BMJ Open Gastroenterology

Cost-effectiveness modelling of use of urea breath test for the management of *Helicobacter pylori*-related dyspepsia and peptic ulcer in the UK

D. Mark Pritchard,[1] Jan Bornschein,[2] Ian Beales,[3] Ariel Beresniak,[4] Hocine Salhi,[5] Peter Malfertheiner[6,7]

To cite: Pritchard DM, Bornschein J, Beales I, *et al*. Cost-effectiveness modelling of use of urea breath test for the management of *Helicobacter pylori*-related dyspepsia and peptic ulcer in the UK. *BMJ Open Gastro* 2021;**8**:e000685. doi:10.1136/bmjgast-2021-000685

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgast-2021-000685).

Received 19 April 2021
Accepted 24 June 2021

For numbered affiliations see end of article.

Correspondence to
Professor D. Mark Pritchard; Mark.Pritchard@liverpool.ac.uk

ABSTRACT

Objective Clinical data comparing diagnostic strategies in the management of *Helicobacter pylori*-associated diseases are limited. Invasive and noninvasive diagnostic tests for detecting *H. pylori* infection are used in the clinical care of patients with dyspeptic symptoms. Modelling studies might help to identify the most cost-effective strategies. The objective of the study is to assess the cost-effectiveness of a 'test-and-treat' strategy with the urea breath test (UBT) compared with other strategies, in managing patients with *H. pylori*-associated dyspepsia and preventing peptic ulcer in the UK.

Design Cost-effectiveness models compared four strategies: 'test-and-treat' with either UBT or faecal antigen test (FAT), 'endoscopy-based strategy' and 'symptomatic treatment'. A probabilistic cost-effectiveness analysis was performed using a simulation model in order to identify probabilities and costs associated with relief of dyspepsia symptoms (over a 4-week time horizon) and with prevention of peptic ulcers (over a 10-year time horizon). Clinical and cost inputs to the model were derived from routine medical practice in the UK.

Results For relief of dyspepsia symptoms, 'test-and-treat' strategies with either UBT (€526/success) and FAT (€518/success) were the most cost-effective strategies compared with 'endoscopy-based strategy' (€1317/success) and 'symptomatic treatment' (€1 029/success). For the prevention of peptic ulcers, 'test-and-treat' strategies with either UBT (€208/ulcer avoided/year) or FAT (€191/ulcer avoided/year) were the most cost-effective strategies compared with 'endoscopy-based strategy' (€717/ulcer avoided/year) and 'symptomatic treatment' (€651/ulcer avoided/year) (1 EUR=0,871487 GBP at the time of the study).

Conclusion 'Test-and-treat' strategies with either UBT or FAT are the most cost-effective medical approaches for the management of *H. pylori*-associated dyspepsia and the prevention of peptic ulcer in the UK. A 'test-and-treat' strategy with UBT has comparable cost-effectiveness outcomes to the current standard of care using FAT in the UK.

Summary

What is already known about this subject?

- Cost-effectiveness studies comparing strategies used for the management of *Helicobacter pylori*-associated diseases are limited.
- Timely detection of *H. pylori* infections in individuals presenting with symptoms of dyspepsia is an important public health issue in order to prevent the development of serious long-term complications such as gastric cancer.
- In the UK, faecal antigen test (FAT) is the most widely used noninvasive screening procedure for *H. pylori*, but no recent data about the relative cost-effectiveness of this strategy are available.

What are the new findings?

- 'Test-and-treat' strategies with either UBT or FAT are the most cost-effective medical approaches for the management of *H. pylori*-associated dyspepsia and the prevention of peptic ulcer in the UK.
- 'Test-and-treat' strategy with UBT has comparable cost-effectiveness outcomes to the strategy using FAT.

How might it impact on clinical practice in the foreseeable future?

- Provide decision-makers with comparative data on the cost-effectiveness of noninvasive tests for testing and retesting for *H. pylori* infection.
- Confirm that noninvasive tests such as UBT represent cost-effective and practical options for use in routine clinical practice in the UK.

