Australian Government

CARBON-LABELLED UREA BREATH TESTS FOR DIAGNOSIS OF HELICOBACTER PYLORI INFECTION

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ASSESSMENT REPORT

Medical Services Advisory Committee

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Medical Services Advisory Committee
Strengthening evidence-based health care in Australia

Carbon-labelled urea breath tests for diagnosis of Helicobacter pylori *infection*

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Renea Johnston, Ms Trang Vu, Dr Veronica Pitt, Ms Sharon King, Ms Amanda Weeks, Dr Silva Zavarsek, Associate Professor Anthony Harris and Associate Professor Sally Green from the Monash Institute of Health Services Research and the Centre for Health Economics, Monash University. The report was edited by Dr Alana Mitchell, ScienceLink Pty Ltd. The report was endorsed by the Minister for Health and Ageing on 8 June 2006.

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The carbon-labelled urea breath test (C-UBT) is a new investigative measure used to determine if an individual has a *Helicobacter pylori (H. pylori)* infection. The test relies on the production by the *H. pylori* organism of relatively high concentrations of urease, an enzyme that hydrolyses urea to give ammonium and bicarbonate. The bicarbonate generated in the gastric mucosa enters the blood stream and is rapidly excreted by the lungs as carbon dioxide (CO_2). To identify *H. pylori* using C-UBT, the patient is orally administered carbon-labelled urea, which is hydrolysed to produce isotopically labelled CO_2 (Gisbert & Pajares 2004). The isotopically labelled CO_2 enters the blood stream and is excreted by the lungs. Collection and analysis of the patient's breath samples enables the detection of the presence of *H. pylori*. The urea can be labelled with the stable isotope of carbon, ^{13}C, or the radioactive isotope, ^{14}C.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Monash University Evaluation Group was engaged to conduct a systematic review of literature on carbon-labelled urea breath tests. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of carbon-labelled urea breath tests for diagnosis of *H. pylori* infection

Clinical need

The original purposes of this assessment were to:

- examine the use of the UBT in patients who test positive to a serological test, that is to use the UBT as a second line diagnostic test
- examine the use of the UBT as a first line diagnostic test in patients with symptoms of dyspepsia without a history of duodenal ulcer, gastric ulcer, gastric neoplasia, and without alarm features (including weight loss, vomiting, dysphagia, bleeding, anorexia or an abdominal mass).

However, no studies were identified that reported the use of UBTs as second line tests, so only the accuracy and effectiveness on health outcomes of UBTs as first line tests could be assessed in this report. Expert opinion suggests that the use of UBTs as a routine second line test is inappropriate and does not represent a reasonable primary care strategy for use of the test. Current guidelines only recommend the use of UBTs following serology in particular, uncommon circumstances.

Safety

The potential risk for patients undergoing C-UBTs for the purposes of diagnosing *H. pylori* infection are minimal due to the non-invasive nature of the procedure.

Reports in the literature outlining potential risks associated with the procedure are lacking, despite numerous studies outlining the relative effectiveness of the breath tests. Data from four case series indicated that the procedure was well tolerated by patients and that systemic, gastrointestinal and allergic-type events are extremely rare. To date, there have been no reported adverse events resulting from use of the ^{13}C test. For the ^{14}C test, there is an exposure to a very low trace of radioactivity.

Effectiveness

Studies were identified that reported the diagnostic accuracy and effectiveness (including use of the test in management of patient health outcomes), as a first line test. No studies were identified that reported the use of the UBT as a second line test. As noted, the use of UBTs as second line tests is inappropriate in routine use and is confined to special circumstances, according to expert opinion and current guidelines.

Diagnostic accuracy – use of UBTs as first line tests

Twelve cross-sectional studies reporting the diagnostic characteristics of UBTs against the reference of endoscopy and testing of biopsy samples as a first line diagnostic test were included for critical appraisal. The studies varied considerably in the breath test regimens, including delivery of the labelled urea, the number of breath samples and time after ingestion of labelled urea that they were taken and the cut-off values of CO_2 to distinguish between participants with and without *H. pylori* infection. These differences precluded pooling results of individual studies via meta-analysis.

In general, studies met most of the validity (quality) criteria used to measure the susceptibility of the results to bias. Across studies, sensitivity ranged from 90 to 100 per cent, specificity from 86 to 100 per cent, and positive and negative likelihood ratios from 6.8 to 66.7 and 0.0 to 0.1, respectively. The median sensitivity and specificity were 96 and 98 per cent, respectively. These diagnostic characteristics indicated that UBTs are the most accurate non-invasive tests for diagnosing both the presence and absence of *H. pylori* infection in the settings reported.

Patient outcomes following testing – use of UBTs as first line tests

Included for critical appraisal were four prospective, randomised controlled trials (RCTs) comparing health outcomes of participants undergoing UBTs as a first line diagnostic test for *H. pylori* infection and subsequent management in dyspeptic patients, with those of patients receiving endoscopy and subsequent management or empirical treatment.

Empirical treatment refers to treatment of dyspeptic symptoms using an antisecretory drug in the absence of confirming *H. pylori* infection. Only patients not responding to empirical treatment continue to confirmatory diagnosis of *H. pylori* infection using endoscopy, serology or UBT. The primary outcome for all of the included studies was improvement or resolution of dyspepsia symptoms, measured at six or 12 months of follow-up.

None of the studies met all of the validity criteria used to assess the methodological quality of studies, suggesting that non-appraisable bias may have affected the results. For example, although it is difficult to blind participants and investigators to treatment allocation, lack of blinding for outcome assessors in the majority of the studies may have led to bias in the measurement of subjective outcomes, and failure to describe the method of randomisation or concealment of allocation may have led to exaggerated treatment effect. Results suggest improved outcomes for people undergoing the UBT followed by management compared to empirical treatment, and similar outcomes compared to endoscopy and subsequent management.

A potential risk associated with using the UBT instead of endoscopy to diagnose *H. pylori* infection in dyspeptic patients is the possibility of missing upper gastrointestinal malignancy. This type of *H. pylori*-based management strategy is not recommended for patients displaying alarm symptoms and does not obviate the need for individually tailored clinical decisions. Thus, a breath test based test-and-treat strategy forms part of the available management pathways for dyspeptic patients. These RCTs were not designed to detect a difference in the incidence of upper gastrointestinal malignancy in those allocated to UBT followed by management compared to other management strategies, nor did our literature search identify any such trials.

Cost-effectiveness

The costs and effects of a set of diagnostic and treatment strategies for uncomplicated dyspepsia with and without UBT were calculated in a decision-analytic model. The model compared four alternative management strategies for patients presenting with uncomplicated dyspepsia from a health system perspective:

1. Use of endoscopy to identify the underlying condition, test for the presence of *H. pylori* and treat according to the endoscopic result (hereafter referred to as endoscopy).

2. Use of serology to detect antibodies to *H. pylori* and treat with eradication therapy if test positive (hereafter referred to as serology).

3. Use of UBT to test for the presence of *H. pylori* and treat with eradication therapy if the test is positive.

4. Empirical treatment using an antisecretory drug followed by investigation of non-responders using endoscopy, serology or UBT (hereafter referred to as antisecretory treatment).

The model captured all resources used, such as the costs of general practitioner (GP) or specialist visits, tests and treatment. The primary outcomes of interest were the total cost, total quality-adjusted life years (QALYs) and time living without dyspepsia (dyspepsia-

free time) for each strategy for a one-year period from presentation to resolution of dyspeptic symptoms and cure. Secondary outcomes of interest were:

- Time to cancer detection for each strategy
- Number of peptic ulcers and gastric cancers attributable to *H. pylori* averted in future years by UBT compared to serology.

In the longer term, strategies that failed to treat *H. pylori* increase the risk of future gastric cancer as *H. pylori* is a risk factor for gastric cancer with 30-55 per cent of cases attributable to *H. pylori* infection. The increased accuracy of UBT compared to serology was used to project the number of gastric cancer attributable to *H. pylori* averted in future years. The same approach was used to predict the number of peptic ulcers potentially averted in the future. An additional true positive diagnosis of *H. pylori* made by UBT was estimated to result in a potential 0.0074 gastric cancer and 0.25 peptic ulcers averted in the longer term. Using UBT to test 1,000 patients presenting with uncomplicated dyspepsia would prevent 0.296 future cases of gastric cancer and 10 cases of peptic ulcer disease.

Results of a cost-effectiveness analysis of UBT as a first line diagnostic test in the management of uncomplicated dyspepsia compared to serology, empirical antisecretory treatment and endoscopy suggested that, under baseline assumptions, serology and UBT were similar with respect to total cost, total QALYs and time living without dyspepsia over a one-year timeframe. The initial cost of UBT is $30.60 more than serology, but there are potential cost offsets ($20) and health gains from a more accurate test-and-treat strategy that reduces the future risk of peptic ulcer disease and gastric cancer. The results of an analysis of the financial implications to the health system of replacing 50 per cent of current usage of other strategies by UBT suggested that there may be financial cost savings of about $15 million per annum and some savings from the treatment of gastric cancer and peptic ulcer disease.

Recommendation

Carbon-labelled urea breath testing is safe. Effectiveness and cost effectiveness have been demonstrated for use as a first line procedure for the diagnosis of *Helicobacter pylori* infection.

MSAC recommended that public funding should be supported for the use of carbon-labelled urea breath testing as a first line procedure for the diagnoisis of *Helicobacter pylori* infection.

- The Minister for Health and Ageing accepted this recommendation on 8 June 2006. -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of carbon-labelled urea breath tests (UBTs) which are diagnostic tests used for the detection of active *Helicobacter pylori* (*H. pylori*) infection. *H. pylori* infection is a known cause of peptic ulcers and gastritis and is associated with gastric cancer. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer affairs and health administration.

This report summarises the assessment of current evidence for UBTs for diagnosis of *H. pylori* infection.

Background

Helicobacter pylori

The discovery of the bacterium *Helicobacter pylori* (*H. pylori*) and its association with gastritis, peptic ulcer and gastric cancer in 1984 was the work of Dr Robin Warren of the Department of Pathology, Royal Perth Hospital, Western Australia and Professor Barry Marshall of the Department of Medicine, University of Western Australia. Their work was recently recognised with the award of the Nobel Prize for Medicine in 2005.

Description of *H. pylori* bacterium

H. pylori is a spiral gram-negative bacterium that inhabits the epithelial cells of the stomach and duodenum. The organism's helical shape and its specialised motility enable it to enter the gastric mucosa where it is able to avoid the effects of gastric acidity because of its ability to break down endogenously produced urea (via the activity of its urease enzyme) to produce a layer of alkaline ammonia. A small proportion of *H. pylori* bacterium will adhere to the epithelium at the gastric surface via specific adhesion molecules while a larger proportion will swim freely in the mucus gel.

The release by *H. pylori* of bacterial products such as enzymes and cytokines in the stomach lining causes structural damage and an inflammatory response. The body's natural defences are unable to combat *H. pylori* because white and killer T cells cannot easily penetrate the stomach lining. The defence cells eventually die, spilling their superoxide radicals on the cells lining the stomach, on which *H. pylori* can feed (Helicobacter Foundation). The resultant inflammatory response results in a histological lesion and the development of active chronic gastritis (Gastroenterological Society of Australia [GESA] 2005).

H. pylori is transmitted through person-to-person transmission by faecal-oral, oral-oral, or gastro-oral routes (Bellon 2004, Crone & Gold 2004, Gold 2001). *H. pylori* is commonly acquired during childhood, however acquisition or re-infection during adulthood can also occur. Infection with one strain of *H. pylori* does not protect against subsequent co-infection with a different strain. Infection with multiple strains is quite common and occurs more frequently in developing countries (Logan & Walker 2001).

Symptoms associated with *H. pylori* infection

Infection with *H. pylori* can cause a range of gastroduodenal diseases including histological gastritis, duodenal ulcer disease, gastric ulcer disease, gastric malignancy and non-ulcer dyspepsia (Crone & Gold 2004, GESA 2005, van Duynhoven & Jonge 2001). There are limited signs within a patient's history or physical examination that may reliably lead to the identification of *H. pylori* infection as the primary cause of a patient's symptoms (Czinn 2005).

All infected people have histological gastritis, however the majority are asymptomatic. Approximately 15 per cent of individuals infected with *H. pylori* will develop peptic ulcer (duodenal or gastric) or gastric cancer (Logan & Walker 2001). Manifestation of gastroduodenal disease depends on the severity and topography of histological gastritis. The symptoms commonly associated with gastroduodenal diseases include abdominal

pain, dyspepsia or indigestion, bloating, nausea, belching and regurgitation, and a strong sense of feeling full early when eating (Pennhealth 2001, HealthScout).

Link between *H. pylori* infection and peptic ulcers

A strong link has been found between *H. pylori* infection and peptic ulcers (Windsor et al 2005). In particular, the *H. pylori* bacterium is the causative agent of about 90 per cent of duodenal ulcers and 70 per cent of gastric ulcers (GESA 2005). When treated with antibiotics, duodenal ulcers heal completely and have a low rate of recurrence (GESA 2005).

Link between *H. pylori* infection and gastric cancer

H. pylori is one of several risk factors associated with gastric cancers including gastric carcinoma and low-grade mucosa-associated lymphoid tissue (MALT) lymphomas (Windsor et al 2005). MALT lymphomas are associated with *H. pylori* infection in more than 90 per cent of cases and the lymphoma regresses when *H. pylori* infection is treated in 75 per cent of cases (GESA 2005).

There is increasing evidence that successful eradication of the *H. pylori* infection reduces the incidence of intermediate histological changes associated with gastric carcinoma. A recent review (Crowe 2005) suggested that the incidence of gastric cancer arising from *H. pylori* infection had not significantly declined worldwide, which is attributable to the ongoing high burden of infection, particularly in developing countries. In developed countries, including Australia, gastric cancer is declining in prevalence but high-risk subgroups—migrants, the elderly and people in institutions— remain within the population.

Diagnostic tests that identify *H. pylori* infection

Many invasive and non-invasive diagnostic tests are available for the detection of *H. pylori*.

Non invasive tests

Serology

H. pylori infection elicits a local mucosal and a systemic antibody response. The antibodies can be detected by enzyme-linked immunosorbent assay (ELISA) or latex agglutination tests, which are generally simple, reproducible and inexpensive and can be conducted on stored samples. The performance of serology tests varies with the antigens used in the test (Lambert & Badov 1997). Factors affecting test performance include consumption of non-steroidal anti-inflammatory drugs (NSAIDs) and underlying atrophic gastritis. Loy et al (1996) reviewed studies comparing commercial test kits and found that there was no significant difference in the accuracy among the various kits. They reported an overall sensitivity of 84 per cent and specificity of 79 per cent for serology tests.

It is recommended when using serology tests that *H. pylori* ELISA is locally validated and results sought from the provider (GESA 2005, Logan & Walker 2001). In addition, it is recommended that serology tests not be used to determine the eradication of *H. pylori* or to measure re-infection rates as antibody titres fall slowly after successful eradication (Braden et al 2000, Logan & Walker 2001).

Faecal antigen test

The faecal antigen test is no longer funded under the Medicare Benefits Schedule (MBS) in Australia. The test uses a simple sandwich ELISA to detect and monitor the presence of *H. pylori* antigens shed in the faeces. Studies have reported sensitivities and specificities of greater than 90 per cent (Logan & Walker 2001). The test takes about 90 minutes.

Breath tests

Several breath tests are based on the ability of *H. pylori* to produce urease. These include the ^{13}C-UBT and the ^{14}C-UBT. The tests are easy to perform and are reproducible (Lambert & Badov 1997, Savarino et al 1999). The diagnostic characteristics of breath tests are assessed in this report.

These tests may be used as screening tests for *H. pylori,* to assess eradication and to detect infection. Breath test results are usually negative within one month of eradication of *H. pylori*.

A further description of these tests can be found in 'The Procedure' section of this report.

Invasive tests

H. pylori can be detected at endoscopies by histology, culture or urease tests. Each modality has inherent advantages and disadvantages. It is recommended for diagnosis that multiple biopsies be taken from both the antrum and corpus for histology and for one additional method to confirm the infection (GESA 2005, Logan & Walker 2001).

Histology

The sensitivity and specificity using histology are high, ranging between 96 and 98 per cent (Logan & Walker 2001). The advantages of using histology include provision of historical record (medical and histological history), the ability to examine sections at any time and the additional ability to assess gastritis, atrophy, or intestinal metaplasia. However, the use of histology is substantially more expensive than many of the other diagnostic tests for *H. pylori*.

Factors influencing the detection of *H. pylori* include both the type of stain used and the relatively uneven distribution of the organism within the gastric mucosa. Haematoxylin and eosin, modified Giemsa, Warthin Starry silver or acridine orange stain are used (Lambert & Badov 1997, GESA 2005, Logan & Walker 2001).

Culture

Cultures taken from gastric mucosal biopsies are often reported as the theoretical gold standard for identifying *H. pylori* (Destura et al 2004, Lambert & Badov 1997). Sensitivity and specificity of cultures range from 90 to 100 per cent (Lambert & Badov 1997), however isolation of the organism by culture can be highly variable. Failure to detect the organism may be due to sampling error, inappropriate transport or culture media, insufficient incubation period or to the patient having recently taken antimicrobial therapy. Disadvantages of culture include the expertise required for culture of *H. pylori* and the relatively high cost and slow turnaround time compared to other diagnostic tests.

Rapid urease test

Rapid urease test solutions contain urea, which is converted to ammonia in the presence of *H. pylori* urease. The presence of ammonia elevates the pH of the medium to change the colour of a pH-sensitive indicator and give a positive result. The test shows a positive result within an hour or two in approximately 70 per cent of infected patients, however sometimes tests may require up to 24 hours for a positive result (Lambert & Badov 1997). Sensitivity and specificity of the rapid urease test have been reported to range from 90 to 95 per cent (Lambert & Badov 1997).

Treatment for *H. pylori*

Recommended first line treatment for *H. pylori* infection comprises a proton pump inhibitor (PPI) and two antibiotics to eradicate the organism. Amoxycillin and clarithromycin are used (although metronidazole may be substituted with only modest loss of efficacy where there is penicillin allergy). There are alternative combinations for re-treatment after first line treatment failure that are difficult to access in primary care, so this problem is usually dealt with at the specialist level. Both triple and quadruple therapies have been found to achieve eradication rates of more than 85 per cent in trials, although results are lower in a primary care setting (Fischbach et al 2004, GESA 2005). Eradication of *H. pylori* is associated with reductions in the incidence and severity of gastritis, ulcers and gastric cancer. The effectiveness of the various treatment modes is most dependent on the prevalence of pre-treatment drug resistance and compliance and less related to treatment duration, exposure to sources of re-infection and geographical location (GESA 2005).

Common adverse effects to these treatments include taste disturbance, nausea and mild diarrhoea. Most adverse events have been found to be mild and do not normally lead to discontinuation of therapies. Adherence rates to the various therapies have been found to range from 85 to 100 per cent (Fischbach et al 2004).

In recent years, consensus worldwide has recommended the use of triple therapies (Fischbach et al 2004, GESA 2005, Katelaris et al 2000, Malfertheiner et al 2002). However, the efficacy of these triple therapies is substantially reduced in the presence of clarithromycin and/or metronidazole-resistant *H. pylori* infections (Fischbach et al 2002, Fischbach et al 2004).

Guidelines for the management of *H. pylori*

Although consensus exists for treatment for *H. pylori* infection, the literature indicates a degree of uncertainty about the best strategy for initial diagnosis and management of dyspepsia. For those presenting in primary care with uninvestigated dyspepsia, the options include non-invasive testing (eg with UBTs or other tests) followed by eradication therapy for those with positive test results (test-and-treat strategy), non-invasive testing followed up with endoscopy for positive test results (test and endoscope), selective endoscopy based on clinical presentation at the GP's discretion, or empirical eradication treatment.

The European Helicobacter Pylori Study Group's Maastricht 2-2000 Consensus report (Malfertheiner et al 2002) recommended a test-and-treat approach using the UBT or stool antigen test to confirm the presence of *H. pylori* in patients with the following characteristics:

- Adults under 45 years of age
- Presentation in primary care with dyspepsia
- No use of NSAIDs
- Presentation without predominantly gastro-oesophageal reflux disease.

The health technology assessment and systematic review produced by the National Health Service (NHS) in the United Kingdom (Delaney et al 2000) reported that for uninvestigated dyspepsia in primary care:

- initial endoscopy was not significantly more effective than empirical therapy
- non-invasive *H. pylori* testing followed by confirmation of positive test results with endoscopy was no more effective or cost-effective than selective endoscopy referral by the GP
- non-invasive *H. pylori* test-and-treat strategy was as effective as early endoscopy and resulted in reduced costs associated with referral for investigation, but was of uncertain cost-effectiveness compared with empirical acid suppression treatment
- modelling indicated that test-and-treat strategies were more cost-effective than strategies involving endoscopy or empirical therapy.

A decision-analysis based in the USA primary care setting also recommended non-invasive testing followed by eradication therapy over initial endoscopy for patients presenting with uninvestigated dyspepsia who tested positive for *H. pylori* (Ofman et al 1997).

Thus, there appears to be some consensus and data to support the recommendation for non-invasive testing over initial endoscopy for uninvestigated dyspepsia in some settings, but the applicability of these data to the Australian setting is unknown. Furthermore, there is uncertainty regarding the relative benefits of non-invasive testing compared to empirical eradication therapy, whether the effectiveness and cost-effectiveness of the test-and-treat strategy vary if different tests are employed and whether the effectiveness and cost-effectiveness of different strategies differs in certain subgroups (eg, in younger compared to older patients or in those with different symptoms).

