in the past three days. However, at the lower threshold of 3.5‰, sensitivity was 68% and specificity was 91% in the 41 patients taking acid suppression or antibiotic medication in the past three days.

Otsuka

We retrieved six studies that reported on the accuracy of devices related to the technology in current Otsuka NDIRS devices.

1. An American study included 178 fasted patients undergoing upper gastrointestinal endoscopy for "any reason" who had not received eradication therapy (acid suppression, bismuth preparations, or antibiotics) within 1 month (41). The Meretek ^{13}C urea breath test was compared to gastric biopsy culture and stain as part of a larger study comparing the accuracy of serology, rapid urease testing, and breath testing. The breath samples were collected in a sampling device 30 and 40 minutes following ingestion of ^{13}C urea and a pudding designed to delay gastric emptying. Samples were analysed by the manufacturer who reported the 30 minute result in all but one patient. Sensitivity of the Meretek ^{13}C device was 97% (95% CI 94-100%) and specificity 94% (95% CI 87-100%) with an overall accuracy of 95% (95% CI 91-98%). The authors did not report the threshold used.

2. A Taiwanese study included 177 patients undergoing upper endoscopy for dyspepsia if they had taken no bismuth salts, proton pump inhibitors, or antibiotics within the previous 8 weeks. Patients with a past history of HP eradication therapy, gastric malignancy, penicillin allergy, or previous gastrointestinal surgery were excluded (42). Breath samples were collected in 20ml glass test tubes for IRMS analysis (ABCA, Europa Scientific, UK) and in 200ml gas storage bags for UBiT IR200 anaysis at baseline, and 10 and 15 min after the ingestion of 50 mg of urea and 100-mL of citric acid. Comparing a threshold of 3.5‰ to a reference standard of histology or culture from gastric biopsy, a close correlation of was found between UBiT IR200 and IRMS at 10 and 15 minutes (r=0.983 and 0.992, respectively). At 10 minutes sensitivity was 94% for both techniques, and specificity was 96.4% for IRMS and 94.6% for UBiT (confidence intervals not reported). At 15 minutes the same sensitivity (96.4%) and specificity (98.9%) were achieved.

3. A Spanish multicentre study including 41 patients, some with dyspepsia who had not undergone prior eradication therapy and some with gastric ulceration receiving eradication compared the UBiT IR200 NDIRS device to an IRMS device, using a reference standard of histology and the rapid urease test (33). No difference was found between the mean values obtained for the IRMS and NDIRS devices with identical AUROCs (0.96), however the NDIRS device was more sensitive (100% vs 90%) and less specific (89% vs 96%).

4. A second Taiwanese study included 586 patients aged between 20 and 70 years who were undergoing upper endoscopy without receiving eradication therapy (43). Patients with ulcer complications, previous stomach surgery, gastric cancer, drug allergies, who had used benzimidazoles or bismuth preparations within the previous 7 days, were pregnant, had taken HP eradication therapy, or had a severe systemic disease were excluded . Culture, histology, and rapid urease test on biopsies from the antrum and corpus of the stomach were used as a reference standard for HP infection. Breath samples were collected before and 20 min after drinking 100 mg ^{13}C-urea in 100 mL water. After 15 min a breath sample was collected into a collection bag and analysed using NDIRS (IR20) which printed the results in 5–6 minutes. The AUROC was 0.994. At a threshold of 3.5‰, a sensitivity of 97.8%, a specificity of 96.8% and an accuracy of 97.5% were reported. At a threshold of 5‰, a sensitivity of 97.0%, a specificity of 99.5% and an accuracy of 97.8% were reported (confidence intervals not reported).

5. A third Taiwanese study assessed NDIRS in a population of 100 patients undergoing routine gastrointestinal endoscopy (44). HP was defined as the presence of a positive culture or positive results of both histology and rapid urease test following gastric biopsy. 100 mg of ^{13}C-urea was dissolved in 50 ml sterile water and breath samples collected in a 200-ml gas storage bag before and 15 min after consumption. Using a threshold of 4.8‰ the sensitivity, specificity, positive predictive value and negative predictive value of NDIRS was 100% (95% CI, 100-100); 85.1% (95% CI, 74.8-95.2), 88.3 (95% CI, 80.2-96.4) and 100% (95% CI, 100-100), respectively.