INTRODUCTION

Between 20% to 30% of people in Western Europe are infected with *Helicobacter pylori* (*H. pylori*)[1] and these infections play a causative role in the development of dyspepsia, peptic ulcers, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma.[2–7] However, in most cases, *H. pylori* infections can be successfully eliminated with appropriate antibiotic treatment.[8] For this reason, timely detection of *H. pylori* infections in individuals presenting with symptoms of dyspepsia is an important public

health issue in order to prevent the development of serious long-term complications.[9–11] Moreover, in spite of the initial cost, screening for *H. pylori* has been shown to generate significant reductions in total dyspepsia-related healthcare costs over the long term.[12] Such screening programmes may also be cost-effective for the prevention of gastric carcinoma.[13 14]

Historically, *H. pylori* infections were typically diagnosed by analysis of biopsy samples taken from the stomach during endoscopy. However, this is an invasive procedure requiring hospital attendance and is resource consuming in terms of endoscopists' time and laboratory testing. For this reason, alternative diagnostic methods that are simpler to use and can be performed in the community are of interest. In this respect, two types of noninvasive tests have been developed. The faecal antigen test (FAT) involves collecting a faecal sample that is sent for assay of *H. pylori*-specific antigens using enzyme immunoassay or immunochromatography.[15 16] The urea breath test (UBT) involves ingestion of [^{13}C]-urea, which is broken down in the stomach by urease produced by *H. pylori* to ammonia and carbon dioxide. The presence of [^{13}C]-CO_2 in exhaled air is then detected by mass spectroscopy or infrared technologies.

Individual patient meta-analysis has demonstrated that test-and-treat strategies using FAT or UBT provide comparable effectiveness at relieving symptoms of dyspepsia as first-line endoscopy, but at a greatly reduced cost.[17] Similar, although less robust, conclusions may be drawn for noninvasive test-and-treat strategies compared with empirical symptomatic treatment.[18 19] For this reason, noninvasive *H. pylori* screening is now recommended in young patients with dyspepsia who do not have alarm symptoms.[8 19] In England and Wales, practice guidelines produced by the National Institute for Health and Clinical Excellence (NICE) recommend that clinicians offer patients with dyspepsia under 55 years and who do not have alarm symptoms noninvasive *H. pylori* testing using UBT, FAT or laboratory-based serology where its performance has been locally validated.[20]

We have recently performed a cost-effectiveness modelling study comparing a 'test-and-treat' strategy with UBT, 'test-and-treat' using endoscopy and empirical symptomatic treatment in the Spanish treatment setting.[21] This study demonstrated that the UBT 'test-and-treat' strategy was the most cost-effective medical approach for management of dyspepsia and for the prevention of peptic ulcers and gastric cancer. However, this modelling study did not compare UBT with FAT, which is not widely used in Spain. In contrast, in the UK, FAT is the most widely used noninvasive screening procedure for *H. pylori*,[22] but no recent data about the relative cost-effectiveness of these different strategies are available. For these reasons, we undertook a second modelling study based on practices and costs in the UK. The objective of this study was to compare the cost-effectiveness of four different management strategies (UBT, FAT, endoscopy and empirical symptomatic treatment) in the context of the British healthcare system.

MATERIALS AND METHODS

Study design

This medicoeconomic modelling study estimated the cost-effectiveness of the 'test-and treat' strategy using UBT in the diagnosis of *H. pylori* infection and in the subsequent prevention of *H. pylori*-related complications. The 'test-and treat' strategy using UBT for primary detection of *H. pylori* was compared with three other diagnostic strategies, namely, 'test-and treat' using FAT, an 'endoscopy-based strategy' and a 'strategy starting directly with empirical symptomatic treatment'. Two therapeutic outcomes were evaluated, relief of symptoms of dyspepsia and prevention of peptic ulcers. Values and costs were estimated from a decision tree model simulating the four strategies. The management pathways modelled correspond to those used in routine clinical practice in the UK, and transition probabilities were based on British data whenever available. Due to uncertainty associated with the estimates of several model inputs, probabilistic simulations were used to derive estimates of costs and outcomes. The analysis was performed from a public health insurance perspective, taking into account direct medical costs only. No cost discounting was applied.

