Economic consequences of near-patient test results - the case of tests for the Helicobacter Pylori bacterium in dyspepsia

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Abstract

Diagnostic tests and in particular laboratory tests are often important in diagnostic work-up and monitoring of patients. Therefore the economic consequences of medical actions based on test results may amount to a substantial proportion of health service costs. Thus, it is of public interest to study the consequences and costs of using laboratory tests.

We develop a model for economic evaluation related to the diagnostic accuracy (sensitivity and specificity) of near patient tests. Blood sample based tests to detect the bacterium Helicobacter Pylori (HP) are useful in diagnosing peptic ulcer and suitable to illustrate the model. First, general practitioners' initial management plans for a dyspeptic patient are elucidated using a paper vignette survey. Based on survey results, and medical literature, a decision tree is constructed to visualize expected costs and outcomes resulting from using three different HP tests in the clinical situation described in the vignette.

Tests included are two rapid tests for use in general practice, and one hospital laboratory test for comparison. The tests had different sensitivities and specificities. Then a cost-effectiveness analysis is undertaken from a societal perspective. Finally we use sensitivity analyses to model the decision uncertainty.

Estimating for a follow-up period of 120 days, the rapid test with lower sensitivity and specificity than the hospital HP test is cost-effective because the laboratory result is available immediately. Further, in general practice, the rapid test with the highest sensitivity is significantly cost effective compared to the test with the highest specificity when the willingness to pay for each dyspepsia-free day exceeds €42.6.

When deciding whether a laboratory analysis should be analysed in the office laboratory or not, it is important to consider both the diagnostic accuracy of the tests and the waiting time for the alternative, i.e. a hospital laboratory result.

Introduction

Diagnostic tests and in particular laboratory tests are often important in the diagnostic work-up and monitoring of patients. Therefore the economic consequences of laboratory tests may amount to a substantial proportion of health service costs. Thus, it is of public interest to study the consequences and costs of using such tests.

Compared with other European countries e.g. Denmark and England, laboratory analyses are much more used in Norway in general practice, mainly due to geographical factors and economic incentives. In Norway about 99% (1900) of all surgeries have office laboratory facilities run by general practitioners (GPs), serving a population of 4.6 million.

Dyspepsia is a fairly common presenting symptom in general practice consultations (Haug [1], Kristensen [2], Logan and Delaney [3], Petersen [4]). Sometimes dyspepsia is due to peptic ulcer, and the bacterium Helicobacter Pylori (HP) has been identified as the main cause of this disease. Thus it is important to be able to detect the bacterium in dyspeptic patients[1]. The presence of this bacterium may be detected by a blood sample based HP *rapid test* in the GP's office, or by sending a blood sample for serological testing in a larger laboratory (*hospital based test*). The rapid test is a simple test kit for single use, and just a drop of blood is needed to test for the presence of specific antibodies against HP. The result is read as negative or positive. Since the test is easy to perform, the analytical quality of the test result depends mainly on the diagnostic accuracy (sensitivity and specificity)[2] of the test kit and less on the level of training of the person performing the analysis.

The advantage of having the test available in general practice is that the GP can get the result of the test immediately, during the consultation. In contrast, if the GP sends a blood sample for serological testing, it takes 2-7 days to get the result, and this may delay the treatment and usually demands more follow-up by the GP. In Norway and elsewhere there have been discussions about whether HP rapid tests have high enough diagnostic accuracy to be used in the office laboratory (Asante [7], Duggan et al.[8]). Thus we aimed to compare hospital based and rapid tests. We chose to study two rapid tests; Immunocard and Helisal; and one hospital based test; HmCap.

The presence of antibodies is often associated with the presence of viable bacteria in the stomach, but not always, since antibodies persist for months after the bacteria have been

[1] Information about HP is based on Atherton et al.[5] and Friedman [6].
[2] The sensitivity of the test is here the probability of getting a positive result if the patient has peptic ulcer, and the specificity of the test is the probability of a negative result if the patient does not have peptic ulcer.

eradicated e.g. by antibiotics. Also, some people are healthy carriers of the bacteria, which may yield false positive results (presence of bacteria without ulcer). Upper endoscopy is the ultimate strategy of further examination if the GP suspects peptic ulcer, because one can detect whether the bacteria have done any damage to the stomach or duodenum, as well as detecting the presence of viable HP bacteria. In that case, so-called triple therapy with antibiotics is prescribed to eradicate the bacteria. In other cases of dyspepsia, e.g. non-ulcer "functional" dyspepsia (NUD), only symptomatic treatment with different kinds of antacids is used.

There are many laboratory tests available for use in the surgery, and the reasons for choosing the HP analysis were several: it is a fairly new test, it can be carried out both as a rapid test and as an ordinary "hospital laboratory" test, it may be a crucial test in that other laboratory tests are usually not needed, and there are more complex procedures or gold standards available to evaluate the benefit (predictive value) of the test.

In this paper, we develop a model for economic evaluation of diagnostic accuracy by comparing three HP tests that vary in diagnostic accuracy. In Fauli and Thue [9] we found that the result of the HP test had a significant and major influence on the GPs' choice of medical actions when dealing with a young dyspeptic patient, which implies that the diagnostic accuracy of the laboratory analysis is crucial.

Our study has four key components:

- First, a case history based survey of GPs' management of a patient with dyspepsia was performed, and several strategies for initial handling of these patients based on HP test results were elucidated (symptomatic treatment, upper endoscopy, triple therapy).
- Second, these strategies were implemented in a decision model. The therapeutic decision problem is constructed using principles of clinical decision analysis, where clinical events and costs of relevant strategies are compared using a decision tree (Hunink et al.[10]).
- Third, the principles of cost-effectiveness analysis are used to compare test-alternatives (Immunocard, Helisal, HmCap) in terms of costs and health outcome, based on Gold et al.[11]. The cost-effectiveness analysis is done from a societal perspective.
- Finally we use sensitivity analyses including a probabilistic sensitivity analysis (PSA) to model the decision uncertainty.

Outcome is quantified in terms of the "Number of dyspepsia-free days" after successful treatment i.e. the expected number of days within a period of 120 days in which the patient is assumed to be "cured" of dyspepsia. A time period of 120 days was chosen since, according to the decision model, it took at most 119.25 days from the first consultation until the actions taken in a follow-up consultation (when necessary) were completed, and since 95% of patients were estimated to be cured within this time span. The patient is categorized as cured if she can be assumed to be without dyspeptic symptoms resulting in need for health care of any kind.

This study demonstrates the importance of diagnostic accuracy as well as the importance of getting the laboratory result immediately. We find that rapid tests with lower sensitivity and specificity than the hospital based test are cost-effective because of the immediate laboratory result. The model we develop is intended for economic evaluation of diagnostic tests, especially when a single test result is crucial to treatment or follow-up.

We are not aware of any other study comparing HP tests focusing on cost-effectiveness from a societal perspective due to variations in diagnostic accuracy and variations in waiting time to receive the laboratory result. There are studies of cost-effectiveness of the management of dyspeptic patients as in Ford et al.[12], Lassen et al.[13] and Ofman et al.[14]. These studies focus on different treatment strategies (compare "test and treat" versus upper endoscopy) and do not study the impact of the variation in diagnostic accuracy of different HP tests. Briggs et al.[15] study the cost-effectiveness of screening for and eradication of HP bacteria. They use an HP test to identify patients with an increased probability of having viable HP bacteria, and found that the sensitivity and specificity of the serology test had an important effect on the effectiveness of the test-and treatment strategy. Further, these studies are from the health service perspective. They only include the direct medical costs but not the indirect costs included in our study: the costs imposed on the patient or the employer.

We assume that the clinical practice of GPs in Norway is representative of the practice of GPs in other western countries. Thus, the same decision tree can be used in other countries although the absolute and relative costs may well be different. It also seems reasonable to assume that we can use this model for clinical situations in which other diagnostic tests are used as important sources of information e.g. MRI, x-ray or other laboratory analyses. Hence, our method has interest beyond the setting used in this article.

Methods

This section includes a detailed description of the first and second key components of the study.