The procedure

Description of the UBTs

The C-UBT was first described by Graham et al in 1987. It relies on the biochemical production by the *H. pylori* organism of relatively high concentrations of urease, an enzyme that hydrolyses urea to yield ammonium and bicarbonate. The bicarbonate generated in the gastric mucosa enters the bloodstream and is rapidly excreted by the lungs as carbon dioxide.

To identify *H. pylori* using C-UBT, the patient is orally administered labelled urea which leads to the exhalation of isotopically labelled CO_2 if *H. pylori* is present (Gisbert &

Pajares 2004). This then enters the blood stream and is excreted by the lungs. The analysis of the CO_2 excreted in the patients breath then enables the presence of *H. pylori* to be detected. The urea can be labelled with either stable or unstable isotopes of carbon (^{13}C or ^{14}C, respectively).

To date, there is little consensus as to the technical requirements of ^{13}C and ^{14}C UBTs. Most studies differ in the dose of the substrate, composition of the standard test meal, time of breath sampling, status regarding fasting or feeding, postural settings and cut-off points (Pathak et al 2005, Perri 2000). A unique cut-off level is not possible because it has to adapt to different factors.

A review of ^{13}C-UBTs conducted by Gisbert & Pajares (2004) concluded that although a standardisation of protocol does not yet exist the following recommendations could be made:

(1) UBT can be carried out by different types of equipment

(2) It is sensible to perform under fasting conditions

(3) Citric acid should be used as test meal

(4) Use of 50-75mg of urea is sufficient to achieve high accuracy

(5) It is recommended to obtain basal breath samples

(6) Use of two breath samples spaced 10-30 minutes after urea ingestion is optimal; and

(7) A unique cut-off point is not possible because it has to be adapted to different figures, although because positive and negative urea breath tests cluster outside of the ranges of two and five percent, a varying cut-off value within this range is expected to have little effect on clinical accuracy of tests.

Of these recommendations, (1), (3), (4), (5), (6) and (7) do not apply to the ^{14}C-UBT.

To optimise the performance of the ^{13}C-UBT and ^{14}C-UBT, it is recommended patients discontinue all antibiotic therapy, bismuth and PPIs for four weeks and all acid suppressant medication for up to 14 days before testing (Bellon 2004).

The ^{14}Carbon-UBT

The patient is orally administered a ^{14}C-urea capsule with a drink of water. Ten minutes later, the patient provides a breath sample, usually by blowing up a small balloon or blowing bubbles in a small bottle of collection liquid. The results are then processed using a liquid scintillation counter.

The ^{13}Carbon-UBT

The ^{13}C-UBT differs from the ^{14}C-UBT in that a baseline breath sample is collected by the patient blowing into a tube. The patient may then be required to ingest orange juice before the test to slow gastric emptying. The patient then ingests a solution of ^{13}C-urea in water before collection of breath samples that are analysed using a mass spectrometer.

Comparison of ^{13}C-UBT to ^{14}C-UBT

Both the ^{13}C- and ^{14}C-UBTs are registered with the Therapeutic Goods Administration (TGA) for use in Australia. Whether use of the different tests results in different health outcomes is not the focus of this Assessment Report. The most notable differences between the two tests are:

- the radioactive status of the isotope (this is may be of relevance to children, pregnant women and women of child-bearing age; however, because the isotope dose is so miniscule, the ^{14}C-UBT has no restrictions imposed on its usage in the USA (Food and Drug Administration [FDA] Transcripts) and for the same reason, it is exempt from the requirement of a radioactive license (US Federal Register)
- the cost of the procedure to the provider
- the application in different population groups as some patients may prefer to choose which test to undertake. The ^{14}C-UBT has been less well studied than the ^{13}C-UBT for use in assessing treatment outcome.

For the user, the ^{14}C-UBT is simpler to administer because:

- baseline breath samples and duplicates are not required
- the test takes only 10 minutes to perform as opposed to the 30 minutes required for the ^{13}C-UBT.

False positive results may occasionally occur when urease-producing bacteria other than the *H. pylori* colonise the oral cavity or the stomach (Perri 2000). Reasons for false negative results include low intragastric load, fast gastric emptying, previous gastric surgery, failure to meet drug cessation recommendations and concomitant administration of urease-inhibiting drugs (Bellon 2004, Pathak et al 2005, Perri 2000).

Intended purpose

Carbon-labelled UBTs detect the presence of *H. pylori* infection in the human stomach.

This assessment examines the use of UBTs in patients who test positive to a serological test (use as a second line diagnostic test) and the use of the tests as a first line diagnostic test in certain patient groups.

Clinical need/burden of disease

Worldwide, *H. pylori* infection affects approximately 50 per cent of the world's population. Prevalence rates among countries range from 20 to more than 80 per cent (Czinn 2005). Low socio-economic conditions, ethnicity, birth order, crowded living conditions and exposure to unclean water and certain animals markedly increase the risk of *H. pylori* infection (GESA 2005, Go 2002).

The prevalence of *H. pylori* increases with age. More than 55 per cent of adults aged over 46 years are infected, while less than two per cent of children are infected (Moore 1994). The pattern of *H. pylori* acquisition with age is identical to that of gastritis (Table 1).

Table 1 Prevalence of *H. pylori* and chronic gastritis with age

Age range (years)	Positive for *H. pylori* antibodies (%)	With chronic gastritis (%)
0–9	<2	<10
18–25	18	10–20
26–35	30	20–38
36–45	46	36–40
46–55	59	40–58
>55	55	60–65

Source: Moore 1994

It is estimated that *H. pylori* is present in up to 54 per cent of the Australian population (Bellon 2004). As with worldwide prevalence rates, Australia's prevalence increases with age. About 40 per cent of adults over 40 years of age are infected, while less than 10 per cent of children are infected in Australia (GESA 2005). In addition, it has been found that males have a sightly higher prevalence of the infection than females and that infection appears to be more common in Indigenous populations (Windsor et al 2005).

Existing procedures and comparators

Several invasive and non-invasive diagnostic tests are available in addition to UBTs for detecting *H. pylori*. Non-invasive tests include serology and faecal antigen tests. However, the faecal antigen test is no longer funded under the Medicare Benefits Schedule (MBS) in Australia. Serology testing is covered under MBS Item number 69384 for one antibody test (more than one antibody test can be requested and is covered by item numbers 69387 for two tests, 69390 for three tests, 69393 for four tests, 69396 for five tests and 69399 for six tests). Expert opinion suggests that due to lack of accuracy, serology is rarely the first line test used in Australia to detect *H. pylori* infection in individuals with dyspepsia.

Gastrointestinal endoscopic procedures used to collect biopsy specimens are reimbursed under MBS Item number 30473 if the endoscopy procedure is not associated with:

- endoscopic sclerosing injection or banding of oesophageal or gastric varices
- polypectomy, removal of foreign body, diathermy, heater probe or laser coagulation, or sclerosing injection of bleeding upper gastrointestinal lesions.

Tests performed following endoscopy and biopsy to confirm *H. pylori* infection include rapid urease tests, histology and culture. Any of these or any combination is used as the reference standard to provide confirmatory proof of *H. pylori* infection. Rapid urease tests are currently not funded under the MBS. Histology and culture of biopsy samples are funded under several MBS Item numbers that also cover indications other than dyspepsia. Thus, the number of services provided to investigate dyspepsia cannot be obtained from these items numbers.

The number of services provided by Medicare for tests covered by Item 30473, for the financial year 2004-05 is summarised in Table 2. There are additional MBS Item numbers used for this procedure. They are not included here due to the lack of specific data about the individuals undergoing those tests.

Table 2 Medicare item 30473 processed from July 2004 to June 2005

Medicare item	Number of services for:								Total services
	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
30473	74,531	64,521	49,813	15,426	16,539	3,958	2,572	728	228,088

Source: http://www.hic.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

It is anticipated that the majority of service provision of UBTs will occur via pathology laboratories and that hospital departments will play a smaller role in service provision.

Marketing status of the technology

[^{14}C]-Urea: contained in PYtest® capsule which bears the Australian Registry of Therapeutic Goods (ARTG) registration number of AUST R 67146 & AUST L 67147.

UBIT urea [^{13}C]: 100 mg granules sachet ARTG number is AUST R 71756. The Helibactertest INFAI [13C] 75 mg powder for oral solution ARTG number is AUST R 80122.

Current reimbursement arrangement

Carbon-labelled UBTs are currently funded under MBS item 12533 for:

- the confirmation of *H. pylori* infection where:
  - suitable biopsy material cannot be obtained at endoscopy in patients with peptic ulcer disease, or where the diagnosis of peptic ulcer is made on barium meal; or
  - endoscopy is not indicated (in patients with past history of duodenal ulcer, gastric ulcer or gastric neoplasia); or
- the monitoring of the success of eradication of *H. pylori* in patients with peptic ulcer disease

where any request for the test by another medical practitioner who collects the breath sample specifically identifies in writing one or more of the clinical indications for the test.

The use of Item 12533 from July 2000 until June 2005 is presented in Table 3.

Table 3 Medicare item 12533 processed from July 2000 to June 2005

Medicare item	Financial year	Number of services for:								Total services
		NSW	VIC	QLD	SA	WA	TAS	ACT	NT	
12533	2000/01	42,290	15,486	13,441	3,845	5,983	384	1,128	296	82,853
	2001/02	42,635	11,417	12,314	3,547	4,852	287	1,214	218	76,484
	2002/03	37,499	13,495	10,217	2,993	5,163	164	1,109	191	70,831
	2003/04	33,675	10,307	10,148	3,155	4,875	124	1,002	181	63,467
	2004/05	34,610	10,712	10,290	3,352	4,942	186	937	165	65,194
	Total	190,709	61,417	56,410	16,892	25,815	1,145	5,390	1,051	358,829

Source: http://www.hic.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

Approach to assessment

Research questions

The research questions are outlined in the table below. In this assessment, dyspepsia is defined to include both epigastric pain and heartburn, and 'uncomplicated dyspepsia' is used to represent dyspeptic symptoms without alarm features in patients without a history of duodenal ulcer, gastric ulcer or gastric neoplasia.

Population	Prior tests	Index test	Comparator	Outcomes
Symptoms of dyspepsia without a history of duodenal ulcer, gastric ulcer, gastric neoplasia, and without alarm features, with no prior serology test (first line diagnosis)	None	UBTs	Serology Endoscopy Empirical therapy	Diagnostic accuracy Change in patient management Change in patient health outcomes
Symptoms of dyspepsia without a history of duodenal ulcer, gastric ulcer, gastric neoplasia, and without alarm features, and with a positive serology test (second line diagnosis)	Serology	UBTs	Endoscopy Empirical therapy	

Research questions

In patients with symptoms of dyspepsia without a history of duodenal ulcer, gastric ulcer, gastric neoplasia, and without alarm features (including weight loss, vomiting, dysphagia, bleeding, anorexia, or an abdominal mass), and

- not tested with serology ie, first line diagnosis; or
- with a positive serology test ie, second line diagnosis;
  - what is the diagnostic accuracy of carbon-labelled UBTs in the confirmation of active *H. pylori* infection; and
  - what is the safety, effectiveness in terms of patient management and patient health outcomes, and cost-effectiveness of carbon-labelled UBTs?

Subgroups of interest:

- aged more than 50 years
- aged less than 50 years

A decision tree depicting the possible diagnostic pathways with the proposed role of the UBTs as a first line diagnostic test is given in Figure 1.

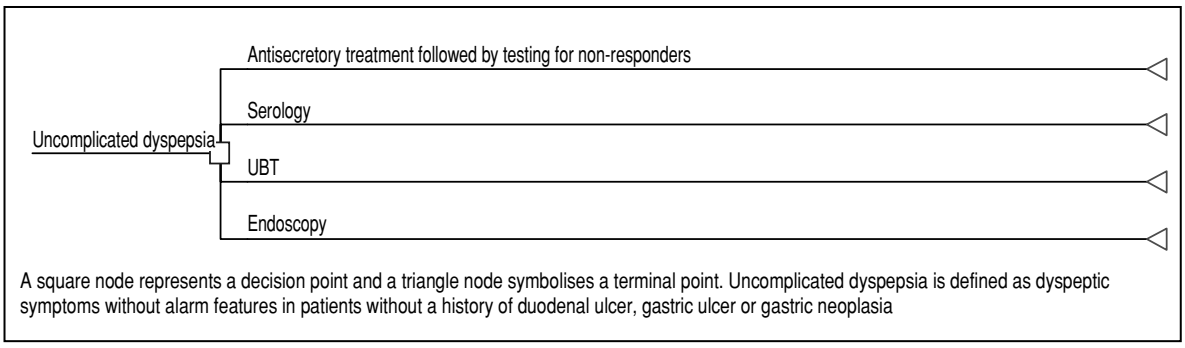


Figure 1 Possible diagnostic pathways in patients with uncomplicated dyspepsia

Review of literature

Electronic resources

The following electronic databases (Table 4) were searched to identify relevant literature.

Table 4 Electronic databases searched

Databases	Period covered in the literature
Australasian Medical Index	1968 -May 2005
Biological Abstracts	1980 -May 2005
CINAHL	1982 -May 2005
Cochrane Library	2005, Issue 2 2005
EMBASE	1968 -May 2005
Medline	1966 -May 2005
PreMedline, Medline in-process & other non-indexed citations	Update to 26 May 2005

Health technology assessment and clinical trial websites

Relevant health technology assessment and clinical trial websites were searched to identify relevant reviews or trials (Appendix D).

Search terms

Search strategies were developed to cover all of the aspects needed for this topic. The strategies focused on the three areas of safety, effectiveness and cost-effectiveness. In order to identify all of the relevant information published in journal articles, the search was performed as a number of separate strategies.

All of the terms that can be used to describe UBTs and the appropriate population for which this test would be used were identified. This set of words formed the core of searching. For safety, the terms for safety, complications and adverse events were added to the core terms. For effectiveness, a diagnostic filter was used with the core terms to identify studies of diagnostic accuracy of UBTs and an RCT and systematic review filter was included with the core terms for patient management and health outcomes. For cost-effectiveness, the terms for economics, costs, pricing and quality-adjusted life years (QALYs) were added to the core terms (Appendix C).

Selection criteria

Effectiveness - diagnostic accuracy

The following *a priori* criteria were used to determine eligibility of relevant studies:

Part 1: Diagnostic Accuracy: What are the diagnostic characteristics of C-UBT for confirmation of active *H. pylori* infection?		
Characteristics	**Inclusion**	**Exclusion**
Population	Participants with the following characteristics are included: symptoms of dyspepsia without a history of duodenal ulcer, gastric ulcer, gastric neoplasia, and without alarm features • not tested with serology ie, first line diagnosis or • with a positive serology test ie, second line diagnosis	Participants with alarm features including weight loss, vomiting, dysphagia, bleeding, anorexia or an abdominal mass
Test	C-UBTs	
Comparator	For first line diagnosis: serology, endoscopy, empirical therapy For second line diagnosis: endoscopy, empirical therapy	
Reference (gold standard)	Demonstration of the presence (or absence) of *H. pylori* following endoscopy	
Outcomes	Diagnostic characteristics of C-UBT should be available to allow construction of the diagnostic two by two table with its four cells: true positive, true negative, false positive and false negative	Studies from which diagnostic characteristics cannot be calculated
Study design	Cross-sectional studies that report the diagnostic characteristics in an independent blind comparison of C-UBT and the reference standard in a consecutively selected group of patients. If no such studies existed, studies that report diagnostic characteristics in an independent blind or objective comparison in non-consecutively selected patients or studies that report diagnostic characteristics in which the reference standard was not applied to all patients were to be included. If none of the above existed, studies that report diagnostic accuracy without a reference standard in a consecutively selected case series may have been considered for inclusion	Narrative reviews, editorials, letters, articles identified as preliminary reports when results are published in later versions, articles in abstract form only, case reports and collections of case reports in which results are only presented by individual study patient and not summarised
Publication	English-language articles, or high-level studies in any language if none existed in English	

Effectiveness - patient health outcomes data

Detection of the pathology of the diagnostic procedure under consideration is not the only indicator of the usefulness of diagnostic tests. Unless application of the procedure improves patient management options, and ultimately patient health outcomes, its usefulness is considered limited (Sackett et al 2000).

Part 2: Patient health outcomes: What is the effectiveness of C-UBT for confirmation of active *H. pylori* infection on patient health outcomes?		
Characteristics	**Inclusion**	**Exclusion**
Population	Participants with the following characteristics are included: symptoms of dyspepsia without a history of duodenal ulcer, gastric ulcer, gastric neoplasia, and without alarm features • not tested with serology ie, first line diagnosis • with a positive serology test ie, second line diagnosis	Participants with alarm features including weight loss, vomiting, dysphagia, bleeding, anorexia, or an abdominal mass
Test/intervention	C-UBT followed by treatment	
Comparators	Group i): Serology plus treatment, or endoscopy plus treatment or empirical treatment Group ii): Endoscopy plus treatment, or empirical treatment	
Outcomes	Patient health outcomes following application of the test: • eradication of *H. pylori* infection • eradication of symptoms of dyspepsia • complications of testing and treating • reduction in endoscopy • reduction in use of antisecretory empirical therapy • other long-term outcomes, eg quality of life, incidence of gastric cancer	
Study design	Effectiveness: Health technology assessments, systematic reviews, meta-analyses and RCTs were sought initially. If these were unavailable, other controlled trials, comparative studies and cohort studies may have been assessed. In the event that these too were unavailable, case series of consecutively selected patients may have been considered for inclusion. Safety: Studies of any design reporting adverse events associated with the use of the test were considered for inclusion	Narrative reviews, editorials, letters, articles identified as preliminary reports when results are published in later versions, articles in abstract form only, case reports and collections of case reports in which results are only presented by individual study patient and not summarised
Publication	English-language articles, or high-level studies in any language if none existed in English	

Methods

Safety

Studies identified after the application of the safety filter to the search strategy were retrieved and examined. Adverse event data relating to C-UBTs or relating to application of the tests and ensuing treatment were extracted and tabulated. Studies of any design (case reports, case series or any comparative studies) were included in the review of safety, as information indicating whether or not a procedure is safe is as important as how safe it is compared to alternatives.

Effectiveness

Critical appraisal of included studies

Two factors are important in determining the effectiveness of a diagnostic test:

- accuracy of the test, ie the diagnostic characteristics
- the effectiveness of undergoing the test on patient management options and patient health outcomes.

Part 1 Accuracy of the test

The most rigorous study design for assessing the validity of diagnostic tests is considered to be a prospectively-designed cross-sectional study that independently compares the diagnostic characteristics of the test with an appropriate reference standard in consecutively-selected patients from a relevant clinical population (Jaeschke et al 1994a, Knottnerus & van Weel 2002, Sackett et al 2000, The Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests 1996). Based on these criteria, the validity of the methodology of included articles was assessed against the following checklist:

- appropriate spectrum of consecutive participants: study included patients that the test would normally be used on in clinical practice, non-consecutive selection, eg, the test is compared in patients already known to have the disorder with a group of normal non-diseased patients (case-referrent) results in overestimation of accuracy
- prospective selection of participants: eligible participants were selected prior to application of the index test and reference standard (to avoid selection bias)
- appropriate reference standard used: the reference standard is likely to classify the target condition correctly
- test is compared with a reference standard in all (or a random sample of) study participants. Participants in the study should have undergone both the diagnostic test in question and a reference test that would provide confirmatory proof that they do, or do not, have the target disorder
- masked assessment of study and reference tests results: the study test and the reference test should be interpreted separately by persons unaware of the results of the other (avoidance of review bias)
- all study participants tested with both study and reference tests: the reference test should be applied regardless of a positive or negative result from the study test (avoidance of differential verification bias), and all or a random sample should receive the reference (to avoid partial verification bias)
- study test measured independently of clinical information: the person interpreting the test should be masked to clinical history and results of any other tests performed previously, with the only clinical information that which would be available in clinical practice (to avoid information bias)

- reference test measured prior to any interventions and time period between test and reference short enough to ensure that the condition did not change (to avoid detection bias).

Diagnostic outcome data

Relationships between a diagnostic test and actual presence of disease are usually summarised in two-by-two tables (Table 5). Individuals who test positive for the disease in both the index or study test under investigation and the reference test are represented in cell "a" and are called true positives (TP). Individuals without the disease who test negative in both tests (the "d" cell) are called true negatives (TN). A diagnostic test may also produce discordance between the index test result and the true disease status of the subject. For example, when the index test is positive for individuals without the disease, a false positive (FP) result is assumed (cell "b"). Conversely, when the test is negative in diseased individuals, a false negative (FN) result arises (cell "c"). Additional information, such as sensitivity and specificity, positive and negative predictive values and positive and negative likelihood ratios of a given test can also be calculated from the above rates.

Table 5 The generic relationship between results of the diagnostic test and disease status

Study test results	True disease status (Reference standard)		Total
	Diseased	Not diseased	
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Abbreviations: a=number of diseased individuals detected by the test; b=number of individuals without disease detected by the test; c=number of diseased individuals not detected by the test; d=number of individuals without disease not detected by the test; a+b=total number of individuals testing positive; c+d=total number of individuals testing negative; a+c=total number of diseased individuals; b+d=total number of individuals without disease; a+b+c+d=total number of individuals studied

Sensitivity and specificity

Sensitivity is a measure of the probability of correctly diagnosing someone with the disease, or the probability that any given case will be identified by the index test.

$$Sensitivity = \frac{a}{a+c} = \frac{TP}{TP+FN}$$

Conversely, specificity is the probability of correctly identifying a person without disease, or the proportion of individuals without disease who test negative.

$$Specificity = \frac{d}{b+d} = \frac{TN}{TN+FP}$$

The complement of specificity is called the false positive rate (FPR), and is equal to 1 minus specificity.