Description of the model

The decision tree model used in the study consisted of a succession of decision nodes identifying decisions to test for *H. pylori*, to undertake endoscopy, to initiate symptomatic treatment or antibiotic treatment for *H. pylori* eradication and to evaluate effectiveness. A corresponding set of event nodes identify the possible outcomes of these decisions. Each branch of the decision tree ends in a terminal node defined by the therapeutic outcome (success or failure). Independent decision trees were constructed for each of the four management strategies evaluated. These decision tree models used in the study are illustrated schematically in online supplemental material.

UBT and FAT strategies

These two strategies follow an identical management pathway. The first step is testing for *H. pylori* with one of the two methods. If the pathogen is detected, first-line antibiotic therapy with clarithromycin-based triple therapy is initiated to eradicate it (according to the reference guide published by Public Health England).[23] If a switch to other first-line therapies would become necessary (ie, clarithromycin resistance >15%), costs of therapy will remain similar. At the end of the prescribed treatment course, the patient is retested by UBT or FAT. In case of persistence of the infection, a second-line eradication treatment is initiated and the patient then tested again. Therapeutic outcomes are modelled after first-line therapy in the case of successful eradication or after second-line therapy regardless of whether eradication had been achieved.

In the case of a negative *H. pylori* test, symptomatic treatment, including mainly a proton pump inhibitor (PPI),

is initiated for 4 weeks, and therapeutic outcome is evaluated at the end of this period. If symptoms have been relieved, the treatment is considered successful. If not, the patient undergoes endoscopy to identify any potential lesion (peptic ulcer or other macroscopic pathology).

Endoscopy-based strategy

In this strategy, the first step is to perform an endoscopy to detect any lesion and to take biopsies for *H. pylori* assay. If the assay result is negative, a 4-week symptomatic treatment is initiated after which outcome (symptom relief) is evaluated. If the result is positive, the patient undergoes first-line, and, if a retest is again positive, second-line, antibiotic treatment to eradicate the pathogen. As in the UBT and FAT strategies, therapeutic outcomes are modelled after first-line therapy in the case of successful eradication or after second-line therapy regardless of whether eradication had been achieved.

Empirical symptomatic treatment strategy

In this strategy, the first step is to start empirical symptomatic treatment with a PPI for 4 weeks. If symptoms have been relieved, the treatment is considered successful. If not, the patient undergoes endoscopy and follows the endoscopy strategy described above.

End states

For each management strategy, two end states were modelled. The first was the relief of dyspepsia symptoms at 4 weeks after initiation of symptomatic treatment (either following a negative *H. pylori* test in the two 'test and treat' and the 'endoscopy-based' strategies or during the first stage of the model in the 'treat-and-test' symptomatic treatment strategy). The second endpoint was prevention of occurrence (or recurrence) of a peptic ulcer over 10 years following a negative *H. pylori* test. Both end states were considered as binary variables (symptom relief vs no symptom relief and ulcer prevented vs ulcer not prevented). A payoff of 1 was assigned if the treatment objective was achieved and a payoff of 0 if it was not achieved.

Model inputs

Analysis population

The analysis population modelled corresponded to patients consulting a gastroenterologist for symptoms of dyspepsia.

Transition probabilities

Transition probabilities for the different chance nodes of the decision tree are listed in table 1.

Cost inputs

For certain items, a fixed cost was applied when this was known. For others, a cost range was applied, corresponding to the different treatment options available (eg, for antibiotic treatment for elimination of *H. pylori*), differences in laboratory costs for test assays or to expert opinion when the exact cost was unknown (eg, for the management of peptic ulcer). All costs used in the model are presented in euros (1 EUR=0,871487 GBP) and are listed in table 2.