First key component: Survey of GPs' management of a patient with dyspepsia

We used data from a case history based survey of GPs' management of a young patient with dyspepsia designed in cooperation with "The Norwegian Quality Improvement of Laboratory Services in Primary Care" (NOKLUS). Nearly all general practices participate in NOKLUS on a voluntary basis to improve the analytical quality of their laboratory tests. More details on the survey are in Appendix A and in Fauli and Thue [9].

The present analysis focuses on the subgroup of GPs in the survey who decided to use a HP test in the clinical situation described in the case history. The GPs using the rapid tests chose many different sets of medical actions at the first consultation with the patient, and we grouped them based on the medical strategies chosen: Symptomatic treatment, (referral for) Upper endoscopy and Triple therapy. The few GPs choosing to refer for the so called breath test to detect viable H pylori bacteria also chose to refer for upper endoscopy, making the breath test superfluous, and therefore only upper endoscopy was included. Table 1 shows that the GPs' choices of medical actions strongly depend on the result of the rapid test. It is therefore crucial that the result is correct. When the result of the rapid test is negative, most GPs choose symptomatic treatment or referral for upper endoscopy, and if the result of the rapid test is positive most GPs choose upper endoscopy or triple therapy with antibiotics to eradicate HP bacteria. In our decision tree we excluded the strategies of symptomatic treatment with positive test results, and triple therapy with negative results, because they were seldom chosen. The GPs with rapid test always chose an action in addition to using the rapid test in the first consultation. In many instances the patient is cured by the actions taken at the first consultation. If she is not cured of dyspepsia, she is assumed to come back for a follow-up consultation, and the GPs stated their medical strategies in this situation as well in the survey.

Table 1

For GPs using a hospital based test we only have information on the choices made at the first consultation, before receiving the laboratory result: no action (15%), symptomatic treatment (72%), symptomatic treatment and upper endoscopy (8%) and upper endoscopy only (5%). In the

calculations we assume that these GPs choose the same actions as GPs with the rapid test when they receive the laboratory result a few days later, although we have no survey data to substantiate this assumption.

Second key component: The decision model

The decision problem for the GP is which test to use, i.e. in principle to have one of the rapid tests on the market available in the office laboratory, or to rely on a hospital based test. Our model therefore is a decision tree with three main branches, one for each test. The branches are mutually exclusive since the GP only uses one test. The structure of the decision tree is based on the main treatment strategies suggested in our survey. We follow the patient from the consultation where it is decided to use the HP test until the patient is cured or until a false laboratory result is detected and treatment is given. The branches for the rapid tests are identical, but with different probabilities for true/false negative/positive, and for simplicity we only present the strategy for Immunocard in Fig. 1.

The patient is assumed to have either ulcer or NUD (non ulcer or "functional" dyspepsia), since other causes of dyspepsia in this age group are considered negligible. If the patient has NUD a negative test is considered a true test, and a positive test is false. If the patient has an ulcer, a positive test is considered true and a negative test is false.

From the survey we have information about the choice of medical actions for GPs with rapid tests at the first and second consultations related to whether the result of the HP test at the first consultation is positive or negative. A second consultation is only needed if the patient is not cured after treatment given at first consultation. Our model does not include further follow-up for the fraction (4.5%) of patients assumed not to be cured by the end of the 120-day period.

Fig.1

For GPs using the hospital based test, we have information on 4 initial medical strategies chosen before having the result of the test (Fig. 2). Since the choices made at the first consultation will have consequences for medical strategies and costs later, the decision tree has a branch for each strategy chosen at the first consultation. For each branch, the rest of the tree structure is identical to the decision tree of the rapid test shown in Fig. 1.

Fig.2

The difference between using a rapid test and a hospital based test will depend on the GP's choice of medical actions at the first consultation. If the GP after knowing the laboratory result and acting in the same way as a GP with a "rapid" test result, does not want to change the medical strategy, there will be no time delay or extra cost. If the GP wants to change the medical strategy, there will both be a time delay of 5 days waiting to receive the result of the test, and the cost of wrong treatment given at the first consultation. If the patient is already referred to upper endoscopy and the GP changes his mind after knowing the laboratory result, this referral is assumed to be used later only if the patient is not cured from symptomatic treatment or triple therapy.

In addition the hospital laboratory result may be followed up by an extra consultation, and we assume this to be done in 75% of the cases if the laboratory result is positive, and in 25% of the cases if it is negative. From the survey we know that 63% used a follow up consultation, and because of the treatment they chose in the first consultation it is reasonable to assume that they more often needed an extra consultation if the test result was positive. The extra consultation gives further delay and extra cost.

If the patient is not cured by the treatment, it is assumed that she will return to the GP. From the survey we know that, at the second consultation, the GP always refers the patient for upper endoscopy, since the dyspepsia is not cured. Hence, we assume that uncured patients in the decision tree are referred to upper endoscopy. If the patient has an ulcer he or she is given triple therapy after upper endoscopy, and if the patient has NUD he or she is assumed to receive new symptomatic treatment. If the patient is not cured after upper endoscopy and triple therapy, we assume a second upper endoscopy will be undertaken to determine which type of antibiotic therapy will be effective.

The probabilities in the decision tree are shown in Tables 2-4, and the cost elements are shown in Table 5. Details about additional consultations and number of days on sick leave are in Appendix B. We used "TreeAge Pro" (TreeAge Software Inc, Boston [16]) for estimating results.

Test-related probabilities in the model

There are several studies comparing the diagnostic accuracy of hospital tests and rapid tests: Asante et al.[7], Cohen et al.[17], Faigel et al.[18], Hawthorne et al.[19], and Laine et al.[20], We chose tests from Asante et al.[7], since their article compared a hospital based test (Hmcap) and two rapid tests (Helisal and Immunocard) in a relevant (to our vignette) population of dyspeptic patients.

Table 2

Table 2 shows that Helisal has lower sensitivity and specificity than the hospital based test, and consequently table 3 shows that Helisal has a higher probability of false test results than the hospital based test. The fraction of true and false negative/positive test results in table 3 varies depending on the sensitivity and specificity of the tests studied (assuming a pretest probability that our patient has NUD of 0.80, and that 15% may have the bacteria and be healthy). These calculations are shown in Appendix C. The hospital test has a higher sensitivity and lower specificity than the Immunocard (table 2) resulting in a higher proportion of false positives and a lower proportion of false negatives.

Table 3

The GP's probabilities for choice of medical strategies at the first consultation depending on the test result were derived from survey data using Discrete Choice Analysis with Multinomial logit models. We have two observations per GP: i.e. one set of medical actions when the rapid test is negative and one set of medical actions when the rapid test is positive. There may be unobservable heterogeneity of the GPs and correlation between the stochastic terms. To take this into account, we use a multinomial logit model with random effects, which is a method used for panel data. This is the reason why some of the probabilities stated in table 2 differ somewhat from the probabilities in table 1. This is further described in Fauli and Thue [9].

How the health effect is measured

Our primary assumption is that if the patient is not cured initially, she will be subject to follow-up including upper endoscopy. Based on the survey (waiting time for upper endoscopy) and assumptions on the duration of various treatment alternatives, it took at most 119.25 days from the first consultation until the actions taken in a follow-up consultation (when necessary) were completed (Fig.1). After 120 days the probability of not being cured is only 4.5%. Therefore we have chosen a time span of 120 days to allow time for all relevant investigations to be carried out.

The effect of the treatment is "Number of dyspepsia-free days" after successful treatment, i.e. days with no need for professional health care for dyspeptic symptoms after the patient has finished follow-up and treatment. Many patients will be free of dyspepsia towards the end of the treatment period, particularly when treatment is symptomatic, but we do not have any information about this and did not include any dyspepsia-free days during treatment. Both the survey and The Norwegian Pharmaceutical Product Compendium [21] have provided information about the length of different medical strategies;

- symptomatic treatment: 14 days,
- triple therapy: 7 days,
- upper endoscopy, implying a waiting time for upper endoscopy of on average 5 weeks.

If a new consultation was needed by GPs using the hospital based test after they received the laboratory result, we assumed the waiting time for this consultation to be 3 days. If the patient was not cured after treatment, we assumed it took on average one week after finishing treatment to the next consultation. Fig. 3 and 4 show the time span for a patient being cured after receiving the first treatment (a) or being cured after the second consultation (b), when the GP uses a rapid test.