Likelihood ratios

Likelihood ratios (LRs) indicate by how much a given diagnostic test result will raise or lower the pre-test probability of the target disorder. The likelihood ratio for a positive test result (LR +) expresses the odds that a given finding would occur in a patient with,

as opposed to without, the target condition, and is related to sensitivity and the false positive rate according to the formula:

$$LR + = \frac{Sen}{FPR}$$

The likelihood ratio for a negative test result (LR–) expresses the odds that a given finding (eg, baseline resistance) would not occur in a patient without, as opposed to with, the target condition (treatment failure)

$$LR - = \frac{1 - Sen}{Spe}$$

A general guide to interpreting likelihood ratios is as follows (Jaeschke et al 1994b):

- Large positive likelihood ratios of 10 or more, and small negative likelihood ratios of <0.1 indicate large, and often conclusive changes in disease likelihood, ie large changes from pre- to post-test probability of having the condition.
- Positive likelihood ratios of 5–10 and negative likelihood ratios of 0.1–0.2 indicate moderate changes in pre- to post-test probability.
- Positive likelihood ratios of 2–5 and negative likelihood ratios of 0.5–0.2 indicate small (but sometimes clinically important) changes in probability.
- If LR+ <2 and LR– >0.5, then there is little or no likelihood that the presence of disease will be diagnosed as a result of the test.

Part 2 Patient-relevant health outcomes

The most rigorous study design for assessing the validity of diagnostic tests on patient health outcomes is considered to be an RCT (Guyatt et al 1993, Sackett et al 2000), comparing outcomes in a group of patients who have undergone the diagnostic test of interest with the outcomes in a group of patients who have not.

Evidence presented in the included studies assessing patient health outcomes following testing (and treatment) will be assessed and classified using the dimensions of evidence defined by the NHMRC (NHMRC 2000).

These dimensions (Table 6) consider important aspects of the evidence supporting a particular intervention and include the three domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 6 Evidence dimensions

Dimensions	Definition
Strength of the evidence	
- Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
- Quality	The methods used by investigators to minimise bias within a study design
- Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 5

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The level of evidence is a measure of the susceptibility to bias of various study designs. Level I evidence implies a study design that is least susceptible to bias, while Level IV evidence implies a study design that is most susceptible to bias. The designations of the levels of evidence are shown in Table 7.

Table 7 Designations of levels of evidence

Levels of evidence[a]	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

[a] Modified from NHMRC (2000)

In addition to recognising the susceptibility to bias inherent in particular study designs by assigning a level of evidence, studies meeting inclusion criteria are critically appraised to assess their internal validity (or bias), to give an indication of the quality of evidence. Methods of critical appraisal are determined by the study design.

Critical appraisal of RCTs

Two reviewers independently appraised trials for methodological quality using an adaptation of validity criteria developed for RCTs (Sackett et al 2000, Schulz et al 1995). The following validity criteria were used:

- adequate method of randomisation to ensure that groups are balanced at baseline for prognostic factors (such as disease severity or age)
- concealment of allocation from study investigators to prevent foreknowledge of group assignment

- blinding of study investigators, trial participants and outcome assessors
- inclusion of all randomised patients in the analysis of results, or data are available to permit intention-to-treat analysis
- adequate (>80%) follow-up of study participants
- study participants treated equally during the trial, apart from the intervention.

Note that, although a pre-hoc judgement assumes that it is difficult to blind participants and investigators to treatment allocation in this case, blinding of outcome assessor was still included as a validity criterion.

Data extraction

Data were extracted using standardised instruments created for the assessment. Two reviewers examined each article and any discrepancies in evaluation were discussed and resolved through consensus.

Expert advice

An Advisory Panel with expertise in UBTs, pathology and gastrointestinal disorders was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for the Advisory Panel, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Search results

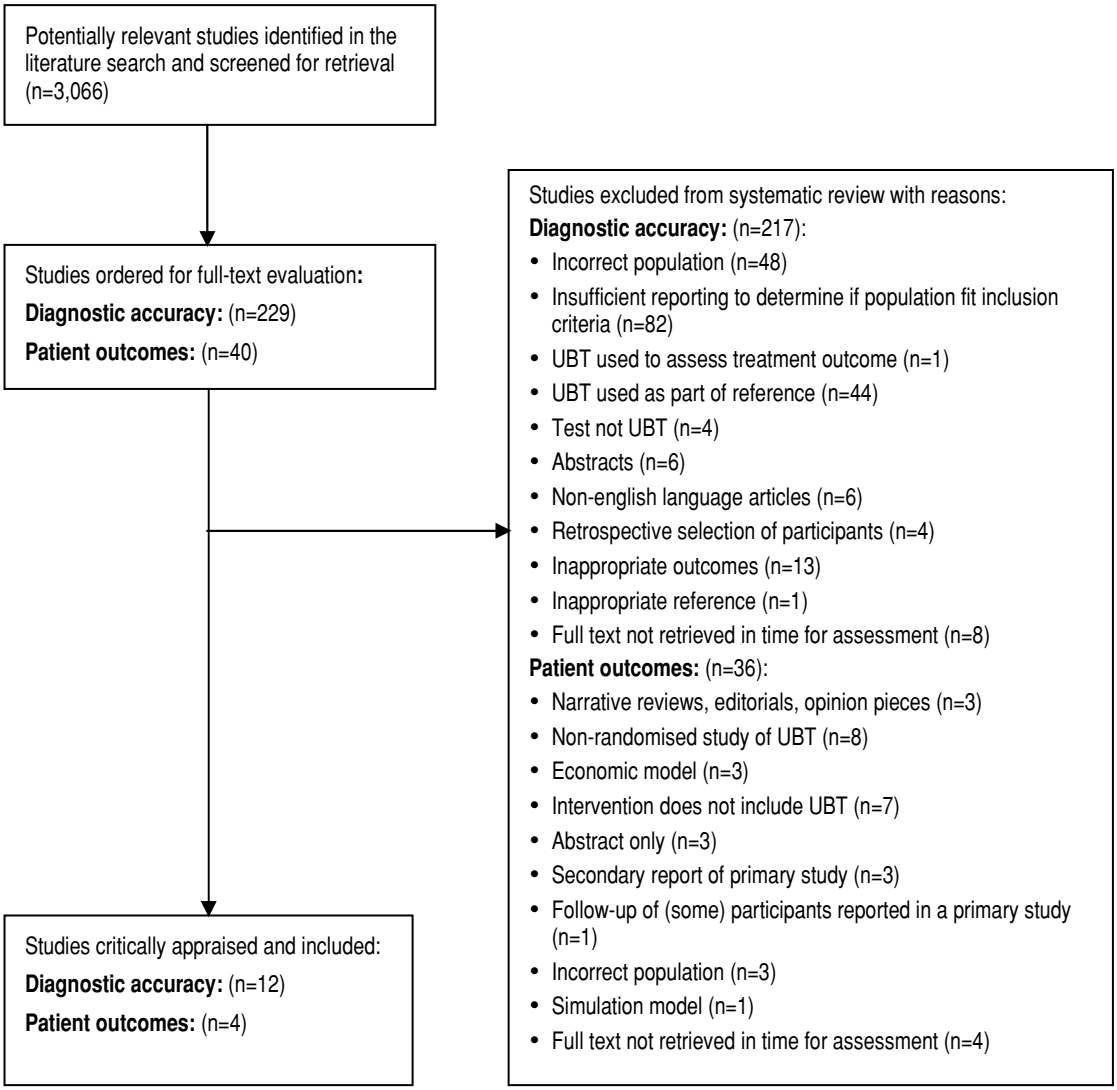


Figure 2 Flowchart of the process used to identify and select studies for the review

All included studies examined use of UBTs as a first line test. No studies were identified that report the use of UBTs as a second line test (due to this representing inappropriate use of the test according to expert opinion and current guidelines).

Is it safe?

The potential risk for patients undergoing C-UBTs for the purposes of diagnosing *H. pylori* infection are minimal due to the non-invasive nature of the procedure. Some Australian physicians avoid the use of the UBT with the ^{14}C isotope for pregnant women and children. However, the radiation dose in the TGA-approved ^{14}C-UBT is less than the

daily background dose received by the population at large. In Australia, some element of consumer choice in undertaking this test is considered preferable. However, in the USA, there is no restriction placed on the ^{14}C-UBT (Trade Mark PYtest®) with regard to gender, age or pregnancy status. Independent dosimetry studies conducted in Sweden (Leide-Svegborn et al 1999) and the Royal Adelaide Hospital Department of Nuclear Medicine (Bellon 2006, personal communication [31 January 2006]) have total agreement with the FDA's ruling.

Reports in the literature outlining potential risks associated with the procedure are lacking, despite numerous studies outlining the relative effectiveness of the breath tests. Where data are available on adverse events, the study design is usually case series. Findings from case series indicate that the procedure is well tolerated by patients and that systemic, gastrointestinal and allergic-type events are extremely rare (Table 8). There have been no adverse events reported following the use of the ^{13}C-UBT and/or the ^{14}C-UBT.

Table 8 Safety of the tests

Study	Study design	Sample size	Length of follow-up	Adverse event	Patient outcome
Bielanski & Konturek (1996)	Case series	N = 114	10, 15, 20, 30 min	No adverse effects or complications reported	Not applicable
Bielanski et al (1996)	Case series	N = 159	5-min intervals for 30 min followed by 10 15, 20 min, 7 days	No adverse effects or complications reported	Not applicable
D'Elios et al (2000)	Case series	N = 492	30, 60 min, 1 day, 7 days	No systemic or severe gastrointestinal events No allergic-type reactions or symptoms reported One patient reported moderate abdominal pain 20 mins post-intervention	Not reported
Gisbert et al (2004)	Case series	N = 736	6 months	Four non-severe events reported in patients receiving *H. pylori* therapy: 2 related to clarithromycin 1 to amoxycillin 1 to clarithromycin	Not reported

Is it effective?

Part 1: Diagnostic accuracy of the test

The primary aim of this assessment report was to evaluate the diagnostic accuracy and effect on patient health outcomes of UBTs overall. It was not the focus to compare the accuracies of the ^{13}C-UBT and the ^{14}C-UBT.

UBT as a first-line test

This report systematically reviewed the diagnostic accuracy of UBT as a first line diagnostic test against the reference standard of demonstration of the presence of *H. pylori* following endoscopy. The exclusion criteria were applied strictly due to the large

number of cross-sectional studies identified that reported the diagnostic accuracy of the UBT against the reference standard.

Several studies were excluded on the basis that there was insufficient description of the population to determine if the participants met the inclusion criteria of this assessment report. Time constraints precluded correspondence with study authors to clarify this aspect. For example, papers that stated they included participants presenting for routine endoscopy without clarifying if participants who had alarm features were included in the published data were excluded from this assessment. In addition, studies that included UBT as part of the reference standard to provide confirmatory proof of the presence of *H. pylori* infection were excluded from this review. Studies that solely reported accuracy of UBTs in assessing if treatment was successful in eradicating *H. pylori* infection were also excluded. Studies that reported both pre-treatment and post-treatment accuracy of UBTs were included, but only results for the pre-treatment part of the study are included in this assessment.

Descriptive characteristics of included studies

The 12 studies critically appraised for this assessment were conducted in the USA, the UK, Taiwan, China, Hong Kong, Italy and The Netherlands (Table G1, Appendix G). Sample sizes ranged from 69 to 604 participants. Where reported, the populations were mostly adult. Three studies (Rauws et al 1989, Savarino et al 2000, Sheu et al 2000) did not report the age of participants.

Selection criteria of included studies are summarised in Table G2 (Appendix G). Studies included participants with symptoms of dyspepsia, which was generally described as upper abdominal/epigastric pain or discomfort of one month's (Peng et al 2000) to three months' (Ng et al 2002) duration. Cave et al (1999) and Sheu et al (2000) did not describe the nature or duration of symptoms. Peng et al (2000) and Rauws et al (1989) specifically included participants with non-ulcer dyspepsia. All studies excluded participants who had recently used medications such as PPIs, bismuth and H_2-antagonists and most studies explicitly excluded participants who had a history of ulcer, previous *H. pylori* infection, gastric malignancy or gastro-intestinal bleeding. Apart from bleeding, studies generally did not explicitly report exclusion of participants with other alarm features (weight loss, vomiting, dysphagia, anorexia, abdominal mass).

Table G3 (Appendix G) provides details of the UBTs and reference tests used in the studies. All studies except Gatta et al (2003a) and Rauws et al (1989) used ^{13}C-urea in the UBT. The UBT regimens, including delivery of the labelled urea, number of samples and time after ingestion of labelled urea that breath samples were taken, varied considerably across studies. The dose of ^{13}C-urea varied from 50 to 250 mg. Gatta et al (2003b) specifically tested the accuracy of low dose (50 mg) and higher dose (100 mg) ^{13}C-urea against the standard 75 mg dose.

Cut-off values of labelled-CO_2 in breath samples to distinguish between participants positive for *H. pylori* infection and those without infection varied across studies, as did the unit of measurement for the cut-off values. Several studies (Cave et al 1999, Gatta et al 2003b, Ng et al 2002, Rauws et al 1989, Savarino et al 1999, Sheu et al 2000, Wong et al 2000) measured diagnostic accuracy at multiple cut-off values, and some determined the cut-off value that resulted in optimal diagnostic characteristics of the UBT as part of the study.

Endoscopy followed by biopsy, with subsequent culture, histology or rapid urease test was used as the reference standard to confirm the presence of *H. pylori* in the included studies. However, the studies varied in the test or combination of tests applied to biopsy samples and the combination of positive results of those tests that was used to confirm *H. pylori* status. Peng et al (2000) and Sheu et al (2000) did not clearly report how non-infected participants were defined, nor did these authors and Savarino et al (2000) describe if participants with equivocal reference test results were excluded. Wong et al (2000) excluded participants with differing histology and culture results.

Validity of included studies

Table G4 (Appendix G) summarises the critical appraisal of studies against pre-defined validity (quality) criteria. The majority of studies met most of the validity criteria (as expected due to the rigorous application of inclusion criteria for this assessment). Ng et al (2002) and Sheu et al (2000) did not explicitly state if they selected consecutive participants, which may result in over-estimation of UBT accuracy. Gatta et al (2003a, 2003b) did not give a sufficiently explicit description of participants to indicate if those with alarm features were excluded. Dill et al (1990) and Peng et al (2000) used part of the reference (endoscopy) to aid selection of participants, thus the UBTs were applied retrospectively, potentially biasing the selection of participants. However, selection bias should be minimal as it was unlikely the *H. pylori* status of participants was known.

All studies used an appropriate reference as clinical expertise provided by the Advisory Panel for this assessment indicated that demonstration of the presence of *H. pylori* following endoscopy and biopsy by use of histology, culture, and/or rapid urease test was acceptable. Theoretically, however, the exclusion of participants with equivocal test or reference results (Ng et al 2002, Wong et al 2000) may have resulted in attrition bias. Similarly, the use of different threshold values for a positive test result, or determining the optimal cut-off *post hoc* may also have resulted in unquantifiable bias.

Results of included studies

Table G5 (Appendix G) summarises the diagnostic characteristics of UBTs in the included studies. Differences in UBT testing regimens and cut-off values to indicate positive results (Table 11) precluded meta-analysis. Across studies, sensitivity ranged from 90 to 100 per cent, specificity from 86 to 100 per cent, LR+ from 6.8 to 66.7 and LR– from 0 to 0.1. The median sensitivity and specificity were 96 per cent and 98 per cent, respectively. These diagnostic characteristics indicate that UBTs are the most accurate non-invasive test in diagnosing both the presence and absence of *H. pylori* infection in the settings reported.

Some of the lower values reported may be attributable to the development of the technology over time. Current tests may be more accurate than some of those reported.

Discussion of results: Diagnostic accuracy of the test

The high sensitivities and specificities and the large LR+ values (most greater than 10) and small LR– values (<0.1) indicate that UBTs are the most accurate non-invasive test in diagnosing both the presence and absence of *H. pylori* infection in the settings reported. There may be theoretical unquantifiable bias associated with exclusion of indeterminate results—a small proportion of the sample was excluded in several studies—and in using arbitrary threshold values to determine a positive test result, as occurred in most studies. However, as most studies met the majority of validity criteria, the extent to which these data were biased should be small.

There appeared to be no differences in the diagnostic characteristics of tests employing ^{13}C-urea and ^{14}C-urea, although these were not compared directly. Both tests meet the minimum standard that allows their use in the Australian setting. These results are consistent with other reports in the literature of both tests providing similar results (de Castro 2004, Dominguez-Munoz 1997).

Positive and negative predictive values were not reported in this assessment. The positive and negative predictive values refer to the proportions of patients with positive or negative test results respectively, who are correctly diagnosed. Positive and negative predictive values are dependent on the prevalence of infection in the study population and thus may not be comparable across studies and may differ in clinical settings other than those in the study from which they are derived (Sackett et al 2000). Likelihood ratios are considered more useful (Sackett et al 2000).

The population of interest for this assessment report was narrow. Many studies were identified in the search but excluded from critical appraisal on the basis that there was insufficient description to determine the absence of alarm features in the participants. As this determination was subjective, consensus between two or three reviewers was sought to exclude these studies. However, there is a possibility that the overall results may be biased in an unknown direction or less generalisable due to the strict interpretation of the inclusion criteria of this assessment. Thus, included studies are representative of the population of interest for this MSAC assessment. Due to the differences in UBT regimens, it is difficult to determine if the accuracy results are strictly applicable to the clinical settings in Australia and to populations that include alarm features.

Part 2: Patient health outcomes following testing

UBT as a first line diagnostic test

This report assessed the effectiveness on patient health outcomes of the UBT as a first line diagnostic test for *H. pylori* infection and subsequent management in dyspeptic patients compared to endoscopy and subsequent management or empirical treatment.

Critical appraisal of RCTs

Four prospective RCTs were selected for inclusion in this assessment report. These were conducted in the USA (Cuddihy et al 2005), Denmark (Lassen et al 2000), Italy (Manes et al 2003) and the UK (McColl et al 2002). Table H1 (Appendix H) presents the descriptive characteristics of each study.

Two studies (Cuddihy et al 2005, Manes et al 2003) compared patient health outcomes between groups receiving empirical treatment for symptoms and those treated for *H. pylori* infection as indicated by UBT. Three studies (Cuddihy et al 2005, Lassen et al 2000, McColl et al 2002) compared patient health outcomes of groups tested for *H. pylori* infection by UBT or endoscopy prior to receiving treatment.

Three studies measured health outcomes after 12 months of follow-up (Lassen et al 2000, Manes et al 2003, McColl et al 2002), whereas Cuddihy et al (2005) measured health outcomes after 6 months of follow-up.

Description of the intervention and comparator(s) used in each RCT are presented in Table H2 (Appendix H).

Patient selection criteria for the RCTs

Eligibility criteria for each of the four included studies are presented in Table H3 (Appendix H). In general, patients were required to have dyspeptic symptoms without alarm features (eg unexplained weight loss, vomiting, dysphagia, bleeding, anorexia or an abdominal mass). There were slight variations in the definition for dyspepsia employed by the different studies.

Three of the four studies specified a minimal age requirement of 18 years (Cuddihy et al 2005, Lassen et al 2000, Manes et al 2002). Only two studies specified a maximum age for participants. Manes et al (2003) excluded participants over the age of 45 and McColl et al (2002) excluded those over 55 years old.

Validity of RCTs

The results of the validity assessment for each study are presented in Table H4 (Appendix H).

Randomisation and allocation concealment

Manes et al (2003) did not state the randomisation method used to assign participants to patient groups nor whether these assignments were initially concealed from the investigators. The remaining three studies employed tables of random numbers (Lassen et al 2000, McColl et al 2002) or a computer generated randomisation scheme (Cuddihy et al 2005) for patient allocation to groups. Sealed numbered envelopes were used to conceal allocation in studies by Lassen et al (2000) and McColl et al (2002). Cuddihy et al (2005) used an independent pharmacy unit to randomise then passed the assignments to the study coordinator once patients were enrolled. This implies concealment of allocation from the investigators.

Blinding

Patients and investigators were not blinded to group assignments in any of the included studies. This would be difficult due to the nature of the interventions. Manes et al (2003) used an investigator who was blind to group assignments for follow-up of participants. It was not stated whether outcome assessment of clinical measures was blinded in each of the other studies.

Follow-up and intention-to-treat

Follow-up of participants in the study conducted by Manes et al (2003) was limited to patients with improved symptoms after four weeks. Results are presented as a figure only. In the absence of numerical data, it cannot be determined if Manes et al (2003) used intention-to-treat analysis for measurement of the primary outcome (dyspepsia scores).

Although Lassen et al (2000) were transparent about the number of participants lost to follow-up, they did not use intention-to-treat analysis when presenting results from the different investigation groups. Furthermore, there are insufficient data provided to permit an intention-to-treat analysis of participants reported in this study.

Sample size and power

Three of the four included RCTs did not report a power calculation for their study (Cuddihy et al 2005, Lassen et al 2000, Manes et al 2003). These studies may have had an insufficient number of participants to detect a significant difference between treatment groups. McColl et al (2002) reported that their planned study of 672 patients (436 positive for *H. pylori* and 236 negative for *H. pylori*) followed up at one year had 90 per

cent power to detect a difference in mean change in the Glasgow dyspepsia severity score of 1.03 in the *H. pylori* positive subgroup and 1.41 in the *H. pylori* negative subgroup at the five per cent significance level overall (2.5% per subgroup).

Results from RCTs

The main results from each of the included RCTs are summarised in Table H5 (Appendix H). The primary outcome for all of the included studies was improvement or resolution of dyspepsia symptoms. The studies varied in the tools used to measure this outcome.

Cuddihy et al (2005) employed a dyspepsia-specific health-related quality of life measure (HR-QOL). At 6 months of follow-up, comparison between groups revealed participants receiving a breath test had better scores than those who were assigned to empirical treatment ($p=0.007$), endoscopy ($p=0.02$), or serology ($p=0.01$).