For the UBT and FAT, costs include kit acquisition and test analysis. For endoscopy, two possible costs were applied. In the case when endoscopy revealed no suspect lesions, the cost applied was the procedure cost of endoscopy along with a rapid urease test. If suspect lesions were identified and biopsy samples were taken, the cost

Table 1 Model inputs: transition probabilities

Event	Probability	Range	Source
H. pylori positivity rate by UBT	0.16		Allison *et al*[22]
H. pylori positivity rate by FAT	0.13		Allison *et al*[22]
Lesion frequency during endoscopy	0.05		Ching *et al*[30]
H. pylori positivity rate by endoscopy (no lesion)	0.12		Moore[31]
H. pylori positivity rate by endoscopy (with lesion)	0.51		Zullo *et al*[32]
H. pylori eradication rate after first line antibiotic treatment	0.84		Nayar[33]
H. pylori eradication rate after second line antibiotic treatment	0.78		Lin and Hsu[34]
Dyspepsia relief after 4 week symptomatic treatment		0.3–0.4	Rabeneck *et al*[35]
Dyspepsia relief after 48 week symptomatic treatment (*H. pylori* negative)	0.12		Pinto-Sanchez *et al*[36]
Dyspepsia relief after *H. pylori* eradication		0.4–0.73	Du *et al*[37]
Dyspepsia relief after *H. pylori* eradication failure		0.32–0.54	Ford *et al*[17] and Heaney *et al*[38]
Peptic ulcer after 4 week symptomatic treatment		0.05–0.25	Rabeneck *et al*[35] and Färkkilä *et al*[39]
Peptic ulcer after *H. pylori* eradication	0.07		Gisbert *et al*[40]
Peptic ulcer after *H. pylori* eradication failure	0.55		Gisbert *et al*[40]

Lesions detected during endoscopy are generally related to gastric or duodenal lesions such as ulceration or precancerous lesions.
FAT, faecal antigen test; UBT, urea breath test.

Table 2 Model inputs: costs

Item	Fixed cost (€)	Cost range (€)	Source
Endoscopy with urease test	474		NHS National Tariff
Endoscopy with biopsy	514		NHS National Tariff
UBT kit and assay		22–36.4	BNF
FAT kit and assay	16.7	13.8–21.8	Expert opinion
Follow-up test after eradication		22–36.4	BNF
Symptomatic treatment		19.2–27.1	BNF
Antibiotic treatment (first line)		19.1–26.9	BNF
Antibiotic treatment (second line)		19.1–34.7	BNF
Management of peptic ulcer		575–1150	Expert opinion

UBT, urea breath test; FAT, faecal antigen test; BNF, British National Formulary.

of histological testing for *H. pylori* was also included. It was assumed that five biopsy samples would be analysed by histology and one rapid urease test. These procedures were costed according to NHS National tariffs. If an ulcer was detected by endoscopy, then the cost of management was included.

Acquisition costs for symptomatic treatment of dyspepsia and for antibiotic treatment for elimination of *H. pylori* were taken from the recommended retail price listed in the NHS National tariff.

Model outputs

Values

For each treatment strategy, the expected value of each outcome of interest was computed as the product of the transition probabilities at each node of the relevant branch of the tree. Monte Carlo simulations were performed with 10 000 iterations, each using a randomly selected transition probability within the prespecified range. Expected values are presented as the mean and SD of the results of the individual Monte Carlo iterations.

Costs

For each treatment strategy, the total cost of each outcome of interest was computed according to the probabilities at each node of the tree. Monte Carlo simulations were performed with 10 000 iterations, each using a randomly selected value within the prespecified cost range. Total costs are presented as the mean and SD of the results of the individual Monte Carlo iterations.

Cost-effectiveness

Cost-effectiveness ratios were calculated for each strategy and each outcome. In the case of dyspepsia relief, costs of the symptomatic treatment course were divided by the value (probability of symptom relief by the treatment course). In the case of ulcer prevention, the cost over 10 years was divided by the value (1—probability of developing an ulcer) and divided by 10 to generate an annual cost/outcome. Monte Carlo simulations were performed with 10 000 iterations, each using randomly selected values for values and costs within the ranges used in the previous step. These ratios are presented as the mean and SD of the results of the individual Monte Carlo iterations.