6. A later Spanish prospective study included 199 patients undergoing endoscopy for dyspepsia who had stopped anti-secretory medication for 2 weeks and not received antibiotics in the previous 4 weeks (45). Breath samples were collected in a collection bag 20 mins after ingesting a 100mg urea solution. The NDIRS (POCone Infrared Spectrophotometer; Otsuka Pharmaceutical) and IRMS (Tau-Kit; ISOmed) methods showed high correlation (r = 0.992). The AUROC for IRMS was 0.948. However, at the manufacturers threshold of 2.5‰, NDIRS was highly sensitive (99.2%) but poorly specific (60%). At a threshold of 8.5% the sensitivity and specificity of NDIRS were 90% and 90% respectively.

Fischer ANalysen Instrumente (FAN)

We retrieved no studies specifically reporting the accuracy of the FAN devices.

Impact compared to existing technology

We retrieved no studies reporting on the impact of POC NDIRS use in primary care. However, a large study included 44,487 breath samples from patients >45yrs from a well-defined region of Denmark, who were judged to "meet criteria" for a test-and-treat strategy by their GPs. Patients were asked to conduct the breath test at home and mail the two breath collection bags to the laboratory for analysis using the IRIS infrared spectroscope (Wagner Analysen Tecknik, Bremen, Germany) (46). One in five patients tested positive for HP, although 726 samples (1.6%) were not included in the analysis because of bag errors. The authors concluded that a test-and-treat system was possible to implement that allowed patients to perform UBTs at their homes.

Health Economics:

Seven studies were identified in the review that evaluated cost-effectiveness of ^{13}C UBT testing, although none said whether they were evaluating point of care tests. Two studies evaluated the costs and consequences of testing, but did not calculate a cost-effectiveness estimate, such as an incremental cost-effectiveness ratio (ICER). Two studies did report an ICER, but only for interim outcomes. Three studies conducted a full cost-utility analysis of incremental cost per quality-adjusted life year (QALY), which took into account the downstream health and cost impact of each strategy (Table 1).

Mahadeva (2008) reported the costs of testing with ^{13}C UBT compared with endoscopy in uncomplicated dyspepsia in young adults in Malaysia, with the Leeds Dyspepsia Questionnaire (LDQ)

score as the primary outcome. The LDQ was not significantly improved in the endoscopy group compared with ^{13}C UBT, although patient satisfaction was higher, as were treatment costs (47). Cuddihy (2005) also compared 13C UBT to endoscopy, this time in a US population with dyspepsia, along with treatment based on empirical judgement alone, and ELISA serology. The primary outcome was symptom resolution, with a time horizon of 6 months. They found no statistically significant differences in costs, quality of life measured with SF-36, or symptom resolution between any of the groups (48).

Citation	Analysis	Population	Device	Comparator(s)	Outcome	Time horizon	Country
Delaney (2008)	Cost-utility	Dyspepsia	Not reported	No testing	Dyspepsia relapse	12 months	UK
Xie (2008)	Cost-utility	Screening	Mass Spectrometer	No screening, serology	gastric cancer	lifetime	Singapore
Xie (2009)	Cost-utility	Screening	Mass Spectrometer	No screening, serology, SAT	gastric cancer	lifetime	Canada
Elwyn (2007)	Cost-effectiveness	Dyspepsia	Not reported	serology, SAT	Correct diagnosis	12 months	UK
Masucci (2013)	Cost-effectiveness	Dyspepsia	Mass Spectrometer	Serology, two-step	misdiagnosis avoided	1 month	Canada
Cuddihy (2005)	Cost consequence	Dyspepsia	Not reported	Empirical judgement, serology, Endoscopy	Symptom resolution	6 months	USA
Mahadeva (2008)	Cost-consequence	Dyspepsia age <45	IRIS	Endoscopy	Leeds Dyspepsia Questionnaire score	12 months	Malaysia

The two cost-effectiveness studies both reported ICERs of cost per additional correct diagnosis. Elwyn (2007) compared serology, ^{13}C UBT and SAT in a population with dyspepsia in the UK over a 12 month follow up. They found that ^{13}C UBT was dominated by SAT, which was both less costly and more accurate (49). Masucci (2013) compared ^{13}C UBT with serology and with a two-step process that confirmed the serology result with ^{13}C UBT. Two step testing dominated ^{13}C UBT alone, over the 1 month time horizon in a Canadian population (50).

Three cost-utility studies reported the value of testing in cost-per-QALY outcomes; the preferred outcome of many national decision makers, as it enables comparison across health conditions. Delaney (2008) conducted an economic evaluation alongside a trial in the UK, from the perspective of the NHS. Comparing ^{13}C UBT against no testing, they reported an ICER of £1000/QALY, a highly cost-effective finding, but with very broad uncertainty, due to the uncertain impact of dyspepsia on quality of life (51). The time horizon was only 12 months, so potential benefits from cancer prevention were not included. Two studies by Xie and colleagues considered cost-effectiveness of testing and treating in an asymptomatic screening population, rather than in patients with dyspepsia. The outcome reported by both was gastric cancer prevention over the patient's lifetime.