The gastrointestinal symptoms rating score used by Lassen et al (2000) indicated similar outcomes for groups 12 months after having either breath test or endoscopy. Likewise, there was no significant difference in the number of participants in these groups reporting no symptoms after 12 months.

Data presented by Manes et al (2003) indicated that patients undergoing the test-and-treat strategy with UBT had significantly lower dyspepsia scores after 12 months than those assigned to empirical treatment for symptoms ($p<0.0001$). This finding is further supported by a significantly higher proportion of symptom-free days reported in the UBT group within the 12-month follow-up period ($p<0.001$).

McColl et al (2002) reported no significant difference in Glasgow dyspepsia scores of patients who had received UBT or endoscopy. Furthermore, complete resolution of dyspeptic symptoms after 12 months follow-up was similar for patients receiving UBT or endoscopy.

Secondary outcomes used to determine the effectiveness of UBTs as a first line diagnostic tool for *H. pylori* infection include the use of medical resources and the overall general wellbeing and satisfaction of patients managed by this strategy.

The UBT followed by management resulted in decreased utilisation of medical resources compared to prompt endoscopy for dyspeptic patients. For the RCTs assessed in this report, two trials reported a significant reduction in the number of endoscopies undertaken by patient groups receiving a breath test compared to those assigned to prompt endoscopy ($p<0.0001$) (Lassen et al 2000, Manes et al 2003). One study reported an increased proportion of endoscopies per patient in the UBT group compared to the endoscopy group (McColl et al 2002), although these results reflect the number of subsequent endoscopies rather than overall number of endoscopies undertaken by the different groups.

Lassen et al (2000) and McColl et al (2002) both reported similarities between UBT and endoscopy patient groups for the number of visits to GPs or attendance at hospitals. This was not a measured outcome in studies by Cuddihy et al (2005) and Manes et al (2003).

Two of the three studies comparing UBT to endoscopy reported similar use of medication in both groups (Cuddihy et al 2005, McColl et al 2002) however, one study reported significantly higher use of eradication therapies in the UBT group (p=0.009) (Lassen et al 2000).

The psychological general wellbeing of patients measured by Lassen et al (2000) revealed no significant difference between the UBT and endoscopy groups after 12 months. Likewise, McColl et al (2002) reported similar SF-36 quality of life scores between these groups at one year after randomisation. In contrast, Cuddihy et al (2005) reported significant differences in SF-36 mental scores although physical scores were similar between groups. Pairwise comparisons at six months of follow-up revealed that those in the UBT group had lower mental scores than those in either the empirical group (p=0.01) or the endoscopy group (p=0.027) (Cuddihy et al 2005).

Two of the four included studies reported on patient satisfaction one year after randomisation to either UBT or endoscopy (Lassen et al 2000, McColl et al 2002). Overall satisfaction was similar between treatment groups in the study by McColl et al (2002), however Lassen et al (2000) reported more dissatisfied patients in the UBT group (12%) than the endoscopy group (4%).

Discussion of results from RCTs

The primary outcome of interest was the improvement or resolution of dyspeptic symptoms within the different treatment groups. Results suggested improved outcomes for UBT followed by management compared to empirical treatment (Cuddihy et al 2005, Manes et al 2003). Furthermore, UBT followed by management led to similar outcomes (Lassen et al 2000, McColl et al 2002) compared to endoscopy and subsequent management. Improved outcomes reported for the UBT compared to endoscopy by Cuddihy et al (2005) may have been due to the shorter-term follow-up (six months) of this study. It was not possible to pool the results for meta-analysis as different studies used different methods of measuring dyspeptic symptoms in patient groups.

There was no evidence identified to assess the effectiveness of UBTs in participants presenting with dyspepsia aged less than 50 years compared to those aged over 50 years.

None of the studies reported on all of the validity criteria, suggesting that non-appraisable bias may have affected the results of each study (Higgins et al 2005, Schulz et al 1995). Although it is difficult to blind participants and investigators to treatment allocation, blinding of outcome assessors was possible. Lack of blinding for outcome assessors in the majority of studies may have led to detection bias in some of the results, especially those that are subjective in nature. Studies that failed to describe the method of randomisation (Manes et al 2003) or concealment of allocation (Cuddihy et al 2005, Manes et al 2003) may have unbalanced patient groups and are more susceptible to exaggerated treatment outcomes than those that took adequate measures to conceal allocation (Schulz et al 1995). Failure to use intention-to-treat analysis (Lassen et al 2000, Manes et al 2003) could also have compromised the randomised balance between treatment groups, leading to a bias in results.

One of the major concerns associated with using the UBT to diagnose *H. pylori* infection in dyspeptic patients is the possibility of missing upper gastrointestinal malignancy in some patients. Therefore this type of *H. pylori*-based management strategy is not recommended for patients displaying alarm symptoms. The patient selection criteria for

this assessment report define alarm symptoms as weight loss, vomiting, dysphagia, bleeding, anorexia or an abdominal mass. Although most of the included studies specify each of these symptoms within their exclusion criteria, the possibility exists that some patient groups may have had alarm symptoms. For example, Lassen et al (2000) described vomiting as a dyspeptic symptom. Interestingly, the same study was the only included study to report detection of gastric cancer in two participants. These studies were not designed to detect a difference in the incidence of upper gastrointestinal malignancy in those allocated to UBT followed by management compared to other management strategies. Furthermore, the literature search identified no such studies.

UBT as a second line diagnostic test

No trials were identified that reported on the use of UBT and subsequent management as a second line diagnostic test due to this use of UBTs being considered inappropriate except in specific, uncommon clinical situations. Furthermore, current guidelines (GESA 2005, Malfertheiner et al 2002) do not recommend the routine use of UBTs following serology.

What are the economic considerations?

The framework for the economic evaluation of any medical technology considered by MSAC is the comparison of the costs and benefits of that technology compared with the current alternatives for patients. The approach taken is to calculate an incremental cost effectiveness ratio $(C_I-C_C)/(O_I-O_C)$ where C_I is the total cost of resources used associated with the intervention, C_C is the total cost of resources used by the comparator, O_I is the output associated with the intervention, and O_C is the outcome associated with the comparator. The perspective taken is a broad one that includes not only the financial implications to the government health budget, but also the value of all socially relevant health-related resource use. Where there is no difference in outcomes or complications, or it seems clear that there will be unmeasurable gains, a comparative cost analysis of the competing pathways is all that is required.

Cost effectiveness of UBT as a first line diagnostic test

Purpose of the model

The type of economic evaluation is a cost-effectiveness analysis of UBT as a first line diagnostic test. We present a decision-analytic model from a health system perspective constructed using TreeAge Pro 2004 to compare four alternative management strategies for patients presenting to their GPs with uncomplicated dyspepsia:

- Use of endoscopy to identify the underlying condition, test for the presence of *H. pylori* and treat according to the endoscopic result (hereafter referred to as endoscopy)
- Use of serology to detect antibodies to *H. pylori* and treat with eradication therapy if test positive (hereafter referred to as serology)
- Use of UBT to test for the presence of *H. pylori* and treat with eradication therapy if test positive (hereafter referred to as UBT)

- Empirical treatment using an antisecretory drug followed by investigation of non-responders using endoscopy, serology or UBT (hereafter referred to as antisecretory treatment).

The model is deterministic and has a time horizon of one year. This horizon is clinically relevant and is typically used in trials and studies of a first line diagnostic test in the management of uncomplicated dyspepsia with an underlying cause of peptic ulcer disease, functional dyspepsia or gastric cancer. However, it should be noted that benefits of *H. pylori* eradication with respect to risk reduction for ulcer disease and cancer may accrue over the lifetime of the patient treated.

Endoscopy is assumed to be the gold standard for investigating dyspepsia. In view of the lack of Australian data on dyspepsia management in general practice, the model was based on best clinical practice and assumed that all unresolved cases are investigated by endoscopy followed by the appropriate treatment indicated by endoscopic findings within the year. The pre-test probability of *H. pylori* infection and the properties (sensitivity and specificity) of the serology and UBT tests were accounted for by including *H. pylori* prevalence as a variable in the model and by utilising Bayes' revision in the model.

The model is designed to capture all resources used, such as the costs of GP or specialist visits, tests and treatment, from presentation to resolution of dyspeptic symptoms and cure. The primary outcomes of interest are the total cost, total QALYs and time living without dyspepsia (dyspepsia-free time) for each strategy for a one-year period from presentation. The time to cancer detection for each strategy was estimated and defined as a secondary outcome of interest. Although gastric cancer is a rare cause of dyspeptic symptoms, particularly in persons with uncomplicated dyspepsia with no alarm features, it is an important consideration in the context of making a timely diagnosis and initiating prompt treatment for a serious disease such as cancer. European and Japanese research now reports 5-year survival rates of greater than 90 per cent for early gastric cancer (Everett & Axon 1997). In contrast, 5-year survival rates of late-stage disease are between 10 and 20 per cent (Berrino et al 1999, Faivre et al 1998, Ries et al 1997).

While a one-year time horizon is relevant for dyspepsia, there may be longer-term benefits in detecting and treating cases of *H. pylori* in the population at large and in those with dyspeptic symptoms. In order to differentiate between serology and UBT in terms of the potential long-term benefits of a more accurate test, the numbers of peptic ulcer disease and gastric cancer attributable to *H. pylori* averted in future years were estimated.

Description of model

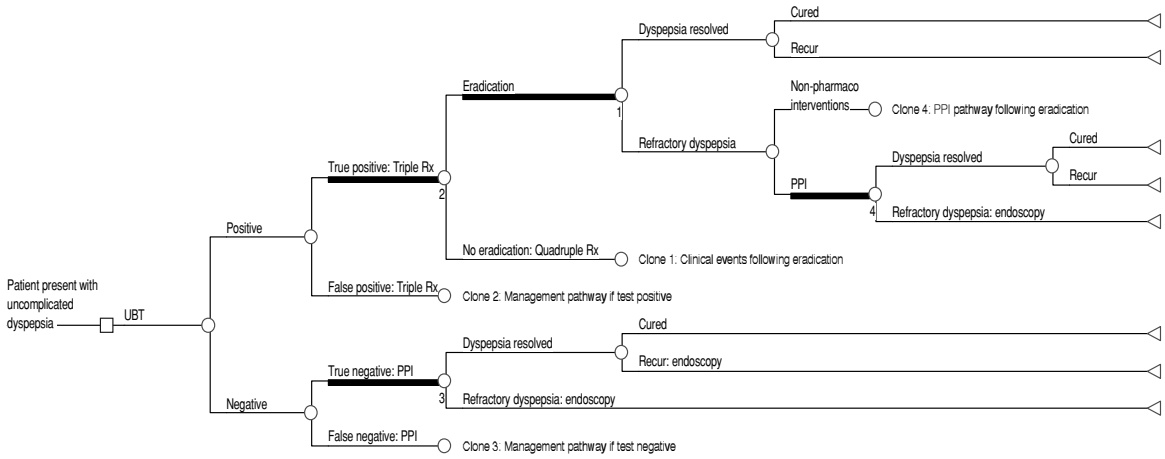
The model begins when a patient with uncomplicated dyspepsia consults his/her GP. The model assumes that the patient has new onset dyspepsia with no alarm symptoms, no NSAID use, and no signs suggestive of other disease on presentation. The model allows the GP to select one of the following four management strategies: endoscopy, serology, UBT or antisecretory treatment. Details of the UBT arm of the model are shown in Figure 3 below. The complete model is available on request.

In Figure 3, the square represents a management decision point, the circles denote chance events with multiple outcomes and the triangles represent clinical endpoints. In order to make the decision tree easier to read, some branches that are copies in structure of other parts of the tree are labelled as a 'clone'. The number assigned to a clone refers

to the node in the tree and the branches to the right that have been copied. It should be noted that clones are used for presentation purposes only. For calculation purposes, probability values used within each clone differ across pathways. Thus the probability of symptom recurrence following eradication therapy in test positive patients differs according to the actual presence (0.5) or absence of *H. pylori* (0.86).

With the UBT initial diagnostic test strategy, all patients presenting with uncomplicated dyspepsia have a UBT test upon presentation. Patients who test positive receive eradication therapy (omeprazole-based triple therapy with amoxicillin) and a second UBT test to confirm the success of *H. pylori* eradication. If eradication is not achieved, quadruple therapy (120 mg bismuth subcitrate four times per day, 500 mg tetracycline four times per day, 200 mg metronidazole three times per day and omeprazole twice daily) is given. Persons who return a negative test result receive a 30-day course of standard dose PPI. Following both types of therapy, symptoms either resolve or the patients are refractory. A proportion of patients who have successfully eradicated *H. pylori* and are asymptomatic in the year are assumed to be cured, while some are assumed to have a recurrence of symptoms for which a course of low-dose PPI is given.

Similarly a proportion of *H. pylori*-negative patients who have become symptom-free after initial treatment with PPI are assumed to be cured, while some have a recurrence of dyspepsia during the model horizon and undergo endoscopy. Endoscopy is also given to patients who fail to respond to initial treatment with PPI. Patients developing refractory dyspepsia after successful eradication of *H. pylori* are assumed to receive either a non-pharmacological intervention or a course of low-dose PPI, and to undergo investigation by endoscopy if their dyspepsia remains unresolved. The likelihood of cure or recurrence of symptoms is dependent on the probability of treatment success, which is in turn conditional upon the presence or absence of *H. pylori*. The probability of successful eradication and cure is therefore dependent in part on the specificity and sensitivity of the test.



Abbreviations: Rx: Therapy, PPI: proton pump inhibitor.

Figure 3 Management of uncomplicated dyspepsia using UBT as the initial diagnostic test

The serology strategy is identical in structure to the UBT strategy, except that the initial test used to diagnose *H. pylori* infection is serology instead of UBT.

In the endoscopy strategy, patients presenting with uncomplicated dyspepsia are referred to a public or private hospital for an endoscopy and treated according to the endoscopic result. Patients diagnosed with peptic ulcer disease are prescribed triple therapy if *H. pylori* positive or standard dose PPI if *H. pylori* negative. A UBT is used to confirm the eradication of *H. pylori* and if the organism is not eradicated, quadruple therapy is offered. The same treatment approach is assumed for functional dyspepsia, except that *H. pylori*-positive patients are given a one-off eradication treatment and no confirmation test. The model conservatively allows for a single eradication course without confirmatory testing because the benefit of *H. pylori* eradication in functional dyspepsia compared to placebo is estimated to be small (risk difference 7%, 95% CI: 4%, 10%) (North of England Dyspepsia Guideline Development Group 2004) and there are no reliable data to model further risk reduction associated with quadruple therapy. The management of gastric cancer involves cancer therapy and treatment for *H. pylori* if present. Under the endoscopy strategy test results are assumed to be 100 per cent sensitive and specific, so patients would receive appropriate treatment and require no further investigation.

The strategy of empirical treatment with antisecretory drugs does not involve diagnostic testing before initiation of therapy with a 30-day course of standard dose PPI. If dyspepsia is not resolved after this course of treatment, patients undergo investigation by:

- serology or endoscopy according to current management algorithm
- serology, endoscopy or UBT according to proposed management algorithm.

Assumptions used in the modelling

The model is based on the following assumptions:

1. The population of interest is assumed to have new onset dyspepsia with no alarm symptoms, no use of NSAIDs, no signs suggestive of other disease on presentation and no prior investigations. For simplicity, it is further assumed that within the model horizon of one year there would be no complications such as bleeding arising from the recurrence of ulcer.

2. Patients start the model with similar quality of life, that is, everyone is assumed to have the same severity of dyspepsia at entry into the model.

3. Endoscopy is assumed to be 100 per cent sensitive and 100 per cent specific for the diagnosis of peptic ulcer disease, gastric cancer and, by exclusion, functional dyspepsia. For simplicity, the possibility of oesophagitis is not considered here although it is acknowledged that symptoms resulting from this condition could overlap with those caused by peptic ulcer disease, gastric cancer and functional dyspepsia.

4. Endoscopy is performed as a same-day procedure in public or private hospitals on an open-access basis.

5. The average waiting time for endoscopy is 10 weeks for public patients and one week for private patients (according to Advisory Panel).

6. Under the endoscopy strategy, patients are assumed to be managed by their GP initially and, depending on the endoscopy results, may be referred to a specialist for appropriate management, eg in the case of gastric cancer.

7. Patients on the remaining strategies, who are diagnosed with gastric cancer, are assumed to be managed by a specialist following their diagnosis.

8. The survival time for gastric cancer is assumed to be five years (National Cancer Institute 2005), hence the cost of treating gastric cancer within the model horizon is assumed to be 1/5 of the lifetime cost of gastric cancer. The lifetime cost of gastric cancer is assumed to cover the cost of specialist consultations.

9. Patients who fail triple therapy are prescribed quadruple therapy. For simplicity, quadruple therapy is assumed to have 100 per cent eradication success.

10. Patients prescribed eradication or PPI therapy are assumed to be 100 per cent compliant.

11. A two-week washout period is needed before patients taking PPI can undergo testing for refractory dyspepsia using UBT or endoscopy (Laine et al 1998). For those having UBT, the washout period is added to the time living with dyspepsia. For those having endoscopy, the washout period is within the waiting time for endoscopy, therefore no additional time is added to the time living with dyspepsia.

12. Patients who have refractory dyspepsia after a second course of treatment are referred to a specialist for management.

13. UBT is assumed to be 100 per cent accurate when used to confirm the success of *H. pylori* eradication treatment. It is further assumed that all patients, except those with *H. pylori*-positive functional dyspepsia, would have this test following eradication therapy (triple or quadruple therapy) and that a two-week washout period would elapse between cessation of therapy and testing.

14. Re-infection with *H. pylori* is assumed to be negligible in the context of low *H. pylori* prevalence and hence not included in the model.

15. The duration of antisecretory treatment is assumed to be four weeks. Given that PPI is more effective than histamine-2-receptor antagonists (Delaney et al 2003) this drug is used in the model. The PPI dosage for initial therapy is the standard dosage. Low dosage is used for maintenance therapy.

16. Good to excellent symptom relief and improvement in quality of life is assumed to occur at the end of a course of therapy (one week for PPI-based triple therapy, two weeks for quadruple therapy and four weeks for antisecretory therapy).

Table 9 summarises the key assumptions and probabilities used in the model. Probability data come from a rapid review of the literature conducted to identify relevant trials, studies, systematic reviews and meta-analyses. An explicit quality review was not attempted. The point estimate used in the base case was taken from meta-analyses if these were available and values used in the sensitivity analysis were taken from the same source. Estimates were taken from the highest level of evidence available within the review and Australian data were preferred. It should be noted that for simplicity, the distinction between gastric and duodenal ulcer was not made, however a range of literature-based estimates covering both types of ulcer was used in the model.

Table 9 Key assumptions and probabilities used in the model

Variable		Base case	Range	Source
1	Sensitivity of serology	86%	80%–95%	Loy et al (1996), Laheij et al (1998)
2	Specificity of serology	86%	80%–95%	Loy et al (1996), Laheij et al (1998)
3	Sensitivity of UBT (when used to establish a diagnosis)	96.5%	90%–100%	'Results of assessment' section above. Note the point estimate used in the base case is the median value taken from studies listed in Table 13
4	Specificity of UBT (when used to establish a diagnosis)	97.7%	86%–100%	'Results of assessment' section above. Note the point estimate used in the base case is the median value taken from studies listed in Table 13
5	Prevalence of *H. pylori* in Australia	36%	10%–91%	Peach et al (1997), Patel et al (1994), Windsor et al (2005)
6	Eradication rate of omeprazole-based triple therapy with amoxycillin in *H. pylori* positive peptic ulcer disease	83.3%	76.2%–82.4%	Kim et al (2002) (patients with duodenal ulcer), Mones et al 2001 (patients with duodenal ulcer), Malfertheiner et al (1999) (patients with gastric ulcer). Note the possibility of allergy to amoxycillin is ignored because the prevalence of this allergy is reportedly only 1% (Park 2005)
7	Probability of ulcer recurrence	9%	9%–12%	Penston (1996)
8	Probability of having dyspeptic symptoms resolved after antisecretory treatment for uninvestigated dyspepsia	40%	34%–57%	Bytzer et al (1995), Delaney et al (2005) (Cochrane review), Lewin-van den Broek (1999)
9	Probability of gastric cancer at endoscopy	1%		Froehlich et al (1999)
10	Probability of peptic ulcer at endoscopy	13.5%		Froehlich et al (1999)
11	Probability of functional dyspepsia at endoscopy	85.5%		Froehlich et al (1999)
12	Percentage of same day endoscopies (DRG G45B) performed in the private sector	67.9%		National Morbidity Data 2002–03
13	Proportion of endoscoped patients having one biopsy taken for diagnostic purposes	69.2%		HIC data for items 72823 and 72824 for 2004–05, assuming no patients would have more than 4 biopsies taken for investigation and that the HIC data are representative of patients undergoing upper endoscopic procedures
14	Proportion of endoscoped patients having 2–4 biopsies taken for diagnostic purposes	30.8%		HIC data for items 72823-72826 for 2004–05
15	Quality of life (QOL) with dyspepsia	0.80	0.79–0.91	Upper limit of 0.91 is the median utility value for moderate level of symptoms. Lower limit of 0.79 is the lower limit of the 95% CI of median utility for severe dyspepsia (Groeneveld et al 2001)
16	Quality of life of patients living with gastric cancer	0.5	0.5-0.8	No specific estimate was found in the literature. The value used in the base case is an estimated QOL of patients treated with any chemotherapy (Barosi et al 1998). Lower and upper limits are QOL of patients with metastatic disease at diagnosis and patients with very good prognosis, respectively (Statistics Canada 2006)
17	Weighted average waiting time for endoscopy	3.2 weeks		Weighted by the proportion of endoscopy performed in public and private hospitals
18	Probability of *H. pylori* if gastric cancer	0.89		Froehlich et al (1999)

Table 9 (cont) Key assumptions and probabilities used in the model

	Variable	Base case	Range	Source
19	Probability of *H. pylori* if peptic ulcer	0.90		Froehlich et al (1999)
20	Probability of having *H. pylori* if functional dyspepsia	0.46		Froehlich et al (1999)
21	Probability of having refractory dyspepsia after successful eradication of *H. pylori*	0.50		Chiba et al (2002)
22	Probability of requiring PPI for refractory dyspepsia after successful eradication of *H. pylori*	0.5		Advisory Panel
23	Probability of having refractory dyspepsia after antisecretory treatment for uninvestigated dyspepsia	0.40	34%-57%	Delaney et al 2005 (Cochrane review), Bytzer et al (1995) and Lewin (1999)
24	Probability of having functional dyspepsia resolved after PPI treatment	0.37		CCOHTA 2002 (meta-analysis estimate)
25	Attributable risk of *H .pylori* in gastric cancer causation	30%	30%–50%	Tytgat (1998), Webb & Forman (1995)
26	Lifetime prevalence of peptic ulcer disease in the general population	10%	5%–15%	Hunt & Thomson (1998)
27	Proportion of complicated peptic ulcers	24%		National Hospital Cost Data Collection 2002–03

Definition and measurement of costs

Total costs included in the cost-effectiveness analysis are medical fees (Table 10), the cost of diagnostic tests (Table 11) and the cost of treatment (Table 12). Drug cost is the only treatment cost included.

