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Value of calprotectin in screening out irritable bowel syndrome

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Informing procurement - Encouraging innovation

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Summary

The standard practice for patients who present in primary care with lower gastrointestinal symptoms suggestive of irritable bowel syndrome (IBS) is to carry out diagnostic tests to detect whether there is inflammation of the bowel. The tests currently used include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); however, these can lack diagnostic accuracy for inflammation. Faecal calprotectin is an alternative diagnostic test which has been reported to be more accurate for distinguishing IBS from inflammatory bowel disease (IBD). An economic analysis was therefore conducted to evaluate the use of calprotectin compared with ESR and CRP. In addition, a comparison of laboratory-based calprotectin testing and point-of-care calprotectin testing was undertaken.

For each analysis, the two diagnostic strategies were evaluated in terms of costs and outcomes using a decision tree approach. The economic model followed a cohort of 1,000 hypothetical patients with suspected IBS until the point of confirmed diagnosis involving the use of endoscopy in some patients. The analysis was undertaken from the payer's perspective, hence the costs were limited to direct health care costs. Costs comprised the costs of the tests or endoscopic procedures, medication and the associated clinical consultations. Outcomes were analysed in terms of the number of correctly diagnosed IBS and IBD patients. Data inputs were drawn from published studies, established national databases, and expert clinical opinion.

The base case analysis found that the use of calprotectin compared with ESR plus CRP resulted in an additional 63 correctly diagnosed IBS patients and an additional 55 correctly diagnosed IBD patients at the initial test. Total costs were £312,143 for the calprotectin cohort compared to £325,606 for the ESR plus CRP cohort, making the calprotectin diagnostic strategy cost-saving. Sensitivity analysis identified the specificity and sensitivity of the tests as being key drivers of the results, in addition to the endoscopy cost and calprotectin test cost.

This analysis has demonstrated that faecal calprotectin is less costly and more effective, in terms of diagnostic accuracy, than the standard tests currently used for distinguishing IBS from IBD. The calprotectin testing strategy led to additional patients receiving the correct diagnosis for IBS and IBD, with fewer unnecessary endoscopies being undertaken. When comparing laboratory-based calprotectin with point-of-care calprotectin, point-of-care calprotectin was the dominant strategy for identifying IBS, due to correctly identifying more IBS patients, avoiding unnecessary endoscopies and having lower total costs for the cohort.

The use of calprotectin for the detection of inflammation of the bowel has the potential to improve the management of IBS patients in primary care, reducing the need for referral to secondary care. Health care resource utilisation would therefore be reduced, and ultimately result in cost savings.

Introduction

Background

Irritable bowel syndrome (IBS) is believed to affect 10 to 20% of the general population, with an estimated prevalence of 2.34 million in the UK [1]. The symptoms associated with IBS can often resemble those associated with inflammatory bowel disease (IBD) and result in unnecessary referral to secondary care, with IBS accounting for 29% of gastroenterology referrals [2]. Patients presenting with lower gastrointestinal symptoms are initially assessed for Rome criteria and 'red flag' alarm symptoms, *ie* symptoms that may be caused by another condition that needs investigation[1]. In order to distinguish between IBS and IBD in primary care, tests for inflammation of the bowel are undertaken.

The current practice for detecting inflammation in primary care involves the use of serological tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, such tests can lack diagnostic accuracy for inflammation as they are not a direct reflection of bowel inflammation and can be influenced by nonintestinal diseases [3]. As a result, patients may be referred for further investigation involving invasive endoscopy procedures when in fact there is no inflammation present. In addition to the impact this can have on patients in terms of delayed diagnosis and inconvenience, the unnecessary endoscopies can have a substantial impact on health care resources and the costs incurred by health care providers.