RESULTS

Value outcomes

For dyspepsia relief, the expected value of the treatment strategy ranged from 0.38 for endoscopy to 0.58 for the FAT (table 3). For prevention of peptic ulcer occurrence/recurrence, the expected value of the treatment strategy ranged from 0.10 for symptomatic treatment to 0.15 for the UBT and for the FAT (table 3).

Cost outcomes

For dyspepsia relief, the total cost of the treatment strategy ranged from €298 for the FAT to €497 for endoscopy (table 3). For prevention of peptic ulcer occurrence/recurrence, the total 10-year cost of the treatment strategy

Table 3 Model outputs: costs and values according to management strategy

	Dyspepsia relief		Peptic ulcer prevention	
	Cost/treatment	Value	Cost/year	Value
Urea breath test	€302±228	0.57±0.03	€174±305	0.85±0.05
Faecal antigen test	€298±227	0.58±0.02	€159±306	0.85±0.05
Endoscopy	€497±14	0.38±0.03	€610±306	0.84±0.05
Symptomatic treatment	€479±342	0.47±0.02	€584±423	0.90±0.02

Values are presented as mean values±SD.

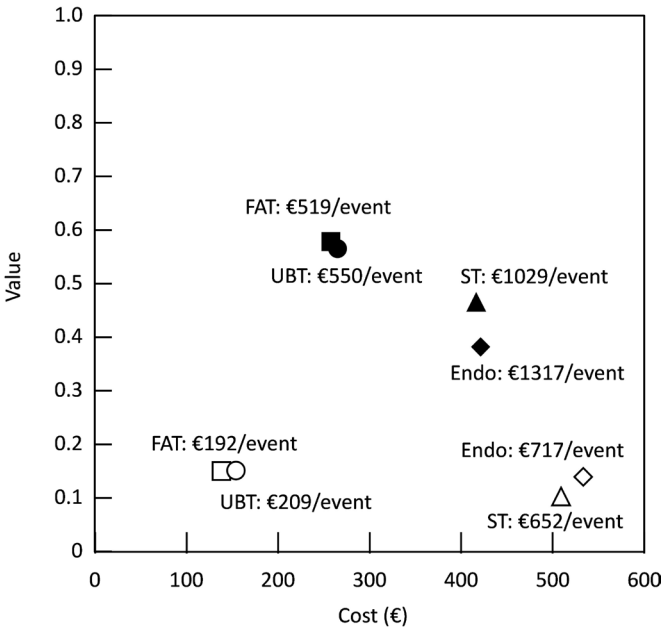

Figure 1 Cost-effectiveness ratio for each strategy. Filled symbols: dyspepsia relief; open symbols: prevention of peptic ulcer occurrence/recurrence. Endo, endoscopy (♦,◊); FAT, faecal antigen test (■,□); ST, symptomatic treatment (▲,△); UBT, urea breath test (●,○).

ranged from €1595 for the FAT to €6105 for endoscopy (table 3).

Cost-effectiveness

Costs and values for each treatment strategy are displayed on a cost-effectiveness plane in figure 1. For both outcomes (dyspepsia relief and ulcer prevention), the FAT and the UBT dominated endoscopy and symptomatic treatment, being more effective and cheaper. The cost-effectiveness ratio for FAT and for UBT was very similar, €518±397 per event and €526±400 per event, respectively, for dyspepsia relief and €191±371 per event and €208±368 per event, respectively, for ulcer prevention.

DISCUSSION

This modelling study indicates that a test-and-treat strategy in patients with dyspepsia using FAT or UBT for *H. pylori* offers a probability of relief of dyspepsia or of ulcer prevention at least as high as that offered by endoscopy or by an empirical symptomatic treatment. However, the cost of the strategy per patient successfully treated is over three times lower for dyspepsia relief and over two times lower for ulcer prevention with the noninvasive strategies compared with endoscopy or empirical symptomatic treatment. Compared with FAT, UBT shows a very similar cost-effectiveness profile. These findings are consistent with current recommendations from NICE,[20] the Scottish Intercollegiate Guidelines Network[24] and other international professional bodies,[8] which recommend a noninvasive test-and-treat strategy for diagnosis of *H. pylori* infections and management of *H. pylori*-related disease.