Table 10 Medical fees and costs of hospital admission

Variable	MBS item	Unit cost ($)	Comment
Surgery consultation	23 (Level B)	30.85	
Specialist, referred consultation	110	128.05	
Specialist, subsequent consultation in a single course of treatment	116	64.10	
Oesophaguscopy, gastroscopy, duodenoscopy or panendoscopy	30473	150.30	
Pre-anaesthesia consultation	17603	36.40	
Initiation of management of anaesthesia for upper gastrointestinal endoscopic procedures	20740	84.25	
Anaesthesia perfusion time 15 min or less	23010	16.85	
Average cost for DRG G45B in public sector	NA	939.80	National Hospital Cost Data Collection 2002–03. Note unadjusted cost is $871. An inflation rate of 7.9% for the period 2002–03 to 2004–05 has been used in the adjustment (ABS 2005)
Average cost for DRG G45B in private sector	NA	406.80	National Hospital Cost Data Collection 2002–03. Note unadjusted cost is $377. An inflation rate of 7.9% for the period 2002–03 to 2004–05 has been used in the adjustment (ABS 2005)
Lifetime cost of stomach cancer	NA	23,903	AIHW health system expenditure on cancer and other neoplasms in Australia, 2000–01 (Table 2.5, p19). Note unadjusted cost is $21,573. An inflation rate of 10.8% for the period 2001–02 to 2004–05 has been used in the adjustment (ABS 2005)
Weighted average cost of treating an uncomplicated peptic ulcer (AR-DRG G-63Z)	NA	1,284.90	National Hospital Cost Data Collection 2002–03. Weighted by proportion of separations in public and private hospitals, and adjusted for inflation to September 2005
Weighted average cost of treating a complicated peptic ulcer (AR-DRG G-62Z)	NA	4,072.40	National Hospital Cost Data Collection 2002–03. Weighted by proportion of separations in public and private hospitals, and adjusted for inflation to September 2005

Source: MBS July 2005 unless indicated otherwise.
Abbreviations: NA, not applicable

Diagnostic tests usually performed on endoscopic biopsies include the rapid urease test (which does not attract Medicare reimbursement) and histology. Additional tests such as Gram stain and culture might be undertaken to inform treatment in patients who fail to achieve adequate response to triple therapy. The cost of endoscopy includes the costs of endoscopist, anaesthesia (consultation, management and perfusion time), hospital accommodation and diagnostic tests.

For public patients the average cost recorded for DRG G45B (other gastroscopy, non-major digestive disease same day) is the total cost incurred. For private patients, the cost of endoscopy consists of the average cost for DRG G45B for the private sector plus the costs of endoscopist, anaesthesia and diagnostic tests. The cost of endoscopy is calculated as weighted average cost using the following formula:

Cost of endoscopy = $(C_{pub} \times W_{pub}) + (C_{pri} \times W_{priv})$ where C_{pub} is the average cost of endoscopy in public hospitals, W_{pub} is the proportion of endoscopy performed in the public sector, C_{pri} is the average cost of endoscopy in private hospitals and W_{pri} is the

proportion of endoscopy performed in the private sector. The average cost of endoscopy in private hospitals is calculated as follows:

$$C_{pri} = Cost\ of\ hospital\ bed + Medical\ \ fees + Cost\ of\ diagnostic\ tests$$

Cost data and the number of separations come from the National Hospital Cost Data Collection (NHCDC) 2002–2003 (Australian Government Department of Health and Ageing 2004) and are adjusted for increases in the price of goods and services (totalling 7.9% to 2004-05). Medical fees for relevant Medicare Benefits Schedule (MBS) items are taken from the MBS July 2005 edition (Australian Government Department of Health and Ageing 2005).

Table 11 Unit cost of diagnostic tests

Variable	MBS item	Unit cost ($)	Comment
Examination of biopsy materials: 1 separately identified specimen	72823	97.95	
Examination of biopsy materials: 2–4 separately identified specimens	72824	142.30	According to the Advisory Panel, most patients have two biopsies taken
Rapid urease test	NA	0.00	According to the Advisory Panel, there is no fee for this test
UBT	12533	71.75	According to the Advisory Panel, collection fee is not applicable
Serology	69384	15.75	Other items might be used for serology tests for *H. pylori* (69387, 69390, 69393, 69396, 69399). Due to the lack of data differentiating cost of *H. pylori* serology from cost of other bacterial serology, the item 69384 is used to provide an indication of the cost of the test
Fee for collecting serology specimen	73907	17.40	According to the Advisory Panel, this fee is applicable to >90% of ambulatory patients. In this analysis it is assumed that all serology tests would attract an initiation fee and therefore the total cost of the test is $33.15
Culture of endoscopic biopsy for *H. pylori*	69321	48.45	According to the Advisory Panel, this fee also covers the cost of a Gram stain for *H. pylori*
Weighted average cost of endoscopy without Gram stain and culture	NA	855.75	See text above for calculation method
Fee for collecting histology specimen	73915	9.80	According to the Advisory Panel, this fee is applicable to private patients only
Weighted average cost of endoscopy with Gram stain and culture	NA	888.64	See text above for calculation method

Source: MBS July 2005 unless indicated otherwise
Abbreviations: NA, not applicable

Table 12 Drug costs

Drug	PBS item	Cost/pack ($)	Comment
Eradication treatment			
Omeprazole-based triple therapy with amoxycillin	8272J	98.12	
Second line quadruple eradication treatment: bismuth subcitrate 120 mg 4 times/day, tetracycline 500 mg 4 times/day, metronidazole 200 mg 3 times/day, omeprazole twice daily	No item	100.20	Total cost = cost of bismuth + cost of omeprazole 20 mg + cost of metronidazole + cost of tetracycline. Note: Bismuth is SAS
Proton pump inhibitors			
Standard dose for initial therapy			
Omeprazole 20 mg tablet or capsule	8331L	42.56	20 mg/day or 1 pack/30 days
Esomeprazole 40 mg tablet	8601Q	75.35	40 mg/day or 1 pack/30 days
Pantoprazole 40 mg tablet	8007K	46.51	40 mg/day or 1 pack/30 days
Rabeprazole 20 mg tablet	8509W	46.50	20 mg/day or 1 pack/30 days
Lansoprazole 30 mg sachet	8528W	42.50	30 mg/day or 1 pack/30 days
Weighted average cost of standard PPI dose	NA	65.04	Refer to Appendix J for details of the calculation
Low dose for maintenance therapy			
Esomeprazole 20 mg tablet	8600P	46.28	20 mg/day or 1 pack/30 days
Omeprazole 10 mg tablet	8332M	29.09	10 mg/day or 1 pack/30 days
Lansoprazole 15 mg capsule	8198L	28.58	15 mg/day or 1 pack/30 days
Pantoprazole 20 mg tablet	8399C	27.26	20 mg/day or 1 pack/30 days
Rabeprazole 10 mg tablet	8507R	27.69	10 mg/day or 1 pack/30 days
Weighted average cost of low PPI dose	NA	43.70	Refer to Appendix J for details of the calculation

Source: PBS August 2005 unless stated otherwise. Dosage Australian Medicines Handbook
Abbreviations: SAS, Special Access Scheme

Calculation of total cost

A health sector perspective was used to calculate the total cost of each strategy. Given the short duration of the model, discounting was not relevant. The formula used to calculate the total cost was:

Total cost = cost of consultation + cost of tests + cost of treatment

The cost of consultation includes the total cost of visits to GP and specialist (if applicable) within the one-year timeframe. The cost of tests includes all tests performed until an organic cause of dyspepsia is established (diagnostic strategies) or dyspepsia is resolved (antisecretory strategy). The cost of treatment includes the cost of therapy until a state of 'cured' is achieved. The unit cost of PPI (both initial and maintenance therapies) is weighted by the proportion of brands on the PBS prescribed in the period 2003-05 (Health Insurance Commission 2005), assuming that prescribing data are applicable to the model (refer to Appendix J for details of the calculation).

For example, consider a patient who consults a GP for uncomplicated dyspepsia, undergoes an endoscopy followed by PPI-based triple therapy for *H. pylori* ulcer and who is cured and has no ulcer recurrence thereafter. The total cost for such a patient would be $1,087.20, comprising $855.80 for endoscopy, $61.70 for two GP consultations, $97.88 for a course of PPI-based triple therapy and $71.80 for a UBT test to confirm

eradication. If this patient experienced a recurrence, additional costs, such as for additional GP visits and a course of low dose PPI, would be added to this total. The total cost of the endoscopy strategy is weighted by the probability of having *H. pylori* ulcer, gastric cancer or functional dyspepsia.

Calculation of QALYs

Patients living with dyspepsia are assumed to have a less than optimal quality of life due to the morbidity of dyspeptic symptoms. Other events, such as experiencing an endoscopy or experiencing adverse effects from therapy, also influence the quality of life of the patients, but the morbidity of these events has been ignored for simplicity. The total number of QALYs for each management strategy over one year is calculated using the following formula:

Total QALYs = [Dyspepsia free months + (Months living with dyspepsia × quality of life with dyspepsia) + (months on chemotherapy × quality of life on chemotherapy)]/12

Estimates of the quality of life with dyspepsia are taken from the literature (Groeneveld et al 2001). For example, a private patient diagnosed with a *H. pylori* ulcer by endoscopy, cured by PPI-based triple therapy and who experienced no ulcer recurrence thereafter would have 0.5 month of dyspepsia and therefore total QALYs for the duration of the model calculated as:

Total QALYs of a cured *H. pylori* ulcer diagnosed by endoscopy is

$$\frac{11.5 + (0.5 \times 0.8)}{12} = 0.99$$

If this patient experienced an ulcer recurrence within the model horizon and was treated with a four-week course of maintenance PPI, the total time living with dyspepsia is assumed to be 1.5 months and the total QALYs for the duration of the model would be 0.98. If this is a public patient with a 10-week wait for an endoscopy, then the total time with dyspepsia is 4 months and the total QALYs is 0.93.

For patients diagnosed with gastric cancer, it is assumed that their quality of life would diminish to about 50 per cent of full health as a result of undergoing cancer treatment (Barosi et al 1998). It is further assumed that the morbidity of dyspepsia would be dominated by the morbidity of cancer treatment. Therefore, in the base case (based on assumptions and probabilities listed in Table 9), these patients would have total QALYs of 0.5 for the period after diagnosis. In the sensitivity analysis it is assumed that the quality of life with gastric cancer in the first year would be no worse than that for dyspepsia.

Calculation of time living without dyspepsia

The time living without dyspepsia is calculated in months as follows:

Time living without dyspepsia = 12 – time living with dyspepsia.

Calculation of number of future gastric cancers averted

For every additional *H. pylori* case detected by UBT compared to serology and successfully treated, the number of gastric cancers averted is:

Probability of *H. pylori* infection if gastric cancer × lifetime probability of gastric cancer × attributable risk of *H. pylori* in cancer causation/Prevalence of *H. pylori*

$= 0.89 \times 0.01 \times 0.3/0.36 = 0.0074$

Calculation of number of future peptic ulcer disease averted

For every additional *H. pylori* case detected by UBT compared to serology and successfully treated, the number of future peptic ulcer disease averted is:

Probability of *H. pylori* if peptic ulcer × lifetime probability of peptic ulcers in general population × attributable risk of *H. pylori* in peptic ulcer disease/Prevalence of *H. pylori*

$= 0.10 \times 0.9 \times 1/0.36 = 0.25$

That is, for every 1,000 cases of *H. pylori* detected and treated there will be 7.4 fewer patients with gastric cancer and 250 fewer with peptic ulcer disease in the longer term.

Sensitivity analysis

A one-way sensitivity analysis was performed to test the robustness of results obtained from the model. In this analysis the value of the following key variables was changed one at a time:

- Prevalence of *H. pylori* in Australia
- Sensitivity of UBT when used to establish a diagnosis
- Specificity of UBT when used to establish a diagnosis
- Sensitivity of serology
- Specificity of serology
- Probability of ulcer recurrence
- Effectiveness of PPI in resolving symptoms of uninvestigated dyspepsia
- Proportion of patients remaining dyspeptic after successful eradication of *H. pylori*
- Cost of PPI
- The quality of life with gastric cancer
- The quality of life with dyspepsia

The values used in the sensitivity analysis are given in Tables 19 and 22.

Results of the cost-effectiveness analyses

Results for primary outcomes

The results of the base case (based on the assumptions and probabilities listed in Table 9) of the analysis incorporating UBT as a first line diagnostic test are presented in Table 13. The model predicts that UBT is no worse than serology with respect to quality of life and dyspepsia-free time and is similar in terms of total cost ($30.60 per patient more over a one-year timeframe). Empirical therapy is slightly more expensive than serology; however, the strategy would lead to 4.7 weeks on average more time living with dyspepsia. Endoscopy is the most expensive strategy overall and offers no advantage over serology or UBT in terms of QALYs. It is clear from Table 13 that within the one-year model horizon, the main advantage of the test-and-treat strategies over empirical therapy is the additional time living without dyspepsia.

Table 13 Cost-effectiveness of management strategies for uncomplicated dyspepsia, base case

Strategy	Total cost ($)	Total QALY	Dyspepsia-free time (weeks)	Extra cost per patient compared to least cost strategy ($)	Extra dyspepsia-free time (weeks) compared to least effective strategy
Serology	972.50	0.94	38.4	0.00	4.7
UBT	1,003.10	0.94	38.2	30.60	4.5
Empirical antisecretory treatment followed by testing of non-responders using serology (12.5%), endoscopy (12.5%) or UBT (75%) (proposed algorithm)	982.50	0.93	33.7	10.00	0.0
Endoscopy	1,143.10	0.94	38.3	170.60	4.6
Empirical antisecretory treatment followed by testing of non-responders using serology (12.5%) or endoscopy (87.5%) (current algorithm)	1,074.10	0.93	35.1	101.60	1.4

The results for antisecretory strategy presented in Table 13 are based on two sets of assumptions about the relative usage of UBT as a method to investigate non-responders. These sets of assumptions reflect the strategies for treatment and diagnosis with and without the availability of UBT. If 75 per cent of refractory cases have a UBT and the remainder have endoscopy or serology then the cost of antisecretory strategy is $982.50 which is similar to serology ($972.50) with little difference in quality of life (0.01 QALY), although there is an increase of about five weeks in time with dyspeptic symptoms. If serology is used to investigate the majority of refractory cases, the model predicts that antisecretory treatment is the cheapest strategy overall at $966 for 0.93 QALY and 33.9 weeks of dyspepsia-free time. These results suggest that the cost of the antisecretory strategy is strongly influenced by the test used to investigate non-responders.

The results in Table 13 suggest that if confirmation of *H. pylori* infection was required following serology, UBT would be cost saving compared to endoscopy, given that UBT is cheaper and results in similar quality of life. Whether confirmation is necessary or desirable depends not only on the accuracy of the serology test, but also on the prevalence of *H. pylori* and the patient's risk factors.

The one-way sensitivity analysis (Table 14) suggests that within the range of values for the majority of the key variables used in the analysis, there is no difference between serology and UBT in terms of time without symptoms of dyspepsia. However, the total cost for UBT over a one-year timeframe is marginally higher than serology. Given the model assumptions and the timeframe of analysis, it could be argued that the cost difference is negligible. The analysis further indicates that if the prevalence of *H. pylori* is at or above 62 per cent, UBT would become the least expensive and most effective strategy overall.

Regarding the effectiveness of PPI in uninvestigated dyspepsia, the sensitivity analysis found that increasing the effectiveness of PPI would decrease the total cost for the antisecretory strategy, however the level of effectiveness does not affect the choice of an optimal strategy. Finally, the results in Table 14 suggest that the assumptions used do not affect the determination of which strategy is the least preferred in terms of quality of life. The present model finds that under the assumption of a quality of life with dyspepsia of ≤0.87 QALY the antisecretory strategy is associated with greater morbidity than any other strategy, yet it is the most commonly used according to information from the Advisory Panel.

Table 14 Results of the sensitivity analysis

Variable	Serology		UBT		Antisecretory treatment followed by testing of non-responders		Endoscopy	
	Total cost ($)	Dyspepsia-free time (weeks)	Total cost ($)	Dyspepsia-free time (weeks)	Total cost ($)	Dyspepsia-free time (weeks)	Total cost ($)	Dyspepsia-free time (weeks)
Effectiveness of PPI in uninvestigated dyspepsia								
Base case 40%	972.50	38.4	1,003.10	38.2	982.50	33.7	1,143.10	38.3
Lower limit: 34%	972.50	38.4	1,003.10	38.2	1,002.00	33.4	1,143.10	38.3
Upper limit: 57%	972.50	38.4	1,003.10	38.2	927.20	34.5	1,143.10	38.3
Prevalence of *H. pylori*								
Base case value: 36%	972.50	38.4	1,003.10	38.2	982.50	33.7	1,143.10	38.3
Lower limit: 10%	1,047.70	36.6	1,107.80	35.5	1,059.20	31.8	1,143.10	38.3
Upper limit: 91%	813.60	42.2	781.60	43.7	820.30	37.7	1,143.10	38.3

Results for secondary outcomes

Table 15 shows the results for the secondary outcome, time to cancer detection. The model predicts endoscopy to be the preferred strategy with the shortest time to detection of 5.2 weeks, and serology and UBT the next best alternatives with similar time delays of 13.6 weeks. The antisecretory strategy is estimated to lead to a delay of 12.4 weeks compared to endoscopy and 4 weeks compared to UBT and serology. In summary, the model suggests that the shortest time taken for a gastric cancer to be detected is 5.2 weeks and the longest is 17.6 weeks when best dyspepsia management practice is followed.

The delay of 5.2 weeks for endoscopy is due entirely to the waiting time for endoscopy. However, the clinical significance of these differences in time to endoscopic detection of cancer is not clear, given the lack of an established association between symptoms of dyspepsia and gastric cancer risk. These figures suggest that when the prevalence of *H. pylori* is below 40 per cent and gastric cancer is rare, the use of an invasive, expensive test such as endoscopy to investigate uncomplicated dyspepsia with no alarm features might not be warranted and a less costly, non-invasive test is more appropriate.

Table 15 Time to cancer detection, base case

Strategy	Time to cancer detection (weeks)	Delay in cancer detection compared to most effective strategy (weeks)
Serology	13.6	8.4
Endoscopy	5.2	0
UBT	13.7	8.5
Antisecretory treatment followed by testing of non-responders by UBT (75%), serology (12.5%) or endoscopy (12.5%)	17.6	12.4

The UBT is a more accurate diagnostic test than serology. One consequence of the increased rate of false negative results from serology is the unnecessary use of antibiotics. The consequence of the reduced detection rate of true positive cases of *H. pylori* by serology is an increased risk of future peptic ulcer disease and gastric cancer. In the latter case, the model predicts that incremental detection of true positive cases for UBT versus serology is 12 per cent. On the further assumption that the prevalence of *H. pylori* is 36 per cent among patients presenting with uncomplicated dyspepsia, the use of UBT as a diagnostic test will result in four per cent more *H. pylori*-positive patients being treated with eradication therapy.

Each additional true positive diagnosis of *H. pylori* made by UBT is estimated to result in a potential 0.0074 gastric cancers and 0.25 peptic ulcers averted in the longer term (see above). This suggests that using UBT to test 1000 patients presenting with uncomplicated dyspepsia would prevent 0.296 future cases of gastric cancer (40×0.0074) and 10 cases (40×0.25) of peptic ulcer disease (on the assumption that they are independent).

The lifetime cost of treating a case of gastric cancer is reported to be $23,903 (AIHW 2001) (Table 10). Most ulcers (75%) are likely to be simple and may not require hospitalisation, however some will be more complicated and will require both a period of primary care and subsequent hospitalisation. The cost of treating a case of peptic ulcer in hospital is estimated to be $1,284 for an uncomplicated ulcer, and $4,072 for a complicated ulcer (National Hospital Cost Data Collection 2002-03, see Table 10). Using $1,284, this suggests that for every 1000 patients tested at an incremental cost of $30.60 per patient there will be both gains in illness prevented and health system cost offsets from future cancers and ulcers prevented of at least $19,915 ($7,075 + $12,840), or about $20 per patient presenting with uncomplicated dyspepsia. Note that these estimates of cost offset are only approximate as they do not account for the lower cost of treating non-hospital ulcer cases, the higher costs of treating more complicated ulcers in hospital, or any additional costs pre- and post-hospitalisation. The cost savings from cancers detected are also overstated as the number of early cancers that would have been detected through other means has not been considered.