Fig. 3a

Fig. 3b

Fig. 4a

Fig. 4b

If an ulcer patient is cured after the first triple therapy (see Fig. 3a) she will have 113 dyspepsia-free days (120 days minus 7 days triple treatment). If she is cured after the second triple therapy (see Fig. 3b) she will have 64 dyspepsia-free days (120 days minus 7 days triple treatment minus 7 days before second consultation minus 35 days waiting time for upper endoscopy minus 7 days for 2^{nd} triple treatment) in the ulcer example. The same principles are applied to Fig. 4a and 4b and other arms of the decision tree in Fig. 1. If the patient is not cured during the 120 days period – she will have no dyspepsia-free days.

Recall that for the hospital based test the situation is different. If the GP wants to change the medical strategy after receiving the laboratory result, we will have a time delay consisting of the 5 days waiting to receive the result of the test and further delay if an extra consultation is needed.

Fig. 5

Fig. 5 shows a similar situation as in Figure 3a, but using the hospital based test our patient will have 8 less dyspepsia-free days because of the delay in effective treatment.

Table 4 gives an overview of the probabilities of being cured depending on the diagnosis and the medical action for a time span of at most 120 days.

Table 4

We studied the effect of the medical actions over a short period, thus the placebo-effect may be essential. In patients with NUD, symptomatic treatment by a proton pump inhibitor therapy, which is part of triple therapy, may be more effective than H_2 –blockers (Bytzer and Talley [27]). However, in this situation we assume that the curing probability is the same because some of the patients stop taking the triple therapy because of side-effects. Some patients with NUD are worried about serious diseases (cancer) and therefore feel much better after having upper endoscopy.

In the Norwegian Pharmaceutical Product Compendium [21] the probability of cure after the first triple therapy is stated to be 90%, but in reality it is less because some of the patients stop

taking the therapy because of side-effects. Briggs et al.[15] use 80% curing rate after the first cure and total rate of 94% after the second cure, in line with our estimates.

As regards symptomatic treatment, it is assumed that variation in medication use is negligible, in that all patients obtain prescriptions and all the prescriptions are based on the treatment strategies under evaluation.

Resource use and unit costs

When resources are used to provide medical care for one patient or to compensate for the production loss, they are unavailable for other use. We included the costs of all those goods, services and inputs that may change because of use of the different tests (variable costs). For health care resources (direct costs) we included the cost of consultations, upper endoscopy and costs of drugs (symptomatic treatment and triple therapy). For non-health costs (indirect costs) we included the cost of production loss, the costs of transport of the patient to and from the GP as well as the clinic for upper endoscopy, travelling and waiting time and the time actually spent receiving treatment. Table 5 gives an overview of the sources of different costs. Details are in Appendix D.

Table 5

Our patient had paid employment and the opportunity cost was measured as "production loss". The cost of absence from work is based on a study by Hem [28]. Hem studied 96 Norwegian firms and calculated the loss for the employers as a result of long and short term absence. On average the cost was €216 per day. The cost was higher with short term absence (€ 230) and if the firm did not compensate for the absence by adjusting the production or taking on additional employees (stand-ins).

We calculated the costs of triple therapy and symptomatic treatment and included the prices of the different H_2-antagonists (some sort of antacid) and triple therapies. From our survey we knew that that symptomatic treatment was prescribed before upper endoscopy in 62% of patients with a positive laboratory result and in 56% of those with a negative laboratory result, and this

cost is included, except for GPs using the hospital test that change from symptomatic treatment to upper endoscopy after receiving the laboratory result.

The costs of a visit to the GP and upper endoscopy included are the marginal costs and not the average costs[3]. The cost of a visit to a GP and upper endoscopy includes travelling expenses, which were calculated on the basis of mode of transport used, see Stangeby et al.[30] and on information about travelling time in the survey.

In the survey we also had information about whether the GP suggested sick leave for the patient, and for how many days. We calculated the average number of days depending on the treatment and included this in the cost. Details are in appendix D.

We have not included the cost of using the different HP-tests because we did not know the costs, and believe that the cost-differences between the tests are minor. In Fauli and Thue [33] we found that the remuneration fee (€11 per rapid test) covered the average expenses of using different HP tests. We do not have information about whether the costs of the tests are related to the level of sensitivity and specificity of the tests, and assume they were independent. We assumed that the GPs spent a similar amount of working time on a hospital based test compared to a rapid test. When a rapid test is analysed in the doctor's surgery, the patient may wait in the office for the laboratory result and speak to the GP about it, or the GP may phone the patient later on the same day. With a hospital based test the consultation may be shorter, but since the GP only receives the result after 2-7 days, he may spend more time updating the patient's record.

Results

Third key component: Results of the cost-effectiveness analysis

To estimate the expected costs and dyspepsia-free days within a 120 days period, general principles of cost-effectiveness analysis are applied (Gold et al.[11]). All the health effects of the test, i.e. dyspepsia-free days, are captured in the denominator, and the resource use are captured in the numerator and valued in monetary terms. When we take into account the share of false results from table 3 depending on the HP test, table 6 shows that the two rapid tests have very similar C/E-ratio, since the higher sensitivity of Helisal is balanced by a higher specificity of

[3] The average cost of a consultation was € 34.3 and an upper endoscopy cost € 313.6.
The marginal cost is based on a fixed fee schedule. In the average cost we include practice allowance from the municipalities to the general practice to cover fixed costs such as auxiliaries. The average cost for upper endoscopy includes 50% income from the State, independent of service to the patients.

Immunocard. The hospital based test is dominated by the rapid tests even though the hospital based test had higher sensitivity and specificity than Helisal (see Table 3). The reason for this is that using the hospital based test compared to the rapid tests in many instances will result in a delay in treatment and necessitate extra consultations because of ineffective treatment prescribed at the first consultation.

Table 6

The ICER-rate (incremental costs/incremental effect) shows that the incremental cost of Helisal relative to Immunocard is **€ 42.59** per dyspepsia-free day. Immunocard versus Helisal has €26.35 lower cost and fewer dyspepsia-free days by 0.62. Therefore Helisal is cost-effective if the willingness to pay (WTP) for a dyspepsia-free day is more than € 42.59; otherwise Immunocard is the preferred strategy.

Fourth key component: Sensitivity analyses

There are uncertainties in many parameters. The estimate of production loss varies according to the patient's work, and the costs of consultation and upper endoscopy depend on the length of the consultation and on the local routines at the medical clinic. We test the conclusions for uncertainty in the measurement of cost and effect first by using one way sensitivity analysis and then Monte Carlo simulations.

The cost of production loss, extra consultation, and upper endoscopy are the only cost-elements we assume to be uncertain. Drug prices are not uncertain because either a maximum price is set by the State or the prices are controlled by the manufacturer. The probabilities for choosing medical treatments are estimated based on the characteristics of the GPs in the survey. There is no uncertainty in these characteristics, since these are true values that do not vary.

We first explored the uncertainty in both clinical probability parameters and cost parameters by one-way sensitivity analyses. Several commentators, including the US panel on cost-effectiveness analysis (Gold et al.[11]) and the National Institute of Clinical Excellence (NICE) in the UK[34], have suggested the use of Probability Sensitivity Analysis (PSA) to handle uncertainty in cost-effectiveness models, because a well conducted PSA will engender a more

thorough representation of uncertainty in model results. Monte Carlo simulation in TreeAge recalculates, assigning values that are randomly sampled from probability distributions. This use of Monte Carlo simulation is referred to as PSA. We assume that the parameters are independent. In the Monte Carlo simulation we allow the effects of joint uncertainty across all the parameters of the model to be assessed. By using PSA we find the probability of one test being significantly cost-effective depending on the value of each dyspepsia-free day.

The one-way sensitivity analyses are described in Appendix E and show that the results are very robust. There are no changes in the relative ranking of strategies (1. Immuncard, 2. Helisal, 3. Hospital based) when we change within the 95% CI in Table F1 in Appendix F. We use the gamma and the beta distribution to represent uncertainty with the parameters. We get similar results when we change the waiting time for upper endoscopy and the number of days before receiving the laboratory result for the hospital based test. In general the costs decrease and the numbers of dyspepsia-free days increase when the level of diagnostic accuracy increases (percentage of true results) and when the probability of being cured increases.