The UK is considered a low-prevalence country for *H. pylori*,[25] and the proportion of patients with dyspepsia who are tested positive for this organism is likely to be around 15%.[23] It should be noted that the actual prevalence of *H. pylori* infection in dyspeptic patients in the UK has not recently been comprehensively assessed and that any estimate higher than 15% in *H. pylori* prevalence would benefit test-and-treat strategy cost-effectiveness outcomes. In addition, diagnostic tests need to have high performance rates and to be cheap, in order to be cost effective. The UBT fulfils both these conditions, with sensitivity, specificity, positive predictive value and negative predictive value all being >95%,[26] comparable to the performance of the FAT.[16]

In spite of the fact that UBT is the most accurate noninvasive test for *H. pylori*[27 28] and is recommended by NICE,[20] it remains relatively underused compared with FAT in the UK. A survey of all accredited microbiology laboratories in England, conducted in 2015, found that >90% of laboratories proposed FAT as the first-line diagnostic test compared with <5% who proposed the UBT.[22] Since UBT, unlike FAT, requires prescription of the labelled reagent, the authors of this study speculated that physicians were not encouraged to prescribe by their local funding body.

Compared with our previous cost-effectiveness modelling study in the Spanish setting,[21] and despite the differences between healthcare systems and the prevalence of *H. pylori*, the results were similar. In both Spanish and British settings, the cost per treatment success was higher for the endoscopy and empirical treatment strategies than for the UBT strategy.

The currently available noninvasive strategies for *H. pylori* assessment do not provide information about antibiotic susceptibility. However, real-time PCR tests have been developed that permit assessment of clarithromycin susceptibility using faecal samples.[29] These may be helpful in the future, but at present are not readily available in the UK and elsewhere. If these tests are used for additional characterisation of *H. pylori*-positive patients in the future, this would potentially increase the cost of a stool-based testing strategy but will comply with the demands for a proper antibiotic stewardship in management of *H.pylori* infection.

The study has a number of limitations. In particular, the transition probabilities and certain costs used in the model are not known with precision for the UK context, and a range of values has been tested for most variables using a probabilistic approach. In consequence, the model outputs (costs and values) are also limited in their precision. Second, the model assumes that all patients offered FAT, UBT or endoscopy will actually undertake them. Any differences in test acceptability and patient uptake will not be reflected in the model.

In conclusion, this health economic modelling study predicts that 'test-and-treat' strategies with either UBT or FAT are the most cost-effective medical approaches for the management of *H. pylori*-associated dyspepsia and the

prevention of peptic ulcer in the UK. The 'test-and-treat' strategy with UBT has comparable cost-effectiveness outcomes to the current standard of care using FAT in the UK.

Author affiliations
[1]Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK
[2]Translational Gastroenterology Unit, University of Oxford, Oxford University Hospitals NHS Trust, Oxford, UK
[3]Department of Gastroenterology, Norfolk and Norwich University Hospital, Norwich, UK
[4]Department of Research & Development, Data Mining International, Geneva, Switzerland
[5]Department of Medical Affairs, Mayoly Spindler Laboratories, Chatou, France
[6]Department of Gastroenterology, Otto-von-Guericke University Hospital, Magdeburg, Germany
[7]Department of Medicine II, University Hospital, LMU, Munich, Germany

Twitter D. Mark Pritchard @gastrolivuni

Contributors HS and AB conceived and initiated the experiments. DMP, JB, IB, PM, HS and AB designed the models and the analysis plan. DMP, JB, IB and PM provided clinical advice and healthcare-related costs. AB performed the calculations and simulations. DMP, JB, IB, PM, HS and AB prepared the analysis report. HS drafted the manuscript in consultation with DMP, JB, IB, PM ad AB. All authors provided critical feedback and helped shape the research, analysis and the manuscript.

Funding This study was initiated and funded by Mayoly Spindler Laboratories.