Both studies developed decision analytic models to assess cost-effectiveness: one for a Canadian male population (52), the other for Singapore (53). Both reported that screening with ^{13}C UBT would not be cost-effective compared with serology or SAT (ICER versus serology: US $390,000; ICER versus SAT: CAN $533,000).

No studies have evaluated whether ^{13}C UBT testing is cost-effective in symptomatic patients over a lifetime horizon. Testing and treating dyspepsia is potentially cost-effective, by reducing the costs of treating future dyspepsia, but quality of life benefits appear to be minimal or non-existent. Further health and cost consequences with respect to gastric cancer cases avoided have not been evaluated in this setting.

Guidelines and Recommendations

Public Health England recommends that HP testing should be performed in the following four groups: (1) patients with uncomplicated dyspepsia unresponsive to lifestyle change, antacids, single course of PPI for 1 month and without alarm symptoms; (2) patients with a past history of gastric ulcer or duodenal ulcer who have not previously been tested; (3) patients before starting or taking NSAIDs, especially if a prior history of gastro-duodenal ulcers; (4) unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura & vitamin B12 deficiency (54).

NICE make a number of recommendations in relation to HP. In relation to testing: (1) leave a 2-week washout period after proton pump inhibitor (PPI) use before testing; (2) test using a ^{13}C-urea breath test, stool antigen test, or laboratory-based serology (where its performance has been locally validated); (3) offer a 'test and treat' strategy to people with dyspepsia; (4) offer HP retesting 6 to 8 weeks after beginning treatment using a ^{13}C-urea breath test. Regarding treatment: (1) offer HP eradication therapy to people who have tested positive and who have peptic ulcer disease using first-line a 7-day, twice-daily course of acid suppression therapy, amoxicillin, and either clarithromycin or metronidazole; (2) stop NSAIDS in patients diagnosed with peptic ulcer full-dose acid suppression therapy for 8 weeks and then offer eradication therapy if HP is present; (3) treat patients with endoscopically determined functional dyspepsia with HP eradication followed by symptomatic management (55).

The European Maastricht V / Florence Consensus Report on the management of HP infection makes the following recommendations: (1) acid suppression should be discontinued at least 2 weeks before testing for HP, and antibiotics and bismuth compounds at least 4 weeks; (2) HP testing should be performed in aspirin and NSAIDs users with a history of peptic ulcer; (3) the UBT is the most investigated and best recommended non-invasive test in the context of a ‘test-and-treat strategy’, which is appropriate for uninvestigated dyspepsia without alarm symptoms; (4) HP should be sought and eradicated in unexplained iron deficiency anaemia (IDA), idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency; (5) HP eradication heals gastritis in long-term PPI users and HP gastritis has to be excluded before a reliable diagnosis of functional dyspepsia can be made, (6) HP eradication is the first-line treatment for localised stage gastric MALToma; (7) UBT is the best option for confirmation of HP eradication and should be performed at least 4 weeks after completion of therapy (4).

Research Questions:

1. Does using POC NDIRS ^{13}C-UBT testing in primary care reduce referrals for endoscopy in patients with dyspepsia?
2. Does using POC NDIRS ^{13}C-UBT testing in primary care reduce the prescription of HP eradication therapy?
3. Does using POC NDIRS ^{13}C-UBT testing in primary care reduce GP appointments and reduce delay in gastric cancer diagnosis?
4. Does using POC NDIRS ^{13}C-UBT testing in primary care lead to more rapid confirmation of HP eradication?
5. What is the diagnostic accuracy of POC NDIRS ^{13}C-UBT testing in primary care for the confirmation of active HP and HP eradication?
6. What is the cost of a test-and-treat approach for managing patients with suspected HP infection using POC NDIRS ^{13}C-UBT testing in primary care relative to current practice using other non-invasive tests for HP?

Suggested next steps:

A diagnostic accuracy study comparing the accuracy of POC NDIRS ^{13}C-UBT devices when used in primary care is needed before a prospective cohort study can be conducted to assess the introduction and cost-effectiveness of POC NDIRS ^{13}C-UBT testing into routine primary care practice in relation to endoscopy referrals, specialist referrals, antibiotic prescription, patient attendances, and time to diagnosis compared to a region without POC NDIRS technology.

Acknowledgements:

The authors would like to thank Nia Roberts for performing literature searches, and Professor Barbara Braden for her expert advice on this topic. This work is supported by the National Institute for Health Research (NIHR) Diagnostic Evidence Co-operative Oxford at Oxford Health NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford

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