Because the unit costs are constrained to be positive we used the gamma distribution to represent uncertainty with the cost parameters. Since probabilities are bounded by zero and one, we used the beta distribution to describe probabilities[4]. The distributions for the parameters in the model are summarized in Appendix F, Table F1. PSA was undertaken by randomly sampling from each parameter distribution and calculating the expected costs and expected number of dyspepsia-free days for every new set of parameters. A total of 10 000 replications from the model are presented in the cost-effectiveness (CE) scatterplot in Fig. 6.

Fig. 6

Immunocard with the expected lowest cost is located at the south part of the scatter plot. The Helisal has higher health effect and higher cost than Immunocard and is located north east. The hospital based test is located north west having higher cost and lower effect than the rapid tests, as expected from the C/E analysis

Further, Cost-effectiveness acceptability curves (CEACS) can be constructed from the simulations to present uncertainty surrounding incremental cost-effectiveness ratios (ICERs). Fig.

[4] More information about the gamma and the beta distribution in general is found in Spiegelhalter et al. [35].

7 shows the probability that the different HP tests are significantly cost-effective at a 5% significance level depending on the WTP for each dyspepsia-free day. When constructing the curves, it is assumed that the WTP for health gain is identical to the willingness to accept (WTA) health loss. The acceptability curves are estimated from the proportion of times the test is preferred from the results of the 10 000 simulations depending on the WTP. When the WTP is €0 the effect does not matter and Immunocard with lowest costs is cost-effective in all the simulations. Helisal has greater health effect and the proportion of Helisal being cost-effective is increasing with WTP per dyspepsia free day.

Fig. 7

The acceptability curves for Helisal and the Immunocard in Fig. 7 intersect at WTP= €45 When WTP> €45 the probability for Helisal being cost-effective is higher than for Immunocard and the probability is increasing with WTP. This is consistent with our deterministic sensitivity analysis where Helisal is cost-effective if the WTP is above €42.6 and otherwise the Immunocard is cost-effective. Thus the results do not change when we include uncertainty in the parameters.

Discussion

We will now discuss some objections to the methods we have used.

The survey is based on a questionnaire where the GP is assumed to have enough information to establish a preliminary diagnosis. When we composed the clinical vignette it was important to describe a realistic situation to get valid results. In Fauli and Thue [9] we have described the weaknesses of this method of data collection.

The response rate was 57%. The participants were similar to the total population of Norwegian GPs regarding age and sex, but fewer were on fixed salary (14% vs. 28%) since the H. pylori test was more abundant among GPs on fee-for-service. Still, it is reasonable to assume that the more knowledgeable GPs are more likely to respond, and more likely to adhere to medical guidelines in this field.

We chose to measure the opportunity costs for health care resources by marginal costs and not average costs. This can be discussed because short term fixed costs are generally variable in the long term. For our analysis, the results are independent of whether we use average or marginal costs

In this study we have used the production loss as an opportunity cost to the patient's time. Productivity cost has been studied by Jacob-Tacken et al.[36], Severens et al.[37] and Koopmanschap et al.[38]. These studies have found that colleagues often undertake the absentees' work during normal working hours. Taking this and other compensating mechanisms into account, they find that only one-quarter of the productivity costs remained compared with valuing lost production for each day absent. The cost will depend on the slack or capacity utilization in the companies and the supply of labour. These studies were carried out in the Netherlands, and in view of a higher unemployment rate there, we believe the results are not so relevant in Norway. If the companies have slack or capacity to compensate for absence from work, this is a cost for the companies and the society as they have a larger work force than they need, and therefore we don't take this into account in our analysis.

We have assumed that the GPs choose the same actions independent of using a rapid test or a hospital based test. It takes 2-7 days before the GPs receive the test result with the hospital based test, and the time delay may influence the choices of medical strategies and it may also happen that some GPs will not alter the treatment even though the test result is different from what they expected.

In our studies we have assumed that some of the GPs will follow up an upper endoscopy by a new consultation. A follow up consultation after an upper endoscopy, increases the costs and implies that the number of dyspepsia free days is reduced. If the patient is cured we assume that there is a 30% probability for a new consultation after endoscopy. If the patient is not cured we assume the probability for a follow up consultation to be 50% after symptomatic treatment and 100% after triple therapy. A test with a high diagnostic accuracy will result in more reasonable medical actions and therefore in less follow up consultations.

In Fauli and Thue [33] we found that GPs having the test in general practice had a higher probability of using the test compared to those not having the test in office. Different use of tests will have an impact on which test is cost-effective, but this aspect is not included in our study

Our cost-effective analysis is similar to a cost-benefit analysis based on the assumption that the WTP is equal in all individuals. But health outcomes are valued differently by different individuals and we would need information of patients' preferences to do a full cost-benefit analysis. This can be done in future research.

Concluding remarks

We have developed a model that can be used to evaluate the cost-effectiveness of the diagnostic accuracy of tests, and in particular laboratory analyses. The main result is that rapid tests with lower sensitivity and specificity than the hospital based test are cost-effective because of the immediate laboratory result. Which rapid test that is cost-effective depends on the willingness to pay for each dyspepsia-free day. We have shown that these results are robust for variation in the prevalence of ulcer in the population.

We assume that the clinical practice of GPs in Norway is representative of the practice of GPs in other western countries. Thus, the same decision tree can be used in other countries although the absolute and relative costs may well be different. It also seems also reasonable to assume that we can use this model for clinical situations in which other diagnostic tests are used as important sources of information e.g. MRI, x-ray or other laboratory analyses. Hence, our method has interest beyond the setting used in this article.

The policy implication of these results is that in deciding which test should be analysed in GPs' offices, both the diagnostic accuracy of the test and the waiting time to receive the laboratory result should be considered. In our future work we want study when it is optimal from the GP's perspective to analyse laboratory tests in general practice or in an external laboratory.

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Appendix A. Grouping of the medical strategies chosen in the survey

In May 1999 we mailed a questionnaire to all (739) GPs who had a rapid test available in their surgery, and a similar questionnaire to a random sample (717) of GPs who did not have the rapid test in their surgery. The response rates in both groups were 57%, and 210 GPs with the rapid test and 100 without the test chose to use a HP analysis. The GPs were presented with a case history describing a 30-year old woman with dyspepsia (Box 1), which was used to assess the clinical reasoning and decisions made by general practitioners.

Anette Hansen
is 31 years old and works for 5 hours a day in the afternoon/evening as a cleaner. Married, usually happy at home, two children aged 11 and 6 years.

During the past month she has had epigastric pain with a feeling of hunger, and some relief on eating. Experiences that the pain increases when she under stress. Slightly loose and irregular defecation at times.

She had a similar episode just under a year ago, and then recovered rapidly with Zantac 150 mg x 2, which she took for just over a week during her summer holidays. No other measures were taken at this consultation. She smokes 10 cigarettes a day, 2-3 cups of coffee, consumes little alcohol. No medication.

When you examine her this Tuesday she is slightly tender over her epigastrium, no other findings.

She should be at work later today.

Box A1 The case history in the questionnaire

This clinical situation was considered fairly familiar to the GP, and in fact, with some modifications, the case history depicts a real patient. The questionnaire was piloted and commented on by several clinicians (GPs and a gastroenterologist), as well as a microbiology specialist. It was an important element of the vignette that additional tests should not be necessary.

In the questionnaire the GPs were asked to state:

- the pre-test probability that Mrs Hansen's symptoms were caused by HP
- whether or not they would request a HP analysis in this situation
- which of a number of listed actions they would take based on the case history, or based on the history in addition to the test result, as well as their assessment of the relative importance of these case history elements and test result:
    - symptomatic treatment, e.g. relieving symptoms by issuing prescriptions (2 weeks treatment with different kinds of antacids)

- further diagnostic measures i.e. referring for upper endoscopy, with or without symptomatic treatment,
- immediate treatment by the so-called triple therapy (two antibiotics combined with a drug which abolishes the acid production in the stomach) in order to eradicate the HP bacteria if present, but without further diagnostic measures. Here we included every GP who had prescribed triple therapy. If they had also referred the patient, we assumed that upper endoscopy would not be done if the triple therapy was successful.