Calprotectin is a calcium-binding protein originating from neutrophils which can be measured in faeces in order to detect inflammation in the bowel. Calprotectin remains stable against bacterial degradation, and stool samples may be kept for up to five days at room temperature without appreciable loss of protein [4]. Measurement has routinely been undertaken quantitatively by enzyme linked immunosorbent assay (ELISA), but has more recently become possible semi-quantitatively, using rapid point-of-care tests for faecal calprotectin.

Calprotectin has been reported to be more accurate for distinguishing IBS from IBD than the blood tests currently used in clinical practice. The use of calprotectin has the potential to aid the general practitioner (GP) in confirming the clinical diagnosis of suspected IBS patients without the need to refer to secondary care. The adoption of calprotectin is therefore likely to generate clinical benefits in terms of more accurate diagnosis of IBS and IBD patients, hence reducing the number of unnecessary endoscopies. The availability of calprotectin testing in primary care may have the potential to reduce health care resource utilisation and time to diagnosis.

[1] 'Red flag' symptoms could include anaemia, weight loss or rectal bleeding, for example.

Scope

To date, the economic impact of calprotectin compared with current practice for detecting inflammation in patients who present with symptoms of IBS in primary care has not been evaluated. The analyses included in this report therefore demonstrate the costs and effectiveness associated with the use of calprotectin for screening out IBS in primary care.

This report evaluates the use of calprotectin compared with alternative diagnostic tests for the detection of inflammation in patients who present in primary care with IBS symptoms. The economic evaluation also included a comparison of laboratory-based calprotectin testing and point-of-care calprotectin testing.

Specifically the comparisons included in the report comprise:

- calprotectin alone vs ESR and CRP
- laboratory calprotectin testing vs point-of-care calprotectin testing.

The baseline analysis compares calprotectin with the tests currently used to detect inflammation - ESR and CRP. The different testing strategies included in the analyses are evaluated in terms of the number of correctly diagnosed IBS and IBD patients, hence the number of avoided endoscopies. In addition the total costs for each testing strategy are combined in order to determine the cost-effectiveness of the different tests used to distinguish IBS from IBD.

Incremental cost-effectiveness ratios (ICERs) are presented in terms of the incremental cost per correct diagnosis made. The standard measure of cost-effectiveness is the quality adjusted life year (QALY), a generic measure enabling comparisons across different disease areas. However, data relating to quality of life scores to generate QALYs were not available. As such, whilst the cost per correct diagnosis may be useful for decision makers within this disease area, it does not allow like-for-like comparisons between interventions across different disease areas.

Objectives

The analysis aimed to model the use of faecal caplrotectin by including clinical and economic data in order to compare the costs and effectiveness of different diagnostic tests with calprotectin for distinguishing IBS from IBD. The specific objectives were:

- to estimate the effectiveness of calprotectin for distinguishing IBS from IBD compared with the effectiveness of alternative tests (ESR and CRP)
- to estimate the costs associated with calprotectin for distinguishing IBS from IBD compared with the costs associated with alternative tests
- to compare the relative cost-effectiveness of different test strategies for distinguishing IBS from IBD.

Methods

A full CEP evidence review has been conducted [5]. The evidence review indicates a general absence of economic studies relating to calprotectin and similar tests for IBD or IBS. A supplementary literature review was therefore undertaken which aimed to ensure that all relevant economic data have been identified to inform the modelling exercise. The supplementary review focussed on published economic evidence relating to calprotectin and its comparators.

CEP evidence review

Several databases were searched for clinical and technical information on calprotectin and other biomarkers for inflammatory bowel disease or irritable bowel syndrome. Further databases were searched for economic information on the use of calprotectin measurement to rule out irritable bowel syndrome. Full details can be found elsewhere [5].

The search terms used in the literature search included the following key terms:

- calprotectin;
- irritable bowel syndrome;
- inflammatory bowel disease.

in addition terms relating to other biomarkers were included.