Discussion

The results presented herein are subject to considerable uncertainty, particularly due to the short horizon of the model and the assumption that best clinical practice in the management of uncomplicated dyspepsia is followed in Australia. The longer-term risks have not been comprehensively modelled and all of the clinical events leading to the potential development of cancer or peptic ulcer disease have not been captured. In addition, for simplicity, we have assumed that all age groups share the same probability of *H. pylori* infection and have identical lifetime prevalence of peptic ulcer disease. Furthermore, the additional risk of gastric cancer in *H. pylori*-positive patients with simple dyspepsia is unknown. Under the assumptions of the model, those falsely diagnosed would eventually be endoscoped and correctly detected within the model horizon. Consequently, any symptomatic ulcers would be detected within 12 months. There may be some short delay in the detection and treatment of peptic ulcer disease, but this is not likely to change health outcomes. The model allows for a loss in quality of life associated with delay in treatment within the year, but this has a very small effect in the overall model outcomes.

The results suggest that the antisecretory strategy is associated with greater morbidity than any other strategies. The distinction between UBT and serology in terms of primary outcomes is small, the only difference between the two strategies being a cost increase of $30.60 against UBT within a one-year horizon. In the longer term, UBT is predicted to offer potential benefits. In addition, testing for *H. pylori* infection using the most accurate test available should result in a more judicious use of *H. pylori* eradication therapy and decrease the inappropriate use of PPIs and antibiotics. The model does not take these potential benefits into account, nor does it include the costs resulting from the inappropriate use of eradication therapy and PPIs, however a simple calculation of the potential savings from gastric cancer and peptic ulcer disease avoided in the future suggests cost offsets of $20 per patient.

The model developed for this assessment is comprehensive and based on the best evidence available. However, there are some limitations of the modelling that make the conclusions subject to some uncertainty. The model is of one year duration and, while the outcome of gastric cancer has been projected beyond one year, the model does not capture the potential longer-term costs of treatment nor the cost of complications arising from inadequate or inappropriate treatment for *H. pylori* ulcers. It is unknown how important these are likely to be in the longer term as it depends on the course of the disease in patients with uncomplicated dyspepsia.

Due to the lack of Australian data on the management of uninvestigated dyspepsia, the model is based on best dyspepsia management in general practice. If current practice deviates significantly from best practice, then the model's projections of costs and outcomes might not be realised.

Diagnostic information from an accurate test such as UBT has some value to both patients and their doctors in terms of reassurance or lessening distress, but this value is not taken into account in the model.

The quality of life values used are crude and do not take into account the disutility of adverse events arising from the treatment or diagnostic procedure, the possibility of complications such as bleeding arising from ulcer recurrence or the experience of treatment failure *per se*. The only difference in terms of health-related quality of life allowed for in the model is the time without symptoms of dyspepsia associated with

either treatment failure and the recurrence of symptoms or in differences in the duration of treatment with antisecretory drugs compared to eradication therapy. Consequently there is very little difference in assumed quality of life of patients between the diagnostic and treatment strategies.

Although included in the model, gastric cancer has been modelled simplistically, based on a conservative estimate of the attributable cancer risk. The model ignores the effect of age on the prevalence of *H. pylori* and the probability of gastric cancer. Moreover, it is assumed that all uncomplicated dyspepsia patients with gastric cancer are diagnosed within a year and that this has no impact on subsequent treatment or outcomes. The detection of gastric cancer in the model therefore has no impact on differences between strategies. The model has also been used to project cancers averted in the future, but it does not take account of future costs or the likelihood of detection independently of the diagnostic test. The rationale for this approach is that the impact of a diagnostic test for *H. pylori* on gastric cancer is not likely to be significant in a population with uncomplicated dyspepsia and without alarm symptoms.

Financial implications for the health system

The total financial cost of subsidising UBT in patients presenting with uncomplicated dyspepsia depends on the number of people who present with that condition, the distribution of patients within the current range of test and treatment strategies, the extent to which UBT is already used by clinicians in this context and the extent to which UBT will substitute for other tests within that set of strategies. The previous section looked at the costs and outcomes of optimal test-and-treat strategies. This section looks at the financial implications of moving from what is done now to what might be clinical practice in the future, irrespective of the optimal strategy.

There are no direct data either on the number of patients who present with uncomplicated dyspepsia or the numbers tested with serology or endoscopy or treated with antisecretory therapy. The annual number of PBS prescriptions for eradication therapy (56,906 in 2004-05) gives an estimate of the number of new cases of *H. pylori* infection treated each year. If the prevalence of *H. pylori* is 36 per cent (Peach et al 1997), then there would be 158,072 tests performed each year. Expert advice from the Advisory Panel suggested that about 75 per cent of patients presenting with uncomplicated dyspepsia are currently prescribed empirical antisecretory therapy and the remaining 25 per cent is investigated for *H. pylori* infection using serology (12.5%) or endoscopy (12.5%). An unknown number may have a UBT. The model suggests that of the 75 per cent who are given antisecretory treatment, 60 per cent will be tested subsequently for *H. pylori* in the same year. This suggests that of the estimated 158,072 tests each year, a further 40 per cent (63,229) presented with symptoms and were treated without an initial or subsequent diagnostic test. The total number of people consulting a GP for uncomplicated dyspepsia is therefore estimated at 221,301.

Forecast 1 in Table 16 estimates the current diagnostic and treatment cost for uncomplicated dyspepsia. This is based on the assumption that 75 per cent of patients are given antisecretory treatment initially while 12.5 per cent are tested with endoscopy and 12.5 per cent with serology. The annual cost is about $237 million. If UBT is introduced as a first line diagnostic test, it is estimated that the proposed management algorithm would cost $222 million per annum, a resulting cost saving of about $15 million (Forecast 1). This saving is projected on the basis that UBT replaces 50 per cent

of current usage of other strategies and is the main test used to investigate non-responders to empirical treatment.

The cost saving is forecasted to increase to approximately $17 million if the use of serology and endoscopy is reduced to five per cent each, and the use of empirical treatment remains unchanged (Forecast 2). In addition, to the extent that a more complete eradication of *H. pylori* would reduce the number of cases of peptic ulcer disease and gastric cancer in the future, there may be some additional treatment cost savings. On the basis of the analysis presented above, at a cost saving from future diseased prevented of at least $20,000 per 1,000 patients tested, there would be additional cost savings of $3 million.

These forecasts may be an underestimate of the number of presentations with uncomplicated dyspepsia. If there are larger numbers currently presenting to GPs and being treated according to the algorithm suggested in the model, then there are even greater potential financial cost savings to be found by moving from an empirical antisecretory treatment to an accurate test-and-treat strategy.

Table 16 Financial cost to the health system of current and projected management algorithms

Forecasts	Relative use (%)	No patients	Unit cost ($)	Total cost ($)
Forecast 1: Current management algorithm				
Antisecretory followed by testing of non-responders (by serology (12.5%) and endoscopy (87.5%))	75.0	165,976	1,074.10	178,274,643
Serology	12.5	27,663	972.50	26,901,916
Endoscopy	12.5	27,663	1,143.10	31,621,163
Total	**100.0**	**221,301**		**236,797,721**
Forecast 2: 50% UBT				
Antisecretory followed by testing of non-responders (by serology (12.5%), UBT (75%) and endoscopy (12.5%)	37.5	82,988	982.50	81,535,628
Serology	6.3	13,831	972.50	13,450,958
Endoscopy	6.3	13,831	1,143.10	15,810,581
UBT	50.0	110,651	1,003.10	110,993,572
Total	**100.0**	**221,301**		**221,790,740**
Cost saving				**15,006,982**
Forecast 3: 15% UBT				
Antisecretory unchanged	75.0	165,976	982.50	163,071,256
Serology	5.0	11,065	972.50	10,760,767
Endoscopy	5.0	11,065	1,143.10	12,648,465
UBT	15.0	33,195	1,003.10	33,298,072
Total	**100.0**	**221,301**		**219,778,559**
Cost saving				**17,019,162**

Conclusions

Safety

The potential risk for patients undergoing C-UBTs for the purposes of diagnosing *H. pylori* infection are minimal due to the non-invasive nature of the procedure.

Reports in the literature outlining potential risks associated with the procedure are lacking, despite numerous studies outlining the relative effectiveness of UBTs. Data from four case series indicated that the procedure is well tolerated by patients and that systemic, gastrointestinal and allergic-type events are extremely rare. To date, there have been no reported adverse events resulting from use of the ^{13}C-UBT. For the ^{14}C-UBT, the patient is exposed to a theoretical trace of radioactivity.

Effectiveness

Studies were identified that reported the diagnostic accuracy and effectiveness (including use of the test in management of patient health outcomes) as a first line test. No studies were identified that report the use of UBT as a second line test. Additionally, it is noted that expert opinion and current guidelines consider the use of UBTs as second line tests as inappropriate for routine use.

Diagnostic accuracy – use of UBTs as first line tests

The diagnostic accuracy of UBT against the reference standard of endoscopy and testing of biopsy samples as a first line diagnostic test was assessed by the critical appraisal of 12 cross-sectional studies. Across the studies, sensitivity ranged from 90 to 100 per cent, specificity from 86 to 100 per cent, and positive and negative likelihood ratios from 6.8 to 66.7 and 0 to 0.1, respectively. The median sensitivity and median specificity were 96 and 98 per cent, respectively. These diagnostic characteristics indicate that UBTs are the most accurate non-invasive tests in diagnosing both the presence and absence of *H. pylori* infection in the settings reported.

Patient outcomes following testing – use of UBTs as first line tests

The health outcomes of participants undergoing the UBT as a first line diagnostic test for *H. pylori* infection and subsequent management in dyspeptic patients compared to endoscopy and subsequent management or empirical treatment was assessed by the critical appraisal of four prospective, RCTs. The primary outcome for all of the included studies was improvement or resolution of dyspepsia symptoms, measured at 6 or 12 months of follow-up. Results suggest improved outcomes for people undergoing the UBT followed by management compared to empirical treatment. Furthermore, the UBT followed by management led to similar outcomes compared to endoscopy and subsequent management.

Cost-effectiveness

The results presented here are based on the best estimates available and are indicative of the likely costs and effectiveness of UBT when used as a first line diagnostic test to diagnose and treat patients with uncomplicated dyspepsia, compared to serology, endoscopy and antisecretory treatment. The results should be interpreted with caution in view of the one-year horizon of the model for dyspepsia treatment, the lack of data on the changes in the quality of life of dyspeptic patients managed by the available strategies, and the uncertainty surrounding the longer term impact of *H. pylori* diagnosis on the costs and outcomes associated with the risk of gastric cancer or peptic ulcer disease. The accuracy of the modelled cost-effectiveness is limited by the quality of the data on the diagnostic accuracy of the tests (discussed in the 'Review of the Literature' section), literature-based estimates of the treatment success and the prevalence of *H. pylori*.

Differences in the quality of life between the strategies are minor as these are determined largely by difference in the number of months patients live with dyspepsia before a correct diagnosis is established or an appropriate treatment is initiated. The magnitude of the differences might change if immediate referral for diagnosis following treatment failure is not routine, if it takes significantly longer to establish a correct diagnosis or if outcomes beyond one year are considered. The economic analysis predicts that the total cost of the UBT test-and-treat strategy is similar to that with serology over one year. Quality of life and dyspepsia-free time over this timeframe are also similar. Empirical therapy is similar in cost to serology, but would lead to more time (4.5 weeks on average) living with dyspepsia. Endoscopy is the most expensive strategy overall, but offers no advantage over serology or UBT in terms of QALYs.

There may be some longer-term impact of the more accurate diagnostic tests for *H. pylori* in reducing the future risk of gastric cancer and peptic ulcer disease. Calculations suggest that each additional true positive result made by UBT compared to serology could result in a potential 0.0074 cancers and 0.25 peptic ulcers being averted in the longer term. Given the low prevalence of gastric cancer in Australia in those with uncomplicated dyspepsia, this is likely to be an overestimate and the difference in cancers detected may not be significant. The savings from the cost of treating the additional cases of peptic ulcer in the future could considerably reduce the cost difference between the two strategies.

The model projections are subject to some uncertainty due to the short horizon of the model (12 months) and the lack of good quality data on the management of uncomplicated dyspepsia in clinical practice. The results of an analysis of the financial implications of substituting UBT into current clinical practice suggest that there may be financial cost savings of more than $15 million per annum.

Recommendation

Carbon-labelled urea breath testing is safe. Effectiveness and cost effectiveness have been demonstrated for use as a first line procedure for the diagnosis of *Helicobacter pylori* infection.

MSAC recommended that public funding should be supported for the use of carbon-labelled urea breath testing as a first line procedure for the diagnoisis of *Helicobacter pylori* infection.

- The Minister for Health and Ageing accepted this recommendation on 8 June 2006. -

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	pathology
Professor Jane Hall	health economics
Professor John Horvath	medical advisor to the Department and Health Minister
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Dr Ray Kirk	health research
Associate Professor Donald Perry-Keene	endocrinology
Dr Ewa Piejko	general practice
Mrs Sheila Rimmer	consumer representative
Ms Samantha Robertson	Medicare Benefits Branch
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory Panel for MSAC application 1085
Carbon labelled urea breath tests

Dr Debra Graves (Chair) MBBS, MHA, FRACMA Chief Executive Officer of the Royal College of Pathologists of Australia Member of the Pathology Consultative Committee Prince of Wales Hospital Surry Hills, NSW	MSAC member
Professor Sydney Bell MD, BS, FRCPA, FAFPHM (RACP) Area Director of Microbiology South East Sydney Area Health Service (SEALS) Randwick, NSW	MSAC member
Dr Scott Beuzeville BMed (Hons), FRACP Visiting Medical Officer South Eastern Sydney Area Health Service (SESAHS) Kogarah, NSW	Nominated by the Australian and New Zealand Association of Physicians in Nuclear Medicine
Professor Robert Conyers BSc (Hons), MB, BS, DPhil, FRCPA, FACB (USA) MRACI, MAACB Medical Director - Australasia The Gribbles Group Ltd Clayton, VIC	Nominated by the Royal College of Pathologists of Australasia
Ms Valerie McKeown Dip Pastoral Ministry, Dip Management (Community Services) AHWCA SANTACPE South Australian Consumer Representatives Network Prospect, SA	Consumers' Health Forum of Australia nominee

A/Professor Peter Katelaris
MB BS (Hons) FRACP, FRCP, MD
Clinical Associate Professor
Consultant gastroenterologist
Co-author: *Digestive Health Foundation National guidelines for clinicians on* Helicobacter pylori
Concord Hospital
University of Sydney
Concord, NSW

Nominated by the Gastroenterological Society of Australia

Appendix C Search strategies

Medline May 2005: Core terms

(These terms were also used for searches in CINAHL and Biological Abstracts)

Number	Search term
1	Helicobacter pylori/
2	(campylobacter adj pylori).mp.
3	(helicobacter adj pylori).mp.
4	(H adj2 pylori).mp.
5	or/1-4 Pylori terms
6	dyspepsia.mp. or DYSPEPSIA/
7	(duodenal adj2 ulcer$).mp.
8	exp Peptic Ulcer/
9	(gastric adj2 ulcer$).mp.
10	Stomach Neoplasms/
11	(gastric adj2 (neoplas$ or cancer$)).mp.
12	or/6-11 Condition terms
13	(carbon adj2 label$ adj2 urea).mp.
14	(Urea adj2 breath$).mp.
15	CUT.mp.
16	exp Carbon Isotopes/
17	Breath Tests/
18	(carbon adj2 breath$).mp.
19	16 and 17
20	(CUBT or UBT).mp.
21	or/13-15,18-20 Intervention terms
22	5 and 21
23	12 and 21
24	22 or 23
25	exp Endoscopy/ or endoscopy.mp.
26	Duodenoscopy/ or duodenoscopy.mp.
27	Gastroscopy/ or gastroscopy.mp.
28	Serology/
29	serolog$.mp.
30	(Hp adj IgG).mp.
31	seropositiv$.mp.
32	((rapid adj urease) and test$).mp.
33	(RUT and urea$).mp.
34	(clotest or (clo adj test)).mp.
35	ProntoDry.mp.

(cont'd)

Number	Search term
36	HpOne.mp.
37	ELISA.mp. or Enzyme-Linked Immunosorbent Assay/
38	Immunoglobulin A/bl, du [Blood, Diagnostic Use]
39	Immunoglobulin G/bl, du [Blood, Diagnostic Use]
40	or/25-39 Comparator terms

Embase May 2005

('dyspepsia'/exp) AND ((campylobacter AND pylori) OR ('helicobacter pylori'/exp) OR (`helicobacter AND pylori) OR ('h *2 pylori') OR (campylobacter AND pylori) OR ('helicobacter pylori'/exp) OR (`helicobacter AND pylori) OR ('h *2 pylori')) AND (neoplas* OR cancer* OR ulcer* OR tumour*) AND ((carbon OR urea) AND breath AND test*) OR (cubt OR ubt))

Australasian Medical Index

(("breath test*") AND (pylori))

Cochrane Library

Number	Search term
#1	"carbon label* urea" in All Fields or "Urea breath*" in All Fields or Carbon and (Isotope* or breath* or urea) in All Fields or "Breath Test*" in All Fields or "CUBT or UBT" in All Fields, from 1800 to 2005 in all products
#2	endoscopy or duodenoscopy or gastroscopy in All Fields or seropositiv* or serolog* or elisa or "Enzyme-Linked Immunosorbent Assay" in All Fields or "rapid urease" or (RUT and urea*) in All Fields or "clotest" or "clo test" or ProntoDry or HpOne in All Fields or "Immunoglobulin A" or "Immunoglobulin G" in All Fields, from 1800 to 2005 in all products
#3	pylori in Record Title, from 1800 to 2005 in all products
#4	((#1 OR #2) AND #3)

Appendix D Internet sites searched

HTA sites

NHS Economic evaluation database
http://www.york.ac.uk/inst/crd/crddatabases.htm [Accessed 7 June 2005]

Health Technology Assessment International (HTAi)
http://www.htai.org/ [Accessed 7 June 2005]

Health Economics, Policy and Medical Outcomes Sources. Databases and Health Economics Web Sites http://www.exit109.com/~zaweb/pjp/econ.htm
[Accessed 7 June 2005]

Health Economics Evaluation Database (HEED), Office of Health Economics
http://dmoz.org/Business/Healthcare/Economics/ [Accessed 7 June 2005]

National Institute for Clinical Excellence (NICE)
http://www.nice.org.uk/Cat.asp?pn=professional&cn=toplevel&ln=en
[Accessed 7 June 2005]

NIH Consensus Statements
http://consensus.nih.gov/cons/094/094_statement.htm [Accessed 7 June 2005]

The National Coordinating Centre for Health Technology Assessment (NCCHTA)
http://www.hta.nhsweb.nhs.uk/ and http://www.hta.nhsweb.nhs.uk/rapidhta
[Accessed 7 June 2005]

International Network of Agencies for Health Technology Assessment (INAHTA)
http://www.inahta.org/ [Accessed 7 June 2005]

Institute for Clinical Systems Improvement (ICSI)
http://www.icsi.org/index.asp [Accessed 7 June 2005]

Health Technology Assessment (HTA) Database
http://www.mrw.interscience.wiley.com/cochrane/cochrane_clhta_articles_fs.html
[Accessed 7 June 2005]

HSTAT : Health Services/Technology Assessment Text
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat [Accessed 7 June 2005]

EUROSCAN: The European Information Network on New and Changing Health Technologies
http://www.mrw.interscience.wiley.com/cochrane/cochrane_clhta_articles_fs.html
[Accessed 7 June 2005]

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
http://www.ccohta.ca/ [Accessed 7 June 2005]

Clinical trial sites

CentreWatch clinical trials listing service http://www.centerwatch.com/ [Accessed 7 June 2005]

ClinicalTrials.com http://www.clinicaltrials.com/ [Accessed 7 June 2005]

ClinicalTrials.gov http://www.clinicaltrials.gov/ [Accessed 7 June 2005]

Current Controlled Trials http://www.controlled-trials.com/ [Accessed 7 June 2005]

European Helicobacter Study Group http://www.helicobacter.org/ [Accessed 7 June 2005]

NHMRC Clinical Trials Centre http://www.ctc.usyd.edu.au/trials/registry/registry.htm [Accessed 7 June 2005]

Society for Clinical Trials http://www.sctweb.org/ [Accessed 7 June 2005]

TrialsCentral http://www.trialscentral.org/ [Accessed 7 June 2005]

UK The National Research Register http://www.update-software.com/national/ [Accessed 7 June 2005]

RehabTrials. http://www.rehabtrials.org/index.html [Accessed 7 June 2005]

Appendix E Studies included in this review

Diagnostic accuracy

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Savarino, V., Mela, G.S., Zentilin, P., Bisso, G., Pivari, M., Mansi, C., Mele, M.R., Bilardi, C., Vigneri, S. & Celle, G. 1999. 'Comparison of isotope ratio mass spectrometry and nondispersive isotope-selective infrared spectroscopy for 13C-urea breath test. [see comment]', *American Journal of Gastroenterology*, 94 (5), 1203–1208.