Appendix B. Additional consultations and number of sick leave days in the decision tree

This appendix describes data used in the decision tree regarding the need for additional consultations, and the number of sick leave days related to the treatment prescribed.

Consultations

In general we assume that if the patient is cured after symptomatic treatment or triple therapy, an additional consultation will not be carried out. However, some GPs routinely follow up an upper endoscopy by a new consultation, and therefore we assume that even if the patient is cured there is 30% probability for a new consultation. If the patient is not cured, we assume there is 50% probability for a new consultation after symptomatic treatment and 100% after triple therapy within the 120 days time span.

Number of days on sick leave

From the survey we had information about whether and for how many days the GPs suggested sick leave for the patient at the first consultation, depending on the treatment strategy chosen. Tables B1-B2 show the average number of days for suggested by GPs using the hospital based test

Table B1

We assume that 50% of referrals for upper endoscopy are performed at the first consultation to calm the patient, and the rest after receiving the laboratory result if referral is still assumed to be necessary. In Table B2 these assumptions are included .

Table B2

Table B3 shows the number of days of sick leave for GPs using the rapid test.

Table B3

We have no data on days on sick leave suggested by GPs using the hospital based test after they have received the result of the test. We assume it to be similar to GPs with a rapid test (Table B3), unless the patient is given symptomatic treatment at the first consultation. If the GP changes the medical strategy after receiving the laboratory result, we assume that the patients given symptomatic treatment at the first consultation feel better than those not given symptomatic treatment, and therefore only 20% of those referred to upper endoscopy and 50% of those receiving triple therapy are given prolonged sick leave, as shown in table B4.

Table B4

Appendix C. Calculation of true and false test results

The hospital based test as an example of calculation

The calculations of the rate of true and false negative/positive test results are based on a prevalence of 20%, and the fact that 15% may have the HP bacteria and be healthy, in addition to the sensitivity and specificity of the tests.

In a population of 1000 patients, 200 patients will actually have an ulcer. With a sensitivity of 94%, the test will discover 188 patients (true positive), and the other 12 patients will be false negative. The rest, 800 patients, will have NUD and of these 120 patients (15%) are healthy carriers. The test will discover 94%, thus 113 patients will be false positive. The rest, 7 patients, will be true negative. Of the NUD-patients, 680, did not have the antibody and in 510 of these the test will be negative (specificity 75%), 170 will be false positive. The proportion of false positives is (113+170)/800 = **0.35.** The proportion of false negatives is 12/200=**0.06**. By changing the numbers for sensitivity and specificity (thereby varying test quality) corresponding proportions are obtained with Helisal and Immunocard.

Appendix D. Calculation for resource use and unit costs

Triple therapy

The cost of triple therapy (€ 74) was the average cost of two different therapies in Table D1.

Table D1

The costs of symptomatic treatment

The cost of symptomatic treatment **€ 16** was the average cost of different H_2-antagonists for 14 days.

Table D2

The consultation

In Norway in 1999 the financing of general practice was split between the State (the National Insurance Scheme), the municipalities and the patients. The municipalities paid an input based practice allowance while the State paid a fee-for-service component according to a fixed fee schedule negotiated between The State and the Norwegian Medical Association. In 1999, the income from the municipalities was assumed to be 40% of the total income.

Around 69% of the GPs in the survey were specialists in general practice and we calculated an average cost for the GPs. The patients pay a fixed fee per consultation with an annual ceiling. If the ceiling is reached, the fee is refunded from the National Insurance Scheme. According to Statistics Norway and the National Insurance Scheme, 10% of the population in the age group 30-49 years in 2000 reached this ceiling, thus we assume here that 10% of the out-of-pocket expenses was financed publicly in 1999. When examining publicly financed services, we have followed the guidelines from the Ministry of Finance [39] and multiplied State financed costs by 1.2 to account for loss in social efficiency due to income tax.

Out of pocket costs per consultation	€ 13.5
+ average cost if specialist € 4.75*0.7	€ 3.4

When we take into consideration that 10% are financed publicly and multiply by 1.2, the marginal cost for the consultation is:

€ 13.5 *0.9*1 + (€ 13.5*0.1 + € 3.4)*1.2 = € 12.15+ € 5.7 = €17.85

In addition there was € 2.5 in travel expenses and the marginal cost of a consultation was about € 20.

In 1999, it was assumed that about 60% of the GPs' total income came from the service given to the patients. To calculate the average cost, we add the income from the municipalities, which should be on average 40% of the out of pocket expense per consultation:

(€ 17.85/0.6- € 17.85) *1.2 = €14.28. Thus the average cost is €34.28 (€ 20+€14.28).

Upper endoscopy

In 1999 the medical centres that carried out upper endoscopy were financed by the State. 50% of the income was independent of the service given to the patients, and 50% was assumed to be fee-for-service-income. The State paid a fee-for-service component according to a fixed fee schedule. The total reimbursement in 1999 was €128, including €23 in out of pocket-expenses. The marginal cost using the same principles as for the consultation will be:

(€128- €23) *1.2 + €23(0.9*1+0.1*1.2) =€105 *1.2 + €23.5 = € 149.5

In addition there is the transportation fee of €10 – thus the societal cost is **€ 160**

To calculate the average cost we add the grant from the State €128*1.2= € 153.6, thus the average cost will be **€ 313.6**

Appendix E. The deterministic sensitivity analysis

In this appendix we show some of the results of the sensitivity analysis. The results are very robust. There are no changes in the relative ranking of strategies when we change within the 95% CI in Table F1 in Appendix F. In all the tables the cost is expressed in €, and the effect in dyspepsia-free days. At the end of the appendix we study the effect of changing the waiting time for upper endoscopy and number of days before receiving the laboratory result.

Test related parameters

When we vary the sensitivity or the specificity, we only change the result of one test at a time. Thus in Table E1 we only show the result related to the type of test changed. The health effect only changed from 83 to 84 dyspepsia-free days for Helisal – false positive otherwise unchanged. This is therefore not included in Table E1.

Table E1

Table E1 shows that change in the Helisal share has most effect on the costs.

The probability of having ulcer

Immunocard had a lower sensitivity and higher specificity than the other tests included. Table E2 shows that, as expected, Immunocard behaves well when the probability for ulcer is low (or the probability for NUD is high). The table also shows that the costs of all the tests increase if there is a high level of ulcers, and decreases with a high level of NUD.

Table E2

The probability of being cured

When the probability of being cured increases, the costs decrease and the health effect increase as shown in E3 and E4.

Table E3

Table E4

Cost

Table E5 shows that when the cost for upper endoscopy increases, the total expected cost of the different type of tests increases. The curing rates are the same, and thus the health effect is unchanged.

Table E5

Change in waiting time

Waiting time for upper endoscopy

Comparing Table E6 with Table 6, we find that the patient gets around 4 more dyspepsia-free days when we reduce the waiting time by one week, independent of the test chosen.

Table E6

The effect of changing number of days before receiving the laboratory result

The number of days it takes before receiving the laboratory result in Norway varies from 2-7 days depending on geographical location. We expect that the chosen strategies at the first consultation will depend on the length of the waiting period, and as we have used the information from the survey, this aspect is already included in our analysis.

We chose to use 5 days as our base case. Table E7 shows that when the results arrive after only two days, the patient has 1.8 more dyspepsia-free days than if it had arrived three days later. The gain is less than indicated by number of days – because some GPs will need extra consultations to follow up the result. The change in number of days will only effect the number of dyspepsia-free days and not the costs.

Table E7

When the time delay increases by two days compared with the base case, the number of dyspepsia-free days is reduced by 1.3.

Appendix F. Probability distributions

Here we specify the distributions of the model parameters in order to illustrate uncertainty in their estimation.

Because the unit costs are constrained to be positive and continuous, we used the gamma distributions to represent uncertainty regarding the cost parameters. The probabilities are bounded on the interval 0 -1 and we used the beta distribution.