The search terms for papers on the economic aspects of use of calprotectin measurement in the investigation of bowel disease were:

- calprotectin;
- inflammatory markers;
- inflammatory bowel disease;
- irritable bowel syndrome;
- economics;
- cost effectiveness;
- cost;
- quality adjusted life years (QALY).

The review included studies that were of English language, published within the last 10 years and studies related to human rather than animals. The review excluded studies relating to cancer.

Evidence reviewed

Evidence on the following topics was reviewed systematically:

- clinical performance of faecal calprotectin as a biomarker for organic bowel disease
- clinical performance of faecal calprotectin assays compared with other diagnostic tests
- technical performance of available methods of measuring faecal calprotectin
- economic evidence on the cost of making a diagnosis in patients with gastrointestinal symptoms.

Reviews, prospective studies and case-controlled studies were included in the evidence assessed.

Supplementary economic evidence review

These additional searches were designed to identify studies about: 'costs/economics' of 'calprotectin/erythrocyte sedimentation (ESR)/c-reactive protein (CRP)' in the diagnosis of 'irritable bowel syndrome (IBS)/inflammatory bowel disease (IBD)'; 'sensitivity/specificity/predictive value' of 'calprotectin/ESR/CRP' in the diagnosis of 'IBS/IBD'; 'QALYs' related to 'calprotectin/ESR/CRP' and 'IBS/IBD'; 'point-of-care/laboratory testing' of 'calprotectin'. The searches were restricted by date range to 1999-2009 and to English language only.

The following databases were searched:

- NHS Economic Evaluation Database (NHS EED);
- Health Economic Evaluation Database (HEED);
- Cost-Effectiveness Analysis (CEA) Registry;
- IDEAS (Internet Documents in Economics Access Service);
- Health Technology Assessment (HTA) database;
- MEDLINE;
- EMBASE.

The search strategy used in NHS EED, HEED, CEA Registry, IDEAs and HTA was designed to identify any studies about 'calprotectin/ESR/CRP' or 'IBS/IBD'. As this broad search strategy would have identified relevant studies in each of the areas of interest, the databases were only searched once. The search strategies used in MEDLINE and EMBASE were more specific, and so these databases were searched separately for each of the areas of interest.

Titles and abstracts of bibliographic records were downloaded and imported into EndNote software and duplicate records removed.

The full search strategies used for the supplementary review can be found in appendix 1.

The supplementary review did not identify any additional studies that were relevant for the economic analysis. The studies considered to contain data useful for the economic model were reviewed in depth.

Results

The full literature review findings can be seen elsewhere [5]. The review indicated that faecal calprotectin has significant potential to help in distinguishing IBD and IBS. It is recognised as an informative biomarker of inflammation either alone, or in combination with other tests. Views vary on the adequacy of the reported clinical performance of faecal calprotectin measurement for acceptable screening out of IBS. However, the diagnostic accuracy of faecal calprotectin measurement is better than that of other tests reviewed, such as CRP and ESR.

A raised calprotectin concentration indicates organic rather than functional bowel disease. If calprotectin is included in a panel of biomarkers to improve distinction of IBS from IBD, ideally all tests should be accessible from primary care. Negative results may be sufficient to rule out IBD and avoid colonoscopy but positive results should always be investigated further, probably involving referral to secondary care.

ELISA calprotectin tests produce quantitative results, which should enable a diagnosis of IBS to be made in primary care. Semi-quantitative rapid tests may also be useful in primary care in order to rule out IBD, and could shorten the time to diagnosis although further research is needed.

Diagnostic and social costs of IBS can be high. No cost-effectiveness information relating to faecal calprotectin testing was identified.

National guidance

National guidance on the the diagnosis and management of IBS in primary care for adults has been published by the National Institute for Health and Clinical Excellence (NICE) [6]. Healthcare professionals should consider patients for IBS assessment if there has been abdominal pain or discomfort, bloating or change in bowel habit for at least six months. It is recommended that patients presenting with possible IBS symptoms should be assessed for ‘red flag’ indicators and referred to secondary care if any are present.