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Appendix F Studies excluded from critical appraisal

Diagnostic accuracy

Incorrect population

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Appendix G Diagnostic accuracy

Table G1 Descriptive characteristics of included studies

Study	Study design	Location	Enrolment period	Study population		
				Sample size	Age (years)	Male/female
Cave et al (1999)	Cross-sectional	USA	Not reported	Phase 1: 444 enrolled 331 analysed Phase 2: 160 enrolled 141 analysed	Mean: Phase 1: 48 Phase 2: 50 Range: 18–75	Phase 1: 142/189 Phase 2: 65/76
Dill et al (1990)	Cross-sectional	UK	Not reported	69 (134 tests)	Range: 18–70	35/34
Gatta et al (2003a)	Cross-sectional	Italy	Jan 2001–Dec 2001	119	Mean: 46.6 Range: 22–73	63/56
Gatta et al (2003b)	Cross-sectional	Italy	Dec 2000–Aug 2001	200	Mean: 53 SD: 15	87/113
Ng et al (2002)	Cross-sectional	Hong Kong	Not reported	Total: 234 Study 1: 134 enrolled 123 analysed Study 2: 100 enrolled 90 analysed	Study 1: Mean: 46 SD: 15 Study 2: Mean: 61 SD: 16	1: 45/78 2: 52/38
Peng et al (2000)	Cross-sectional	Taiwan	Mar 1997–Dec 1998	136	Range: 17–76	66/70
Rauws et al (1989)	Cross-sectional	The Netherlands	Not reported	129	Not reported	Not reported
Savarino et al (1999)	Cross-sectional	Italy	Not reported	143 enrolled 134 analysed	Mean: 54 SD: 13	69/65
Savarino et al (2000)	Cross-sectional	Italy	Dec 1997–Dec 1998	354	Mean: 51	207/147
Sheu et al (2000)	Cross-sectional	Taiwan	Jul 1996–Jun 1998	441	Not reported for all	Not reported for all
Van der Hulst et al (1999)	Cross-sectional	Italy	Not reported	Part 1: 604 enrolled 544 evaluated Part 2: 272 enrolled 257 evaluated	Median: 47 Range: 18–75	Part 1: 292/252 Part 2: 130/127
Wong et al (2000)	Cross-sectional	Hong Kong	Not reported	230 (202 evaluated)	Mean: 49 Range: 18–80	90/112

Abbreviations: SD, standard deviation

Table G2 Participant selection criteria of included studies

Study	Selection criteria	
	Inclusion	Exclusion
Cave et al (1999)	Dyspeptic patients scheduled for EGD	Use of antibiotics or PPI within previous 4 weeks, bismuth within 2 weeks, therapeutic (>100 mg/day) doses of aspirin or NSAIDS; pregnant or nursing; active GI bleeding; previous gastric resections
Dill et al (1990)	Outpatients aged 18–70 years referred for routine endoscopy with ulcer-like symptoms: Epigastric pain related to food, relieved by milk or antacids; no ulcer on endoscopy	Endoscopically visible organic lesion of upper GI tract (eg, gastric or duodenal ulcer, cancer, macroscopic gastritis, duodenitis, oesophagitis), ingested drugs other than antacids in previous two weeks; debilitating disease, previous gastric surgery, renal insufficiency, pregnant or breastfeeding, or unable to cooperate
Gatta et al (2003a)	With dyspepsia (pain or discomfort in the upper abdomen of duration at least two months), aged 18 years or older	Use of antibiotics, bismuth preparations, or antisecretory drugs (H_2 antagonists or PPIs) for four weeks prior to endoscopy; pregnant or nursing; previously investigated or treated for *H. pylori* infection
Gatta et al (2003b)	Dyspeptic patients (pain or discomfort in the upper abdomen, with symptoms for at least two months)	Use of antibiotics, bismuth preparations, or antisecretory drugs (H_2 antagonists or PPIs) for four weeks prior to endoscopy; previously investigated or treated for *H. pylori* infection
Ng et al (2002)	Dyspepsia (persistent or recurrent upper abdominal pain or discomfort over the preceding 3-month period)	Previous gastric surgery; previous *H. pylori* eradication therapy; use of antibiotics, H_2-receptor antagonists, bismuth or PPIs within previous 4 weeks
Peng et al (2000)	Clinical (history of symptoms for at least one month, with a symptom score of 3 or more on a symptom scale of 0–10) and endoscopic diagnosis of non-ulcer dyspepsia	Use of NSAIDs, PPIs or antibiotics in previous month; serious medical illness; previous use of anti-*H. pylori* therapy; associated pancreatic biliary tract disease or GI malignancy; reflux symptoms
Rauws et al (1989)	Non-ulcer dyspepsia (epigastric discomfort following meals, feeling of fullness, belching, bloating, and/or abdominal distension), normal physical examination, routine blood chemistry, abdominal ultrasound, upper endoscopy	Use of any medication other than antacids during previous 4 weeks, previous gastric surgery, malignancy
Savarino et al (1999)	Dyspepsia (unexplained epigastric pain or abdominal discomfort centred in the upper abdomen for at least two months)	Recent GI bleeding, history of gastric surgery, use of antibiotics, bismuth, or antisecretory drugs (H_2 antagonists and PPIs) for four weeks prior
Savarino et al (2000)	Dyspepsia (unexplained epigastric pain or abdominal discomfort centred in the upper abdomen for at least two months)	Use of antibiotics, bismuth, or antisecretory drugs (H_2 antagonists and PPIs) for four weeks prior; regular users or use within preceding 7 days of NSAIDS or aspirin; pregnant or breastfeeding; active gastric or duodenal bleeding; previous gastric surgery
Sheu et al (2000)	Dyspeptic symptoms (no further clarification reported)	Use of bismuth, PPIs, antibiotics in previous 8 weeks; allergy to penicillin; previous GI surgery; history of anti-*H. pylori* therapy and malignancy
Van der Hulst et al (1999)	Dyspeptic patients aged between 18 and 75 years, referred for diagnostic upper GI endoscopy	Use of antibiotics or PPIs in previous 4 weeks, use if bismuth in previous 2 weeks, use of NSAIDs or aspirin in previous week; pregnant or breastfeeding; active GI bleeding; previous gastric surgery
Wong et al (2000)	Dyspepsia defined as persistent or recurrent upper abdominal pain or discomfort for preceding three months; patients referred for endoscopy	Previous gastric surgery or *H. pylori* eradication therapy; use of antibiotics, H_2 receptor antagonists, bismuth compounds of PPIs in preceding 4 weeks

Abbreviations: EGD, esopho-gastro-duodenoscopy; GI, gastrointestinal; NSAIDs, non-steroidal antiinflammatory agents; PPIs, proton pump inhibitors

Table G3 Description of UBT and reference test

Study	UBT	Reference
Cave et al (1999)	Laser assisted ratio analyser (LARA) to measure the ratio of $^{13}CO_{2:}{}^{12}CO_2$ in the UBT, 100 mg of ^{13}C-urea ingested in solution, breath samples collected 30 and 60 min later. Positive breath test defined as either the 30 or 60 min value for $^{13}CO_2$ and the baseline exceeding the cut-off value Phase 1: $^{13}CO_2$ cut-off exceeded $\Delta 7.8 \pm 0.8$ Phase 2: $^{13}CO_2$ exceeded $\Delta 6.1 \pm 0.6$	Biopsy following EGD; 2 biopsies each from gastric antrum and body obtained; histology on 2 biopsies; culture on 1 biopsy; rapid urease test (CLO) on 1 biopsy. Reference defined as positive if: - any 2 of culture, CLO or histology were positive or --- CLO was positive Reference defined as negative if all three were negative
Dill et al (1990)	$^{13}CO_2$ UBT, 250 mg labelled urea solution, test performed within 5 days of endoscopy (prior to treatment), and within 3 days following 4 weeks treatment (with bismuth in form of tripotassium dicitratobismuthate) Positive UBT: 3% or more $^{13}CO_2$ of dose recovered 2 h after dose	*H. pylori* culture of antral biopsy obtained at endoscopy to confirm *H. pylori* infection status, ie, positive if culture positive, negative if culture negative (pre- and post-treatment). Positive culture defined if any typically spiral Gram-negative organisms present
Gatta et al (2003a)	^{14}C-urea, administered in a gelatin capsule, with 30 mL water, followed by 30 mL water 3 min later; breath samples (through a straw) taken at baseline and 5, 10, 12.5, 15 min after ingestion; radioactivity calculated (dpm) Positive test: ratio (R) of dpm at sample to dpm at baseline of 3 or more. Test given prior to treatment and 4–6 weeks following eradication therapy (1-week triple regimen with clarithomycin 500 mg b.i.d., amoxycillin 1 g b.i.d, PPI b.i.d.) in infected patients	Endoscopy (one day before UBT) plus 6 biopsy samples: 2 from the antrum and 2 from the corpus for histology, 1 from antrum for culture, 1 from antrum for rapid urease test (pre- and post-treatment). Participants classified as infected with *H. pylori* if culture positive, or rapid urease test plus histology positive for *H. pylori*. All other participants classified as negative for *H. pylori*
Gatta et al (2003b)	^{13}C-UBTs: all participants had 3 UBTs - 50mg-tablet on first day after endoscopy, 100 mg tablet n third day after endoscopy, and conventional 75 mg tablet on fifth day after endoscopy. All 3 tests given prior at baseline and 4-6 weeks following 1-week triple therapy (omezprazole 10 mg twice daily, amoxycillin 1 g twice daily, clarithromycin 500 mg twice daily) in infected patients. Positive test defined as: for 75 mg ^{13}C-UBT >5% $^{13}CO_2$ difference over baseline (DOB), for 100 mg ^{13}C-UBT >1.5% $^{13}CO_2$ DOB, (obtained best cut-off for 50 mg ^{13}C-UBT using receiver-operating curve [ROC] analysis)	Endoscopy plus 6 biopsy samples: 2 from the antrum and 2 from the corpus for histology, 1 from antrum for culture, 1 from antrum for rapid urease test (pre- and post-treatment). Classified as infected with *H. pylori* if rapid urease test and histology were positive, and/or culture of gastric biopsy specimens was positive. All other participants classified as negative for *H. pylori*
Ng et al (2002)	^{13}C-UBT: 75 mg labelled urea, sample at baseline and 30 min after ingestion. Two study sites, 3 testing regimens: 1: Prior fasting (4 h or more) and citric acid test meal 2: Non-fasting and citric acid test meal 3: Non-fasting without test meal Study 1: Testing regimens 1 and 2 on all participants Study 2: Testing regimens 1 and 3 on all participants. Breath test results expressed as delta over baseline (DOB), diagnostic characteristics plotted against various DOBs and best cut-offs for each testing regimen obtained using ROC curves. Cut-offs used: group 1: 5.0‰, group 2: 5.5‰, group 3: 3.5‰	Endoscopy followed by 2 antral and 1 corpus biopsy, 1 antral biopsy used for rapid urease test, rest for histology. *H. pylori* infection defined as both rapid urease test and histology positive, absence of *H. pylori* if both tests negative, equivocal results excluded
Peng et al (2000)	^{13}C-UBT: 100 mg labelled urea in water after milk to delay gastric emptying, breath samples at baseline and 15 min after ingestion of ^{13}C-urea. $^{13}CO_2$ in breath analysed by isotope ratio mass spectrometer (IRMS). Values expressed as excess (15 min – baseline) $\delta^{13}CO_2$‰ excretion. Cut-off for positive test calculated as mean+ 3SD excess $^{13}CO_2$ value in participants with negative biopsy-based tests (CLO, culture, histology), and was >4.8‰	Endoscopy plus 4 biopsy specimens from near the pylorus, 2 specimens were for histology, 1 for the rapid urease test (CLO), and 1 for culture. Reference standard: *H. pylori* infection was confirmed if culture was positive, or both histology and CLO were positive for the organism (unclear how non-infected classified)

Table G3 (cont'd) Description of UBT and reference test

Study	UBT	Reference
Rauws et al (1989)	^{14}C-UBT: 3 µCi ^{14}C-labelled urea mixed with 350 mg ^{12}C-urea after a test meal, breath samples collected at 10-min intervals for 90 min, results reported as [% dose ^{14}C/mmol expired CO_2] body weight (kg). ROC analysis revealed optimal cut-off for positive test of >0.07% at 40 min	Endoscopy plus biopsy (2 antral mucosal biopsy specimens) and culture to confirm *H. pylori* status. Participants classified as infected with *H. pylori* if culture was positive, and not infected if culture was negative
Savarino et al (1999)	^{13}C-UBT: 75 mg ^{13}C-urea in citric acid, breath samples at baseline, 15 min and 30 min after ingestion, analysed by 2 IRMS machines (ABCA and Breath Mat), and a non-dispersive isotope-selective infrared spectroscope. DOB >5/mL indicated a positive test	Endoscopy plus biopsy of antrum and gastric body, followed by histology and rapid urease test (CLO). *H. pylori* infection status: Positive if both histology and CLO positive, negative if both tests negative. Participants with divergent test results (n=9) were excluded
Savarino et al (2000)	^{13}C-UBT: 100 mg ^{13}C-urea in test meal or 75 mg ^{13}C-urea in citric acid (participants randomly assigned in 2:1 ratio); breath samples collected at 30 and 60 min for two breath analyser mass spectrometer machines simultaneously – the traditional and more expensive IRMS and the newer and less expensive LARA. ROC analysis: Optimal cut-off $^{13}CO_2$:$^{12}CO_2$ ratio from baseline to 30 min and 60 min, δ values >5‰ were defined as positive for *H. pylori*	Endoscopy plus biopsy of antrum and gastric body, followed by histology and rapid urease test (CLO). *H. pylori* infection status: Positive if both histology and CLO positive, negative if both tests negative. Unclear if participants with equivocal results were excluded
Sheu et al (2000)	^{13}C-UBT: 100 mg ^{13}C-urea preceded by overnight fasting and a fatty test meal, breath samples at baseline and 15 min after ingestion of ^{13}C-urea. Ratio of $^{13}CO_2/^{12}CO_2$ ($\delta^{13}CO_2$/mL) analysed by an isotope mass spectrometer. Value of Δ15 (15 min sample minus baseline sample) recorded as excess $\delta^{13}CO_2$/mL (ECR) of UBT. Several cut-off ECR values reported and ECR that produced optimal accuracy selected in study	Endoscopy and 6 biopsies: 2 from gastricardia; 2 from lower body; 2 from antrum, 1 each for culture and histology. *H. pylori* infection confirmed by either positive culture or histology. Unclear how non-infected participants defined
Van der Hulst et al (1999)	LARA-UBT, 100 mg ^{13}C-urea preceded by a nutrient-dense test meal; breath samples at baseline, 30 and 60 min. Ratio of $^{13}CO_2/^{12}CO_2$ measured in ROC to determine optimal cut-off for positive test (post-hoc:positive test defined as >7.5±0.8 delta units). Part 1: Desiccant used in breath collectors to remove water Part 2: Cold-trap in breath collectors to remove water	Endoscopy and 4 biopsies of antrum and corpus for histology and culture. *H. pylori* infection was present if either histology or culture was positive, absent if both were negative
Wong et al (2000)	^{13}C-UBT: 75 mg ^{13}C-urea, with (Group 1) or without (Group 2) a citric acid test meal; breath samples at baseline, 15, 30 min and 45, 60 min in some patients. Results: DOB at various cut-offs using ROC curves to determine optimal DOB cut-off for positive test result at different sample times	Endoscopy, then 3 antral and 2 corpus biopsies, 1 antral used for CLO test, 1 for histology. *H. pylori* present if both CLO and histology were positive, absent if both negative. Equivocal results excluded

Abbreviations: DOB, delta over baseline; EGD, esophogastroduodenoscopy; IRMS, isotope ratio mass spectrometer; LARA, laser optogalvanic effect spectroscopy; ROC, receiver-operating curve

Table G4 Validity of included studies

Study	Appropriate spectrum of consecutive participants	Prospective selection of participants	Appropriate reference standard used	All (or random selection) received verification with reference	Same reference to verify positive or negative UBT results	Masked assessment of UBT and reference tests results	Uninterpretable/ indeterminate test results	Withdrawals	UBT interpreted independently of clinical information	Reference test measured prior to any interventions
Cave et al (1999)	Yes	Yes	Yes	Yes	Yes	Not reported	Phase 1: 95/444[a] Phase 2: 16/160 [a]	Phase 1: 18/444 Phase 2: 3/160	Not reported	Yes
Dill et al (1990)	Yes	Endoscopy to aid selection	Yes	Yes	Yes	Not reported	None reported	4/69 (%)	Not reported	Yes[b]
Gatta et al (2003a)[c]	Yes; but unclear if high-risk included	Yes	Yes	Yes	Yes	Not reported	2/119 pre-treatment 3/119 post-treatment	13/119	Yes	Yes (for pre-treatment results)
Gatta et al (2003b)[c]	Yes; but unclear if high-risk included	Yes	Yes	Yes	Yes	Yes	None reported	None reported	Yes	Yes
Ng et al (2002)	Not reported if consecutive	Yes	Yes	Yes	Yes	Not reported	None reported	21/234 (8.9%)[d]	Not reported	Not reported but likely
Peng et al (2000)	Yes	Endoscopy to select NUD	Yes	Yes	Yes	Yes	None reported	None reported	Yes	Yes
Savarino et al (2000)	Yes	Yes	Yes	Yes	Yes	Yes	45/354 excluded[a]	None reported	Yes	Yes
Savarino et al (1999)	Yes	Yes	Yes	Yes	Yes	Yes	9 excluded (ref)	None reported	Yes	Yes
Sheu et al (2000)[c]	Not reported if consecutive	Yes	Yes	Yes	Yes	Not reported	None reported	41 (9.5%)	Not reported	Yes
Van der Hulst et al (1999)	Yes	Yes	Yes	Yes	Yes	Not reported	Part 1: 47/604 (7.8%) Part 2: 14/272 (5%)[a]	Part 1: 13/604 (2%) Part 2: 1/272 (0.4%)	Not reported	Not reported, but likely
Wong et al (2000)	Yes	Yes	Yes	Yes	Yes	Not reported	10/232 (4%)	18/232 (7.8%)	Not reported	Not reported

[a] Uninterpretable/indeterminate test results are those that cannot be defined as either positive or negative; unable to process as CO_2 too low to measure
[b] Part of the study was to measure accuracy of UBT following treatment to determine the optimal washout period before testing
[c] Validity for pre-treatment part of study (authors also report follow-up testing on *H. pylori* positive patients after treatment)
[d] Excluded, indeterminate reference result

Table G5 Diagnostic characteristics of UBT

Study	UBT cut-off for positivity	Reference	Diagnostic characteristics				
			Study group (n)[a]	Sensitivity	Specificity	LR+	LR–
Cave et al (1999)	Phase 1: Δ7.8	2/3: culture, CLO, histology	Phase 1 (331)	94.7[b]	86.4	6.8	0.06
	Phase 2: Δ6.1		Phase 2 (141)	96.8	98.6	69.1	0.03
	Phase 1: Δ7.8	CLO	Phase 1 (331)	91.0	86.0	6.5	0.10
	Phase 2: Δ6.1		Phase 2 (141	96.8	98.6	69.1	0.03
Dill et al (1990)	3%	Culture	(134[c])	90.0	98.7	66.6	0.10
Gatta et al (2003a)	R[d] of 3 or more	Culture/ histology	(117 pre-treatment)[e]	95.9[b,f]	97.7	41.7	0.04
Gatta et al (2003b)	75 mg: >5% DOB[g]	Culture/ histology	75 mg ^{13}C-urea	100.0	100.0	-	-
	100 mg: >1.5%		100 mg ^{13}C-urea (200 pre-treatment)[e]	100.0	98.9	87.0	0.00
Ng et al (2002)[h]	Group 1: 5.0‰	RUT + histology	Group 1 (213)	95.8[b]	97.4	36.9	0.04
	Group 2: 5.5‰		Group 2 (123)	95.2	95.0	19.0	0.05
	Group 3: 3.5‰		Group 3 (90)	93.9	96.5	26.8	0.06
Peng et al (2000)	δ $^{13}CO_2$ >4.8‰	Culture, or CLO+ histology	136	93.8	89.1	8.6	0.07
Rauws et al (1989)	0.07% $^{14}CO_2/CO_2$	Culture	129	94.7	98.1	50.2	0.05
Savarino et al (1999)	DOB: 5/mL	CLO + histology	IRMS 1	98.6	98.3	58.0	0.01
			IRMS 2	100.0	100.0	-	0.00
			IRIS (Total: 134)	97.3	95.0	19.5	0.03
Savarino et al (2000)	δ value >5‰	CLO test + histology	LARA 100 mg[i] (201[j])	95.7	97.6	39.9	0.04
			IRMS 100 mg (209)	98.9	97.7	42.8	0.02
			LARA 75 mg (97)	98.2	97.7	42.7	0.02
			IRMS 75 mg (95)	98.3	97.9	46.8	0.02
Sheu et al (2000)	ECR: 4.0[k]	Histology or culture	(441 pre-treatment)	97.5[b]	96.7	29.6	0.03
Van der Hulst et al (1999)	>7.5±0.8 delta units	Histology or culture	Part 1 (544)	95.0	94.0	16.6	0.06
			Part 2 (257[l])	93.0	96.0	8.6	0.07
Wong et al (2000)	Optimal DOB 5%, at 30 min[m]	Histology and CLO	With test meal	96.5[b]	97.7	42.0	0.04
			Without test meal	94.7	97.7	41.0	0.05