The gamma distributions

The gamma distribution is a two parameter distribution, Y ~ Gamma [a,b] represents a gamma distribution with properties:

Distribution: $P(y \mid a,b) = (b^a y^{a-1} e^{-by})/ \Gamma(a);\ y \in (0, \infty)$

Mean $E(Y \mid a,b) = a/b$ and

Variance are $V((Y \mid a,b) = a/b^2$

Spiegelhalter (35) shows that the gamma distributions are flexible and can have same mean with different shapes depending on a and b. We wanted distributions shaped like the normal distributions as regards the costs. Regarding the cost of upper endoscopy, we expected that 95% of the upper endoscopy would cost between € 194 and € 242. Choosing b = 2.5 and a = € 550 Expected mean = a/b = €550/2.5= € 220.

The beta distributions

The curing probabilities were derived from the medical literature. The patient is either ill (failure - still having dyspeptic symptoms) or healthy (success). The data can be considered as independent Bernoulli trails leading to a binomial form of data – as in Briggs et al.[15].

Y ~ Beta [a,b] represents a beta distribution with properties:

Mean: $E(Y \mid a,b) = a/(a+b)$ and

Variance: $V((Y \mid a,b) = ab/[(a+b)^2(a+b+1)]$

We used the common parametization $\text{beta}(\alpha,\beta) = \text{beta}\ (450, 550)$, if the probability of curing is 45%. Then expected mean = a/(a+b) = 450/(450+550) = 0.45. Fryback et al.[40] describes how the beta density function behaves under increasing certainty about the point estimate.

Table F1

The 95% CI is taken from the medical literature in Tables 2 and 4. For the cost of consultation we used data from NOKLUS reports (unpublished).
By using TreeAge Pro we checked that the distributions in table F1 were correctly specified.

Tables

Table 1. GPs choice of medical strategies for patient with dyspepsia depending on the laboratory result

Medical strategies	**Negative**	**Positive**
1. Symptomatic treatment	112 (56%)	8 (4%)
2. Upper endoscopy	85 (42%)	101(53%)
3. Triple therapy	4 (2%)	83 (43%)

Table 2. Overview over test-related probabilities in the model

Probability parameters in the model	Base case	Source
Prevalence of Non ulcer dyspepsia (NUD)	0.80	Haug [1], Kristensen [2]
Hospital based test, HmCap, sensitivity	0.94	Asante et al.[7]
Hospital based test HmCap, specificity	0.75	Asante et al.[7]
Rapid test - Helisal, sensitivity	0.84	Asante et al.[7]
Rapid test - Helisal, specificity	0.63	Asante et al.[7]
Rapid test - Immunocard, sensitivity	0.75	Asante et al.[7]
Rapid test - Immunocard, specificity	0.87	Asante et al.[7]
If positive test, upper endoscopy	0.52	Estimated from the survey
If negative test, symptomatic treatment	0.58	Estimated from the survey
Upper endoscopy, sensitivity	1.00	See text
Upper endoscopy, specificity	1.00	See text

Table 3. Overview of the proportion of false/true results depending on the test

Type of test	True negative	False positive	True positive	False negative
Immunocard	0.78	0.22	0.75	0.25
Helisal	0.56	0.44	0.84	0.16
Hospital based	0.65	0.35	0.94	0.06

Table 4. Overview of the parameters related to being cured in the model

Probability parameters in the model	Base case	Source
If NUD – cured after symptomatic treatment	0.70	Jones et al.[22], Laheij et al.[23]
If NUD – cured after triple therapy	0.70	Jones et al.[22], Laheij et al.[23]
If NUD – cured after endoscopy	0.85	El-Serag [24], Petersen [4]
If ulcer – cured after triple therapy	0.85	Norwegian Pharmaceutical Product Compendium.[21], Briggs et al.[15].
If ulcer – cured after 2nd triple therapy	0.955	Norwegian Pharmaceutical Product Compendium [21], Briggs et al.[15]
If ulcer – cured after symptomatic treatm	0.50	Imperiale et al.[25], Hopkins et al.[26]

Table 5. Overview over unit costs

Cost parameters in the model	**Cost**	**Source**
Cost of production loss per day	€ 225	Hem KG.[28]
Cost of visit to GP	€ 20*+ production loss 0.4 day	National Insurance Administration.[29], the survey, Stangeby et al.[30]
Cost of triple therapy	€ 74	Norwegian drug and therapeutic formulary for health personnel 2001 [31], Norwegian Pharmaceutical Product Compendium 1999 [21].
Cost of symptomatic treatment	€ 16	The Norwegian Association of Proprietor Pharmacies [32]
Cost of upper endoscopy	€ 160*+ production loss 1 day	National Insurance Administration [29]

*Incl. cost of transport

Table 6. Base-case expected cost and number of dyspepsia-free days per test in a period of 120 days

Strategy	Costs in €	Incremental Costs in €	Effect	Incremental Effect	C/E	Incremental C/E (ICER)
Immunocard	947.99		82.95		11.43	
Helisal	974.34	26.35	83.56	0.62	11.66	42.59
Hospital based HPtest	1046.80	72.46	79.35	-4.21	13.19	(Dominated)

Table B1. Overview over the medical strategies and sick leave chosen by GPs using the hospital based test

Medical strategies	**Number GPs (Percent)**	**Average number of days on sick leave**
No actions	9 (10%)	0.8
Symptomatic treatment	55 (64%)	1.0
Symptomatic treatment and upper endoscopy	13 (15%)	2.7
Upper endoscopy	9 (10%)	2.2

Table B2. Final version of the medical strategies and sick leave chosen by GPs using the hospital based test

Medical strategies	**Number GPs (Percent)**	**Average number of days on sick leave**
No actions	13.5 (15%)	1.3
Symptomatic treatment	61.5 (71.5%)	1.2
Symptomatic treatment and upper endoscopy	6.5 (7.5%)	2.7
Upper endoscopy	4.5 (5%)	2.2

Table B3. Average number of days on sick leave depending on the laboratory result

Medical strategy	**Positive result**	**Negative result**
Symptomatic treatm.	1.5	1.2
Upper endoscopy	1.2	2.1
Triple therapy	3.3	-

Table B4. Average additional number of days on sick leave after symptomatic treatment

Medical strategy	**Positive result**	**Negative result**
Upper endoscopy	0.24	0.42
Triple therapy	1.65	-

Table D1. Overview over cost of different triple therapies

Triple therapies	**Dose**	**Cost in €**
1. Acid inhibitors	Average cost of proton pump inhibitors	24
1. Metronidazole	400 mg* twice daily	15
1. Amoxicillin *or*	750 mg*twice daily	
1. Clarithromycin	250 mg* twice daily	22
1. Total cost		**61**
2. Acid inhibitors	Average cost of proton pump inhibitors	24
2. Amoxicillin	1g* twice daily	18.75
2. Clarithromycin	500 mg* twice daily	43.6
2. Total cost		**86**

Table D2. Overview over cost of different H_2-antagonists

H_2-antagonists	**Dose and duration**	**Cost in €**
Balancid*	2 tablets * 4=8 tablets daily*14 days=112 tablets	13.0
Link*	15ml * 4 daily =60 ml daily *14 days =840ml	17.1
Novaluzid*	40ml daily *14 days=560 ml	10.6
Titralac*	16 tablets daily for 14 days=224 tablets	13.4
Zantac	150 mg * twice daily for 10 days	15.8
Cimal	400 mg * twice daily for 14 days	19.0
Cimetidine	400 mg * twice daily for 14 days	19.0
Tagamet	400 mg * twice daily for 14 days	19.0
Ranitidine	150 mg * twice daily for 14 days	18.8

- Average prices from The Norwegian Association of Proprietor Pharmacies by Julia Nemeth.