For patients who meet the IBS criteria specified in the guidelines, it is recommended that the following tests should be conducted in order to exclude other diagnoses:

- full blood count (FBC)
- ESR or plasma viscosity
- CRP
- antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

However, the guidelines point out that tests such as colonoscopy, barium enema, and sigmoidoscopy are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria.

The NICE guidelines also highlight the need for dietary and lifestyle advice for patients in order to manage their IBS, in addition to the use of pharmacological therapy.

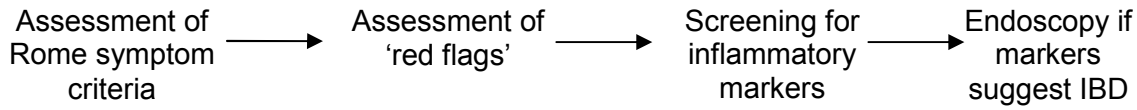
Further guidance on IBS [7] and also IBD [8] has been published by the British Society of Gastroenterology, which include guidelines on appropriate diagnosis and management of IBS and IBD patients. The IBS guidelines [7] state that initial investigation of suspected IBS patients should involve FBC, ESR and CRP tests being conducted, in addition to EMA or TTG antibody testing. The IBD guidelines [8] state that diagnosis of IBD is confirmed by clinical evaluation, in addition to a combination of biochemical, endoscopic, radiological, histological, or nuclear medicine based investigations. Initial laboratory investigations should include FBC, ESR, CRP and additional tests for liver function *etc*.

The 18 week patient pathway from the Department of Health states that it should take no more than 18 weeks from the time the patient is first referred to the start of treatment, on pathways that do or might involve consultant led care. Care should be delivered where the patient requires it [9].

The evidence review reported that the 18 week pathway for change in bowel habit is the non-cancer pathway for change of bowel habit. If cancer is suspected, for example in those having 'red flag symptoms' the cancer 2 week pathway applies. Patients will be referred to secondary care endoscopic investigation to rule out the presence of polyps, adenomas or bowel cancer. Colonoscopy is the gold standard procedure but CT colonography is increasingly the first choice radiological test as it is less invasive and provides an image of the whole colon and extra-colonic structures [9].

Discussion

The information drawn from the reviewed guidance and studies enabled a model structure to be developed and provided parameters for inclusion in the model. The model was developed by considering the following stages for patients who present with lower gastrointestinal symptoms:



Guidance has outlined that the pathway differs for patients who have 'red flag' symptoms, and therefore these patients were not included in the model. Similarly patients over the age of 45 have been excluded from the model, since those over this age would follow a different pathway. The analysis focuses on patients who were negative for 'red flags' and who have suspected IBS , as indicated by Rome criteria[2]. In order to differentiate between IBS and IBD in primary care, tests for inflammation of the bowel are undertaken.

The guidelines from the British Society of Gastroenterology and published studies[3] helped to inform the relevant tests for inclusion in the model. ESR and CRP tests are employed as representative of standard practice in the identification of inflammation.

Tibble *et al* [3] indicated that tests such as ESR and CRP are indirect measures of inflammation and can therefore be influenced by several non-intestinal diseases. As a result the tests can lack diagnostic accuracy for inflammation and may lead to patients being referred for further investigation involving invasive endoscopy procedures when in fact there is no inflammation present.

Calprotectin has been reported to be more accurate for determining which patients should be referred for further investigation due to the presence of inflammation.This in turn will impact on the number of endoscopies performed.

The differences in effectiveness of the various tests for inflammation will be driven by differences in test sensitivity and specificity. Studies containing such data were selected on the basis of relevance to the model design and study quality, in order to inform the development of the model. Further details relating to the studies used for the model are provided in the *Methods* section of this report.

[2] It has been reported that Rome criteria are rarely used formally in routine clinical practice (2).