[a] Number of participants in calculation of accuracy; [b] Sensitivities, specificities as reported in study (raw data could not be extracted, thus calculations could not be independently verified); [c] Data pooled for before and after bismuth treatment; authors reported sensitivity and specificity before treatment as 97% and 100%, respectively; [d] R=ratio of dpm (disintegrations per minute) at sample time to dpm at baseline; [e] Follow-up testing on *H. pylori* positive participants to assess accuracy of UBT on treatment outcome also reported; [f] Values reported at sample taken 12.5 min after ingestion of urea as this is the most accurate, ie optimal LR (study also reports values at 5, 10, 15 min); [g] DOB, difference over baseline. 50 mg ^{13}C-UBT also tested. Cut-off for positive test not predefined, but best cut-off determined as part of study; [h] Note: data extracted from table in paper, paper reports different results in text. Group 1: prior fasting + citric acid test meal, group 2: no prior fasting + test meal, group 3: no prior fasting, no test meal; cut-offs determined during study, results reported for cut-off that produced the highest accuracy in each group; [i] Results reported for pre-treatment, 30 min breath sample; study also reports for 60 min, and post-treatment testing; [j] Study reports 23 tested with 100 mg and 117 with 75 mg; sample in table calculated from accuracy data in Table 1 of study; [k] Results reported for pre-treatment testing, using cut-off that gave best accuracy (range of cut-offs reported in study); study also reported post-treatment testing; [l] Independent calculation of diagnostic characteristics reveals n=514 participants in Part 1, n=248 in Part 2; [m] Results also reported for several other cut-off values and sampling times

Appendix H Patient outcomes

Table H1 Descriptive characteristics of randomised controlled trials

Study	Location	Enrolment period	Follow-up	Study population		
				n	Number of males (%)	Mean age (range) in years
Cuddihy et al (2005)	Rochester, USA	1 year	6 weeks and 6 months	43	14 (33%)	Intervention group: 52 (20–80) Comparator groups: i) 52 (26–78) ii) 53 (25–71) iii) 53 (27–82)
Lassen et al (2000)	Odense, Denmark	Two x one-month periods	1 month, 12 months[a]	500	230 (46%)	Median: Intervention group: 44 (18–88) Comparator group: 47 (19–84)
McColl et al (2002)	Glasgow, UK	2 years	12 months	708	377 (53%)	36 (17–57)
Manes et al (2003)	Naples, Italy	2 years	1, 6, 12 months	219	120 (57%)	Intervention group: 38.9 (18–44) Comparator group: 38 (19–45)

[a] Lassen et al (2004) report further follow-up at median 6.7 years for a small group of participants. However, as some of these were from Lassen et al (2000), the study by Lassen et al (2004) was excluded from critical appraisal

Table H2 Description of the intervention and comparator/s of randomised controlled trials

Study	Intervention	Comparator(s)
Cuddihy et al (2005)	UBT followed by management as determined by the physician	• empirical treatment for dyspepsia as determined by the primary physician • *H. pylori* serology test • EGD
Lassen et al (2000)	UBT followed by management *H. pylori*+ lansoprazole, metronidazole and amoxycillin for two weeks (patients offered endoscopy if symptoms had not improved within a month or if symptoms recurred during follow-up period *H. pylori*- patients who had used NSAIDs (including aspirin) during previous month were examined by endoscopy *H. pylori*- patients not using NSAIDs who had reflux systems were treated with lansoprazole for one month and treatment was continued on demand if this was successful. If unsuccessful, these patients were examined by endoscopy *H. pylori*- patients not using NSAIDs and without reflux symptoms were managed with reassurance and given advice on lifestyle modifications	Endoscopy + treatment in accordance with endoscopic findings (all patients asked to discontinue NSAIDs) • duodenal ulcers – eradication treatment followed by two weeks lansoprazole • gastric ulcers – treated according to *H. pylori* status with either eradication treatment followed by 4 or 6 weeks lansoprazole, or with lansoprazole alone. Gastric ulcers were biopsied every 6 weeks until healed • reflux oesophagitis – 8 weeks lansoprazole then treated with lansoprazole on demand Patients with normal findings or insignificant lesions were diagnosed as having functional dyspepsia and were managed with reassurance and given advice on lifestyle modifications. Certain patients with a known symptomatic effect of acid inhibition were treated with lansoprazole on demand
McColl et al (2002)	UBT *H. pylori*+ 7-day course of eradication treatment (omeprazole, clarithromycin and amoxycillin). Patients allergic to amoxycillin were given metronidazole instead All patients told to see their GP for further treatment if their symptoms persisted	Endoscopy + UBT *H. pylori*+ 7-day course of eradication treatment (omeprazole, clarithromycin and amoxycillin). Patients allergic to amoxycillin were given metronidazole instead All patients told to see their GP for further treatment if their symptoms persisted
Manes et al (2003)	UBT followed by management *H. pylori*+ 1 week triple eradication treatment (omeprazole, clarithromycin and tinidazole). Repeat treatment if still testing positive 4 weeks later. Endoscopy offered if symptoms did not improve *H. pylori*- 4 weeks omeprazole	Empirical treatment (omeprazole) 4 weeks. Patients offered endoscopy if symptoms had not improved

Table H3 Selection criteria for randomised controlled trials

Study	Inclusion	Exclusion
Cuddihy et al (2005)	Patients over age 18 who met 'Rome' criteria for dyspepsia[a]	Investigation or treatment for dyspepsia within the past year, history of radiographically or endoscopically documented peptic ulcer within 5 years, prior attempt to eradicate *H. pylori* infection, alarm symptoms suggestive of malignancy (eg new dyspepsia over age 60, bleeding, weight loss, anorexia), classic GERD symptoms (postprandial substernal burning, nocturnal or postprandial regurgitation of food), irritable bowel syndrome (IBS) symptoms using the 'Rome' criteria for IBS[b], significant intra-abdominal disease, surgery, radiation or history of and medical disorder which could explain symptoms of dyspepsia, such as IBS, chronic pancreatitis, atherosclerosis or vasculitis affecting the splanchnic vasculature, malignancy, cirrhosis, end-stage renal disease, musculoskeletal disorders or neurogenic sources of pain
Lassen et al (2000)	Dyspeptic symptoms (pain or discomfort in the epigastrium with or without heartburn, regurgitation, nausea, vomiting, or bloating) for at least 2 weeks	Age <18, treatment with ulcer-healing drugs (except antacids) in the past month, any sign or suspicion of upper GI bleeding, anaemia, jaundice, unintended weight loss >3 kg, any contraindication to endoscopy, previous upper GI surgery, pregnancy, serious or terminal disorders, or suspected lack of co-operation. Patients were withdrawn from study once enrolled if endoscopy revealed malignancy, or if they became pregnant, developed a terminal illness or if unintended weight loss >3kg ensued
McColl et al (2002)	Upper GI symptoms, age <55	Sinister symptoms (dysphagia, recent weight loss >3 kg, vomiting, first degree relative with upper GI malignancy, recent upper GI bleeding, history of gastric surgery), age >55, use of NSAIDs (excluding low dose aspirin)
Manes et al (2003)	Young adults (18-45 years of age) with uninvestigated upper abdominal symptoms	age<18, alarm symptoms, symptoms of GERD, regular use of NSAIDs, previous upper GI surgery, pregnancy, and treatment with antibiotics, PPI or H_2 antagonists in the previous 4 weeks

Abbreviations: GERD, gastroesophageal reflux disease

[a] Talley et al (1991) symptoms of upper abdominal pain, nausea, vomiting or a feeling of fullness after eating to have been present for greater than 4 weeks, at least 25% of the time and greater than mild in severity

[b] Thompson et al (1989)

Table H4 Validity of randomised controlled trials

Study	Method of randomisation	Concealment of allocation	Blinding	Intention to treat analysis	Losses to follow-up	Outcome measures
Cuddihy et al (2005)	Computer-generated randomisation scheme	Yes, by an independent pharmacy unit	Participants: Not blinded Investigators: Not blinded Outcome assessors: Not reported	Yes	No losses to follow-up	Symptom severity assessed using the modified bowel disease questionnaire (mBDQ)[a], dyspepsia-specific health-related quality of life (HR-QOL)[b], SF-36[c] quality of life assessment, symptoms checklist (SCL-90)[d], somatic symptoms checklist (SSC)[e], use of medical resources
Lassen et al (2000)	Tables of random numbers	Sealed numbered envelopes	Participants: Not blinded Investigators: Not blinded Outcome assessors: Unclear	No	1-month follow-up: Intervention: n=5 Comparator: n=11 12-month follow-up: Intervention: n=22 Comparator: n=15	At 1-month and 12-months follow-up: GSRS[f], PGWB index[g] for quality of life assessment, patient satisfaction, subsequent use of medical resources
McColl et al (2002)	Tables of random numbers	Yes, pharmacy department carried out randomisation, sealed envelope opened by investigator to assign patients to groups	Participants: Not blinded Investigators: Not blinded Outcome assessors: Unclear	Provided figures to permit ITT analysis	Intervention: n=62 Comparator: n=60	Glasgow dyspepsia severity score[h], SF-36 quality of life assessment, subsequent use of medical resources
Manes et al (2003)	Not reported	Not reported	Unclear. Investigator used for follow-up was blinded to group assignment	Follow-up selective for patients reporting improved symptoms after four weeks	All patients identified for follow-up were successfully re-assessed	Dyspepsia severity score (at 1, 6 and 12 months), use of medical resources

[a] Talley et al (1989, 1990)
[b] Shaw et al (1998)
[c] 36-item medical outcomes study short form health survey (Garratt et al 1993)
[d] Derogatis et al (1976)
[e] Attansio et al (1984)
[f] Gastrointestinal symptoms rating scale (Svedlund et al 1988)
[g] The Psychological General Well-Being Index (Dupuy 1984)
[h] El-Omar et al (1996)

Table H5 Results of randomised controlled trials

Study	Length of follow-up (months)	Intervention (I)	Comparator (C)	Outcomes
Cuddihy et al (2005)	6	UBT	i) empirical treatment ii) serology test iii) EGD	SSC[a]: I=0.78 (95% CI: 0.62, 0.94), Ci)=0.68 (95% CI: 0.50, 0.87), Ciii)=0.60 (95% CI: 0.45, 0.75) SF36[b]: (Physical) I=44.0 (95% CI 37.5, 50.5), Ci)=46.1 (95% CI 39.2, 53.0), Ciii)=44.6 (95% CI 38.9, 50.3) (Mental) I=51.0 (95% CI: 46.6, 55.4), Ci)=55.5 (95% CI: 50.9, 60.1) Ciii)=54.4 (95% CI: 50.7, 58.2) Dyspepsia-specific HR-QOL[c]: I=0.38 (95% CI: 0.01, 0.75), Ci)=-0.24 (95% CI: –0.64, 0.17) Ciii)=–0.09 (95% CI –0.42, 0.24) Use of medical resources: Over the counter medication I=55% (95% CI: 0.23, 0.83), Ci)=64% (95% CI: 0.31, 0.89) Ciii)=69% (95% CI: 0.39, 0.91) Prescription medication I=31% (95% CI: 0.09, 0.61), Ci)=9% (95% CI: 0.00, 0.41) Ciii)=31% (95% CI: 0.09, 0.61)
Lassen et al (2000)	1, 12	UBT + management	Endoscopy + management	GSRS[d]: At 1 year, the intervention group had a median score of 1.7 (IQR 1.3–2.2) versus the comparator group 1.7 (IQR 1.3–2.1) (P=0.51) After 1 year, the intervention group reported no symptoms for 50/223 (22%) patients versus 55/224 (25%) of the comparator group (P=0.66) PGWB index[e]: After 1 year, the intervention group had a median score of 108 (IQR 98–117) versus the comparator group score 110 (IQR 99–117) (P=0.38) Patient satisfaction: At 1 year, the number of patients very satisfied was I=124/223 (56%), C=139/224 (62%). The proportion satisfied was I=72/223 (32%), C=77/224 (34%). The proportion dissatisfied was I=27/223 (12%), C=8/224 (4%) Subsequent use of medical resources: Mean endoscopies per person: I= 0.5, C=1.25 (95% CI for difference: –0.88, –0.62, P<0.0001) Mean eradication therapies: I=0.26, C=0.17 (95% CI for difference: 0.02, 0.17, P=0.009) Mean visits to GP (dyspepsia-related): I= 0.98, C=0.66 (95% CI for difference: –0.02, –0.65, P=0.41) Mean visits to outpatients clinics (dyspepsia-related): I= 0.08, C=0.09 (95% CI for difference: –0.09, –0.08, P=0.65) NOTE: 2/250 (1%) endoscopy patients in the comparator group had gastric cancer

(cont'd)

Table H5 (cont'd) Results of randomised controlled trials

Study	Length of follow-up (months)	Intervention (I)	Comparator (C)	Outcomes
McColl et al (2002)	12	UBT (*H. pylori* + treated)	Endoscopy + UBT (*H. pylori* + treated)	Glasgow dyspepsia score[f]: Mean change in score from baseline: I=4.6, C=4.8 (95% CI for difference: –0.7, 0.5, P=0.69) Mean score after 12 months: I=5.6 (SD 3.4; range 0-15), C=5.4 (SD 3.4; range 0–15) Complete resolution of dyspepsia (score<2): I=33/293 (11%) , C=42/291 (14%) (95% CI for difference: –2%, 9%, P=0.25) SF36 quality of life assessment (12 months): No improvement in either group for physical functioning, role functioning – physical, social functioning or role functioning – emotions Median score improvement (IQR) for bodily pain: I=10 (0–28), C=9 (–10 to 26) Improvement in general health scores: I=5 (–5 to 15), C=2 (–5 to 12) Improvement in vitality scores: I=5 (–5 to 20), C=5 (–10 to15) Improvement in mental health scores: I=4 (–4 to 12), C=0 (–8 to 16) Subsequent use of medical resources: Visits to GP: I=108/293 (37%), C=98/292 (34%) Hospital attendance: I=18/293 (6%), C=19/292 (7%) Endoscopy use: I=24/294 (8%), C=4/292 (1%) Drug usage (% treated) (median length of treatment): • PPI: I=77/292 (26%) (20 weeks), C=69/291 (24%) (24 weeks) • H_2 receptor antagonist: I=68/293 (23%) (20 weeks), C=56/291 (19%) (10 weeks) • Antacids: I=90/293 (31%) (10 weeks), C=82/291 (28%) (18 weeks) • Alginates: I=82/291 (28%) (6 weeks), C=73/290 (25%) (12 weeks) Patient satisfaction: Overall mean satisfaction with management based on a 0–10 Likert-type scale: I=8.9 (SD 1.7; 0–10), C=8.9 (SD 1.6; range 0.8–10)

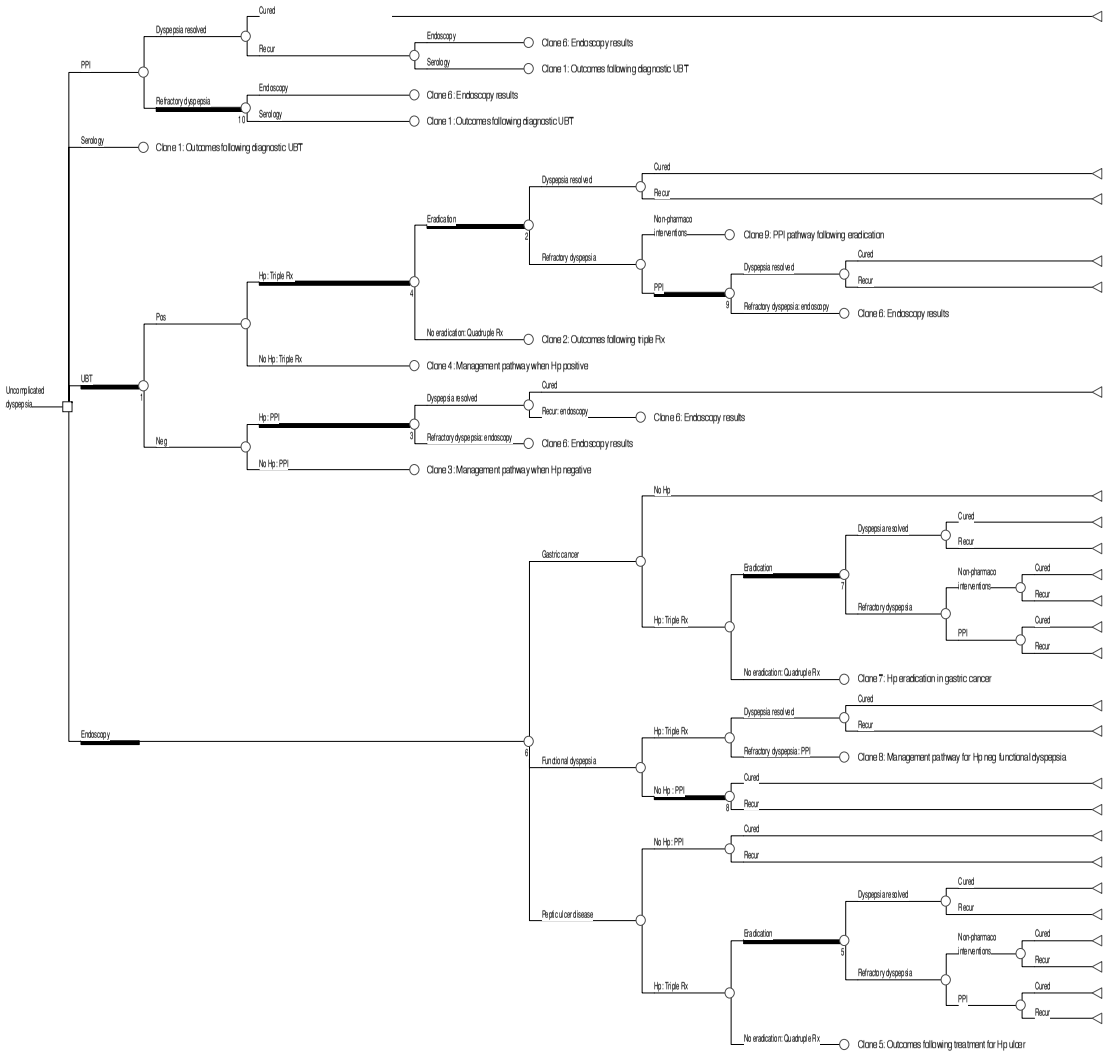
(cont'd)

Table H5 (cont'd) Results of randomised controlled trials

Study	Length of follow-up (months)	Intervention (I)	Comparator (C)	Outcomes
Manes et al (2003)	1, 6, 12	UBT + management	Empirical treatment + management	Dyspepsia severity scores: Values not provided, results presented as a figure (for 1, 6, 12 months) Patient symptoms: Improvement in symptoms after 1 month: I=78/110 (71%) (95% CI: 0.61, 0.79), C=90/109 (83%) (95% CI: 0.74, 0.89) (P=0.05) Mean number of days without symptoms for the 12-month period: I=231.5 (95% CI: 205.7, 257.2), C=139.3 (95% CI: 17.9, 160.7) (P<0.001) Use of medical resources: Endoscopy: I=61 (55%) (95% CI 0.46, 0.65), C=96/109 (88%) (95% CI: 0.8, 0.93) (P<0.0001) Note: no gastric cancer was diagnosed or missed in this study

[a] Somatic symptoms checklist (Attansio et al 1984)
[b] 36 item medical outcomes study short form health survey (Garratt et al 1993)
[c] Dyspepsia-specific health-related quality of life (Shaw et al 1998)
[d] Gastrointestinal symptoms rating scale (Svedlund et al 1988)
[e] The Psychological General Well-Being Index (Dupuy 1984)
[f] El-Omar et al (1996)

Appendix I Model of management strategies for uncomplicated dyspepsia



Appendix J Unit cost of proton-pump inhibitor

PBS code	Drug name	Number of packs dispensed[a]	Percentage (%)	Cost/pack ($)	Weighted cost ($)
Standard dose					
8007K	Pantoprazole 40 mg tablet	424,154	14.0	46.51	6.50
8331L	Omeprazole 20 mg tablet or capsule	324,489	10.7	42.56	4.55
8509W	Rabeprazole 20 mg tablet	286,258	9.4	46.50	4.39
8528W	Lansoprazole 30 mg sachet	4,174	0.1	42.50	0.06
8601Q	Esomeprazole 40 mg tablet	1,995,068	65.8	75.35	49.55
Total dispensed in 2003-05		3,034,143	100.0		
Weighted average cost of standard dose PPI					**65.04**
Low dose					
8600P	Esomeprazole 20 mg tablet	3,122,496	86.3	46.28	39.93
8332M	Omeprazole 10 mg tablet	103,274	2.9	29.09	0.83
8198L	Lansoprazole 15 mg capsule	37,119	1.0	28.58	0.29
8399C	Pantoprazole 20 mg tablet	310,615	8.6	27.26	2.34
8507R	Rabeprazole 10 mg tablet	45,961	1.2	27.69	0.35
Total dispensed in 2003-05		3,619,465	100.0		
Weighted average cost of low dose PPI					**43.74**

[a] Medicare Australia dispensed data for 2003-05, available at http://www.medicareaustralia.gov.au/

Abbreviations

AIHW	Australian Institute of Health and Welfare
^{13}C	carbon 13 (stable isotope of carbon)
^{14}C	carbon 14 (radioactive isotope of carbon)
CI	confidence interval
CO_2	carbon dioxide
C-UBT	carbon-labelled urea breath test
DRG	Diagnosis Related Groups
EGD	esophagogastroduodenoscopy
ELISA	enzyme linked immunosorbent assay
FDA	Food and Drug Administration
FN	false negative
FP	false positive
FPR	false positive rate
GERD	gastroesophageal reflux disease
GESA	Gastroenterological Society of Australia
GI	gastrointestinal
GP	general practitioner
H. pylori	*Helicobacter pylori*
ITT	intention to treat
LARA	laser optogalvanic effect spectroscopy
LR	likelihood ratio
MALT	mucosa-associated lymphoid tissue
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service (UK)
NICE	National Institute for Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
PPI	proton pump inhibitor
QALY	quality adjusted life-year
QOL	quality of life
RCT	randomised controlled trial
ROC	receiver-operating curve
SF36	short form 36
TGA	Therapeutic Goods Administration
TN	true negative
TP	true positive
UBT	urea breath test

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