Table E1. The expected cost depending on the level on false laboratory result and type of test

Parameters in the model	**Base case**	**95% CI**	**Expected cost in €**
Hospital based HPtest – false negative	0.06	0.03-0.09	1047-1047
Helisal – false negative	0.16	0.08-0.28	972-977
Immunocard – false negative	0.25	0.14 -0.38	945-951
Hospital based HPtest – false positive	0.35	0.33 -0.37	1042-1052
Helisal – false positive	0.44	0.33 -0.57	960-991
Immunocard– false positive	0.22	0.16– 0.32	948-948

Table E2. The expected cost and effect depending on the level of false laboratory results and type of test

Level of NUD	Strategy	Cost	Eff	C/E	Incr C/E (ICER)
0.74	Immunocard	986	83	12	
	Helisal	1 010	83	12	36
	Hospital based HPtest	1 087	79	14	(Dominated)
0.76	Immunocard	974	83	12	
	Helisal	999	84	12	38
	Hospital based HPtest	1 075	79	14	(Dominated)
0.78	Immunocard	963	83	12	
	Helisal	988	84	12	40
	Hospital based HPtest	1 063	79	13	(Dominated)
0.81	Immunocard	940	83	11	
	Helisal	967	84	12	44
	Hospital based HPtest	1 038	79	13	(Dominated)
0.83	Immunocard	928	83	11	
	Helisal	956	84	11	46
	Hospital based HPtest	1 025	79	13	(Dominated)
0.85	Immunocard	916	83	11	
	Helisal	945	84	11	48
	Hospital based HPtest	1 013	79	13	(Dominated)

Table E3. The results for a NUD-patient depending of the level of curing after an upper endoscopy

	Strategy	Cost	Eff	C/E	Incr C/E (ICER)
0.8	Immunocard	954	82	12	
	Helisal	981	83	12	45
	Hospital based HPtest	1 052	78	13	(Dominated)
0.83	Immunocard	950	83	11	
	Helisal	976	83	12	44
	Hospital based HPtest	1 049	79	13	(Dominated)
0.85	Immunocard	948	83	11	
	Helisal	974	84	12	43
	Hospital based HPtest	1 047	79	13	(Dominated)
0.86	Immunocard	946	83	11	
	Helisal	972	84	12	42
	Hospital based HPtest	1 045	80	13	(Dominated)
0.88	Immunocard	944	84	11	
	Helisal	970	84	12	41
	Hospital based HPtest	1 043	80	13	(Dominated)
0.9	Immunocard	942	84	11	
	Helisal	968	85	11	40
	Hospital based HPtest	1 041	80	13	(Dominated)

Table E4. The results depending of the level of curing for an ulcer-patient after triple therapy

	Strategy	Cost	Eff	C/E	Incr C/E (ICER)
0.82	Immunocard	957	83	12	
	Helisal	984	83	12	44
	Hospital based HPtest	1 057	79	13	(Dominated)
0.84	Immunocard	951	83	11	
	Helisal	977	83	12	43
	Hospital based HPtest	1 050	79	13	(Dominated)
0.85	Immunocard	948	83	11	
	Helisal	974	84	12	43
	Hospital based HPtest	1 047	79	13	(Dominated)
0.86	Immunocard	945	83	11	
	Helisal	971	84	12	42
	Hospital based HPtest	1 043	79	13	(Dominated)
0.87	Immunocard	942	83	11	
	Helisal	968	84	12	42
	Hospital based HPtest	1 040	80	13	(Dominated)
0.88	Immunocard	939	83	11	
	Helisal	965	84	11	41
	Hospital based HPtest	1 037	80	13	(Dominated)

Table E5. Expected cost and effect for upper endoscopy when the cost increases

	Strategy	Cost	Eff	C/E	Incr C/E (ICER)
120	Immunocard	923	83	11	
	Helisal	949	84	11	42
	Hospital based HPtest	1 022	79	13	(Dominated)
146.67	Immunocard	940	83	11	
	Helisal	966	84	12	42
	Hospital based HPtest	1 038	79	13	(Dominated)
160	Immunocard	948	83	11	
	Helisal	974	84	12	43
	Hospital based HPtest	1 047	79	13	(Dominated)
173.33	Immunocard	956	83	12	
	Helisal	983	84	12	43
	Hospital based HPtest	1 055	79	13	(Dominated)
186.67	Immunocard	965	83	12	
	Helisal	991	84	12	43
	Hospital based HPtest	1 064	79	13	(Dominated)
200	Immunocard	973	83	12	
	Helisal	1 000	84	12	43
	Hospital based HPtest	1 072	79	14	(Dominated)

Table E6. Results of the cost-effectiveness analysis when reducing the waiting time for upper endoscopy from 5 to 4 weeks

Strategy	Costs in €	Incremental Costs in €	Effect	Incremental Effect	C/E	Incremental C/E (ICER)
Immunocard	947.99		87.00		10.90	
Helisal	974.34	26.35	87.69	0.68	11.11	38.51
Hospital based HPtest	1046.80	72.46	83.41	-4.28	12.55	(Dominated)

Table E7. Results of cost-effectiveness analyses for the hospital based test depending on waiting time

Waiting time to result	Costs in €	Effect	C/E
Base case – 5 days	1047.0	79.4	13.2
2 days	1047.0	81.2	12.9
7 days	1047.0	78.1	13.4

Table F1. Specification of the distributions of the model parameters

Parameters in the model	Base case	95% CI	Betadistri
Prevalence of Non ulcer dyspepsia (NUD)	0.80	0.74 -0.85	Beta(800,200)
Hospital based HPtest – false negative	0.06	0.02-0.09	Beta(18,282)
Helisal – false negative	0.16	0.08-0.28	Beta(48,252)
Immunocard – false negative	0.25	0.14 -0.38	Beta(75,225)
Hospital based HPtest – false positive	0.35	0.33 -0.37	Beta(3500,6500)
Helisal – false positive	0.44	0.33 -0.57	Beta(132,168)
Immunocard– false positive	0.22	0.16– 0.32	Beta(66,234)
If NUD – cured after symptomatic treatm	0.70	0.63-0.76	Beta(700,300)
If NUD – cured after triple therapy	0.70	0.63-0.76	Beta(700,300)
If NUD – cured after endoscopy	0.85	0.80-0.90	Beta(850,150)
If ulcer – cured after triple therapy	0.85	0.82-0.88	Beta(2550,450)
If ulcer – cured after 2nd triple therapy	0.70	0.68-0.72	Beta(7000,3000)
If ulcer – cured after symptomatic treatm	0.50	0.44-0.56	Beta(500,500)
Cost of production loss	€225	€180-€275	Gamma(337.5,1.5)
Cost of upper endoscopy	€160	€120-€200	Gamma(400,2.5)
Cost of consultation	€20	€ 10–33	Gamma(40,2)

Figures

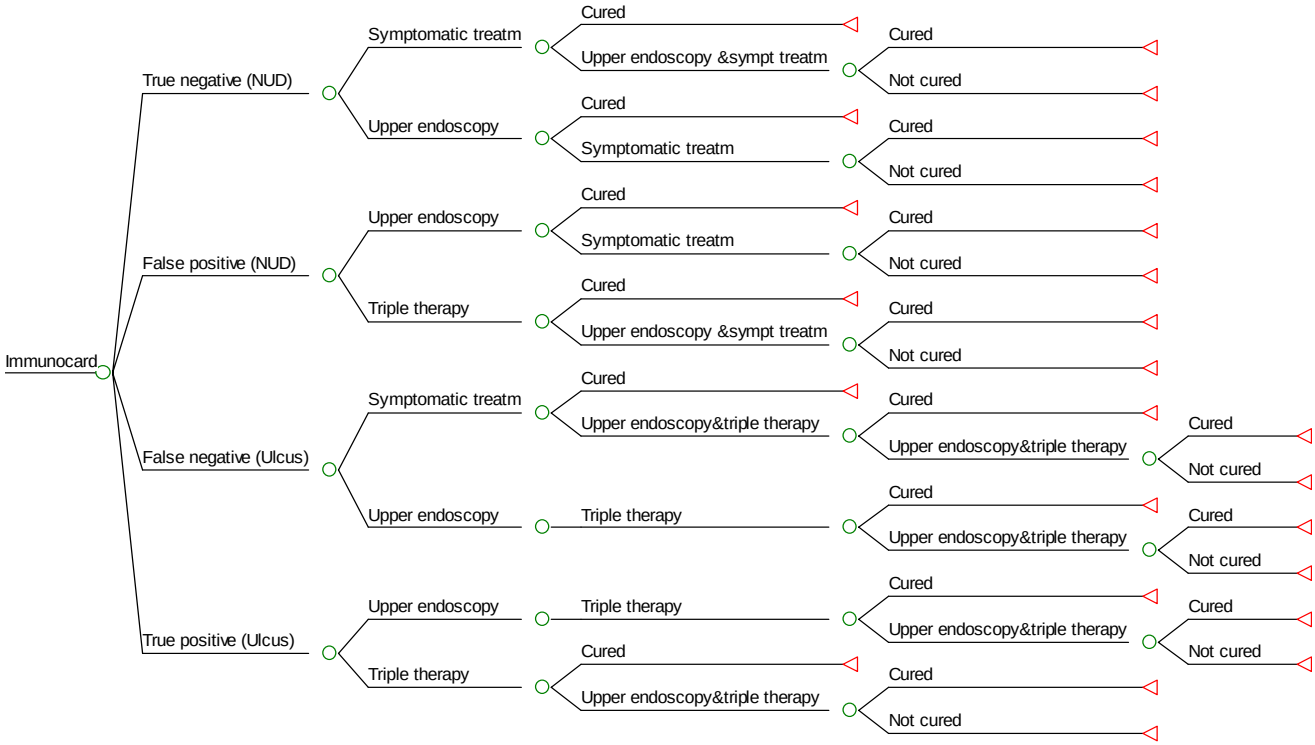

Fig. 1. One branch (strategy) of the decision tree for GPs using the HP-test in a situation with a young dyspeptic patient.