Competing interests DMP, JB, IB and PM have received honoraria from Mayoly Spindler Laboratories for their contribution to the study. HS is an employee of Mayoly Spindler Laboratories. AB has received honoraria from Mayoly Spindler Laboratories for data management and data analyses. DMP has received honoraria for consultancy from Ipsen and Advanced Accelerator Applications. PM has received honoraria for consultancy from Bayer, Danone and speaker honoraria from Alfasigma, Bayer, Dr Falk and Malesci.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. This was a modelling study using only data that is available in the public domain and duly referenced in the Methods section.

REFERENCES

1 Zamani M, Ebrahimtabar F, Zamani V, *et al*. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2018;47:868–76.
2 Marshall BJ. Campylobacter pylori: its link to gastritis and peptic ulcer disease. *Rev Infect Dis* 1990;12 Suppl 1:S87–93.
3 Hansson LE, Engstrand L, Nyrén O, *et al*. Helicobacter pylori infection: independent risk indicator of gastric adenocarcinoma. *Gastroenterology* 1993;105:1098–103.
4 The EUROGAST Study Group. An international association between Helicobacter pylori infection and gastric cancer. *The Lancet* 1993;341:1359–63.
5 Veldhuyzen van Zanten SJ, Sherman PM. Helicobacter pylori infection as a cause of gastritis, duodenal ulcer, gastric cancer and nonulcer dyspepsia: a systematic overview. *CMAJ* 1994;150:177–85.
6 Pereira M-I, Medeiros JA. Role of Helicobacter pylori in gastric mucosa-associated lymphoid tissue lymphomas.. *World J Gastroenterol* 2014;20:684–98.
7 Wotherspoon AC, lymphoma GM, pylori H. Proton pump inhibitory therapy: then and now.. *Yale J Biol Med* 1996;69:61–8.
8 Malfertheiner P, Megraud F, O'Morain CA, *et al*. Management of Helicobacter pylori infection-the Maastricht V/Florence consensus report. *Gut* 2017;66:6–30.
9 Moayyedi P, Hunt RH. Helicobacter pylori public health implications. *Helicobacter* 2004;9 Suppl 1:67–72.
10 Malfertheiner P. Helicobacter pylori treatment for gastric cancer prevention. *N Engl J Med* 2018;378:1154–6.
11 Axon A. Helicobacter pylori and public health. *Helicobacter* 2014;19 Suppl 1:68–73.
12 Ford AC, Forman D, Bailey AG, *et al*. A community screening program for Helicobacter pylori saves money: 10-year follow-up of a randomized controlled trial. *Gastroenterology* 2005;129:1910–7.
13 Lansdorp-Vogelaar I, Sharp L. Cost-effectiveness of screening and treating Helicobacter pylori for gastric cancer prevention. *Best Pract Res Clin Gastroenterol* 2013;27:933–47.
14 Areia M, Carvalho R, Cadime AT, *et al*. Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. *Helicobacter* 2013;18:325–37.
15 Shimoyama T. Stool antigen tests for the management of Helicobacter pylori infection. *World J Gastroenterol* 2013;19:8188–91.
16 Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of H. pylori infection: a systematic review and meta-analysis. *Am J Gastroenterol* 2006;101:1921–30.
17 Ford AC, Qume M, Moayyedi P, *et al*. Helicobacter pylori "test and treat" or endoscopy for managing dyspepsia: an individual patient data meta-analysis. *Gastroenterology* 2005;128:1838–44.
18 Ford AC, Moayyedi P, Jarbol DE, *et al*. Meta-analysis: Helicobacter pylori'test and treat' compared with empirical acid suppression for managing dyspepsia. *Aliment Pharmacol Ther* 2008;28:534–44.
19 Gisbert JP, Calvet X. Helicobacter Pylori "Test-and-Treat" Strategy for Management of Dyspepsia: a Comprehensive Review. *Clin Transl Gastroenterol* 2013;4:e32.
20 National Institute for Health and Clinical Excellence. *Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Clinical guideline [CG184]*. London: NICE, 2019.
21 Beresniak A, Malfertheiner P, Franceschi F, *et al*. Helicobacter pylori "Test-and-Treat" strategy with urea breath test: A cost-effective strategy for the management of dyspepsia and the prevention of ulcer and gastric cancer in Spain-Results of the Hp-Breath initiative. *Helicobacter* 2020;25:e12693.
22 Allison R, Lecky DM, Bull M, *et al*. Audit of *Helicobacter pylori* Testing in Microbiology Laboratories in England: To Inform Compliance with NICE Guidance and the Feasibility of Routine Antimicrobial Resistance Surveillance. *Int J Microbiol* 2016;2016:1–6. doi:10.1155/2016/8540904
23 England PH. *Test and treat for Helicobacter pylori (HP) in dyspepsia. quick reference guide for primary care. For consultation and local adaptation*, 2019.
24 Scottish Intercollegiate Guidelines Network. *Dyspepsia: a national clinical guideline*. Edinburgh: SIGN, 2003.
25 Hooi JKY, Lai WY, Ng WK, *et al*. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology* 2017;153:420–9.
26 Gisbert JP, Pajares JM. Review article: 13C-urea breath test in the diagnosis of Helicobacter pylori infection -- a critical review. *Aliment Pharmacol Ther* 2004;20:1001–17.
27 Nocon M, Kuhlmann A, Leodolter A, *et al*. Efficacy and cost-effectiveness of the 13C-urea breath test as the primary diagnostic investigation for the detection of Helicobacter pylori infection compared to invasive and non-invasive diagnostic tests. *GMS Health Technol Assess* 2009;5:Doc14.
28 Vaira D, Vakil N. Blood, urine, stool, breath, money, and Helicobacter pylori. *Gut* 2001;48:287–9.
29 Gong R-J, Xu C-X, Li H, *et al*. Polymerase chain reaction-based tests for detecting *Helicobacter pylori* clarithromycin resistance in stool samples: a meta-analysis. *World J Clin Cases* 2021;9:133–47.
30 Ching H-L, Hale MF, Sidhu R, *et al*. Reassessing the value of gastroscopy for the investigation of dyspepsia. *Frontline Gastroenterol* 2018;9:62–6.