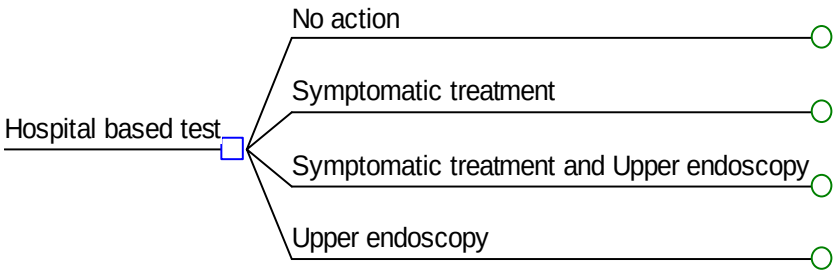

Fig. 2. Part of the decision tree for the hospital based test

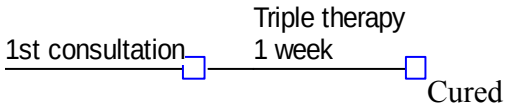

Fig. 3a. Possible time span for an Ulcer-patient receiving triple treatment once

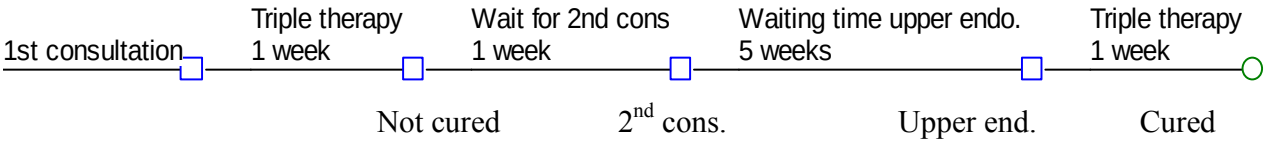

Fig. 3b. Possible time span in weeks for an Ulcer-patient receiving triple treatment twice

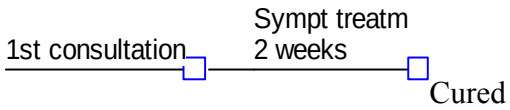

Fig. 4a. Possible time span in weeks for a NUD-patient cured after symptomatic treatment

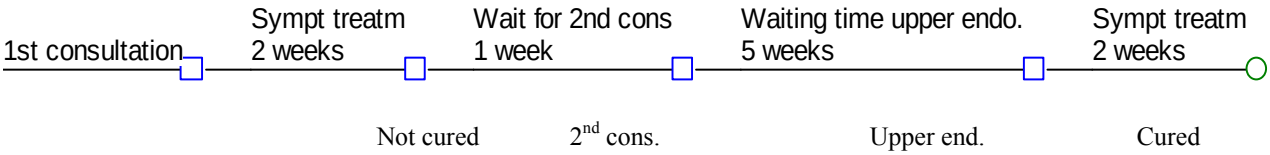

Fig. 4b. Possible time span in weeks for a NUD-patient receiving second symptomatic treatment

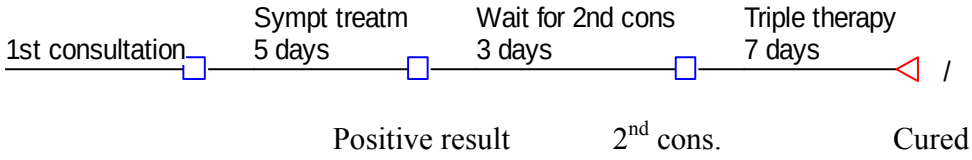

Fig. 5. Using the hospital based test: Possible time span in days for an Ulcer-patient receiving wrong treatment

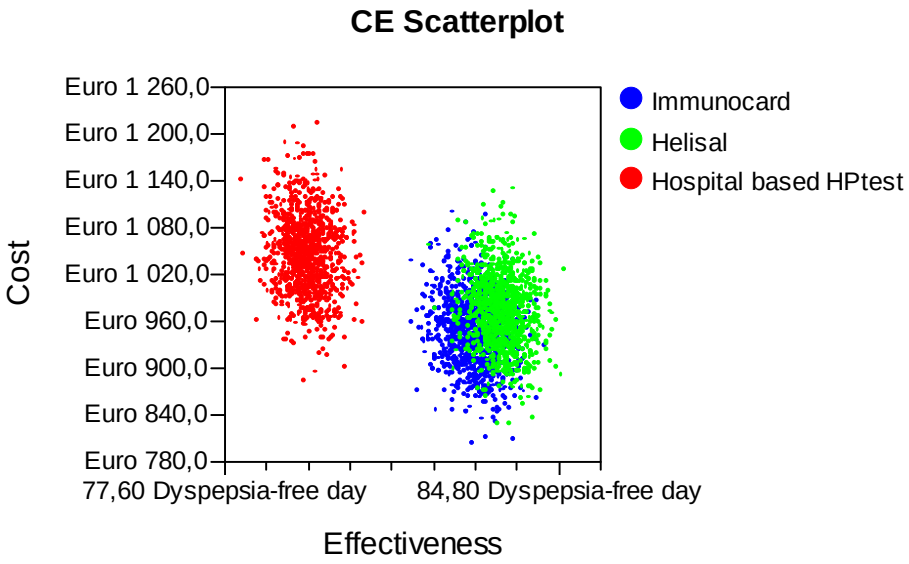

Fig. 6. Results of 10.000 Monte Carlo simulations of the model presented in the cost-effectiveness plane

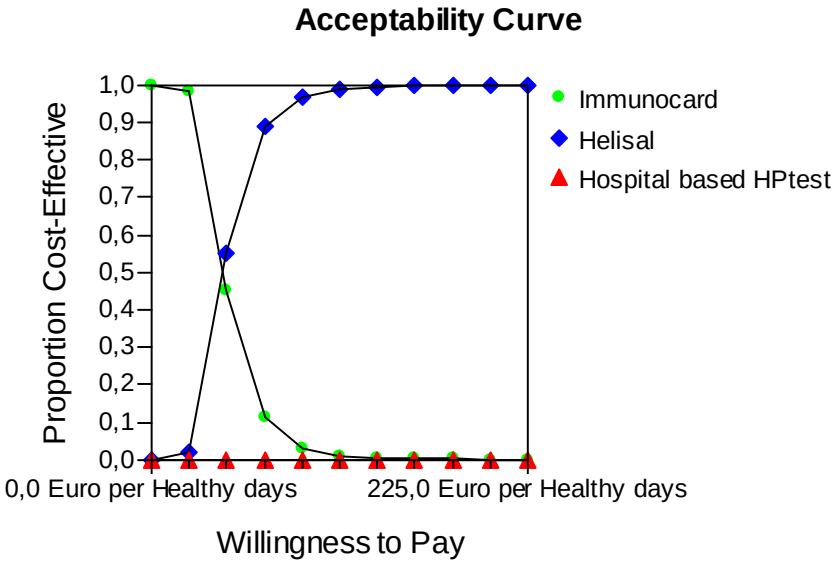

Fig. 7. Acceptability curves for the three tests