31 Moore AR. *An investigation of novel biomarkers of gastric mucosal preneoplasia*. The United Kingdom: University of Liverpool, 2015.
32 Zullo A, Esposito G, Ridola L, *et al*. Prevalence of lesions detected at upper endoscopy: an Italian survey. *Eur J Intern Med* 2014;25:772–6.
33 Nayar DS. Current eradication rate of *Helicobacter pylori* with clarithromycin-based triple therapy in a gastroenterology practice in the New York metropolitan area. *Infect Drug Resist* 2018;11:205–11.
34 Lin T-F, Hsu P-I. Second-line rescue treatment of *Helicobacter pylori* infection: Where are we now? *World J Gastroenterol* 2018;24:4548–53.
35 Rabeneck L, Souchek J, Wristers K, *et al*. A double blind, randomized, placebo-controlled trial of proton pump inhibitor therapy in patients with uninvestigated dyspepsia. *Am J Gastroenterol* 2002;97:3045–51.
36 Pinto-Sanchez MI, Yuan Y, Hassan A, *et al*. Proton pump inhibitors for functional dyspepsia. *Cochrane Database Syst Rev* 2017;11:Cd011194.
37 Du L-J, Chen B-R, Kim JJ, *et al*. Helicobacter pylori eradication therapy for functional dyspepsia: systematic review and meta-analysis. *World J Gastroenterol* 2016;22:3486–95.
38 Heaney A, Collins JS, Watson RG, *et al*. A prospective randomised trial of a "test and treat" policy versus endoscopy based management in young Helicobacter pylori positive patients with ulcer-like dyspepsia, referred to a hospital clinic. *Gut* 1999;45:186–90.
39 Färkkilä M, Sarna S, Valtonen V, *et al*. Does the 'test-and-treat' strategy work in primary health care for management of uninvestigated dyspepsia? A prospective two-year follow-up study of 1552 patients. *Scand J Gastroenterol* 2004;39:327–35.
40 Gisbert JP, Boixeda D, Martín De Argila C, *et al*. Unhealed duodenal ulcers despite Helicobacter pylori eradication. *Scand J Gastroenterol* 1997;32:643–50.