The economic analysis used a decision tree approach to determine the cost-effectiveness of different investigations used in the diagnosis of IBS and IBD. A decision tree allows the prediction of the number of patients who are likely to follow a particular pathway. Each pathway generates a unique outcome in terms of costs and health benefits. The outcomes can then be combined with the number of patients that experience each end state in order to calculate the expected cost for the patient cohort.

The model was developed in Microsoft Excel and aimed to capture the current diagnostic pathway for a cohort of 1,000 hypothetical patients presenting with lower gastrointestinal symptoms. The associated costs and outcomes for different diagnostic strategies were included in the model.

The time horizon of the model is the time taken to reach a confirmed diagnosis of either IBD or IBS. Due to the short time horizon, discounting of costs and benefits was not undertaken for the analysis. The analysis was undertaken from the perspective of the payer, *ie* the National Health Service (NHS) in the United Kingdom (UK).

Patient population

The patient population considered in the model comprised patients presenting to the GP in primary care with lower gastrointestinal symptoms suggestive of IBS, as indicated by Rome criteria. 'Red flag' alarm symptoms (*ie* anaemia, weight loss or rectal bleeding) were considered to be absent, since such patients would require investigation irrespective of laboratory markers [3] and would therefore follow a different pathway to those specified in the model. Patients were assumed to be below the age of 45 years, since those over this age would follow a different pathway. (The cancer two week pathway would apply; patients would be referred to secondary care automatically for endoscopic or radiological investigation.)

Many people who have IBS do not seek medical advice due to the embarrassing nature of the symptoms and may therefore prefer to use over-the-counter remedies. Such patients are not included in this analysis.

Comparisons

Calprotectin was compared with other tests for differentiating IBD from IBS. The comparisons made in the analysis are shown in table 1. The baseline analysis compares calprotectin with the tests currently used to detect inflammation - CRP and ESR.

Table 1. Comparisons for analysis

Comparison	Strategy A	Strategy B
1	Calprotectin alone	ESR + CRP
2	Laboratory calprotectin	Point-of-care calprotectin

Model structure

The model structure is depicted in figure 1, which was validated by clinical experts to ensure that current clinical practice was accurately represented. The diagnostic pathway of patients presenting with lower gastrointestinal symptoms is modelled as follows.

- Patients presenting to the GP with IBS symptoms receive diagnostic tests to detect whether they have inflammation of the bowel (in addition to assessment of history and physical examination).

- At node A[3], the diagnostic tests for inflammation will return either positive or negative results; to receive the test results patients will return to their GP. The proportion of positive and negative results are defined by the diagnostic accuracy of the tests used, along with the prevalence of IBD and IBS in this patient population.

- For the patients who have a positive test result, indicating inflammation, the model assumes that this would be investigated further by endoscopy. Node B shows where the endoscopy will confirm inflammation (IBD true positives) or not (IBD false positives). These calculations are based on the prevalence of IBD in the modelled population, and the specificity and sensitivity of the corresponding tests.

- Patients who have a negative test result for inflammation (*ie* normal test results) are managed for IBS. The first level of IBS management involves dietary and lifestyle advice, which patients are assumed to follow for one to two months, after which time they will return to their GP for a follow-up visit.

- At node C, where patients return to their GP after following IBS dietary and lifestyle advice, their symptoms will either be adequately controlled and will therefore not require any further GP visits (*ie* IBD true negative), or their symptoms will be inadequately controlled. Where symptoms are

[3] Note: reference to nodes A, B, C *etc*. in the text relates to the chance nodes displayed in Figure 1.

inadequately controlled, a second level of more intensive IBS management will be provided, using medication, and tests for IBD repeated.

- Node D indicates that patients who take the IBS medication will either respond to the medication and hence have adequate control of symptoms (IBD true negatives), or the symptoms will not resolve, requiring a further visit to the GP for repeat testing (node E).

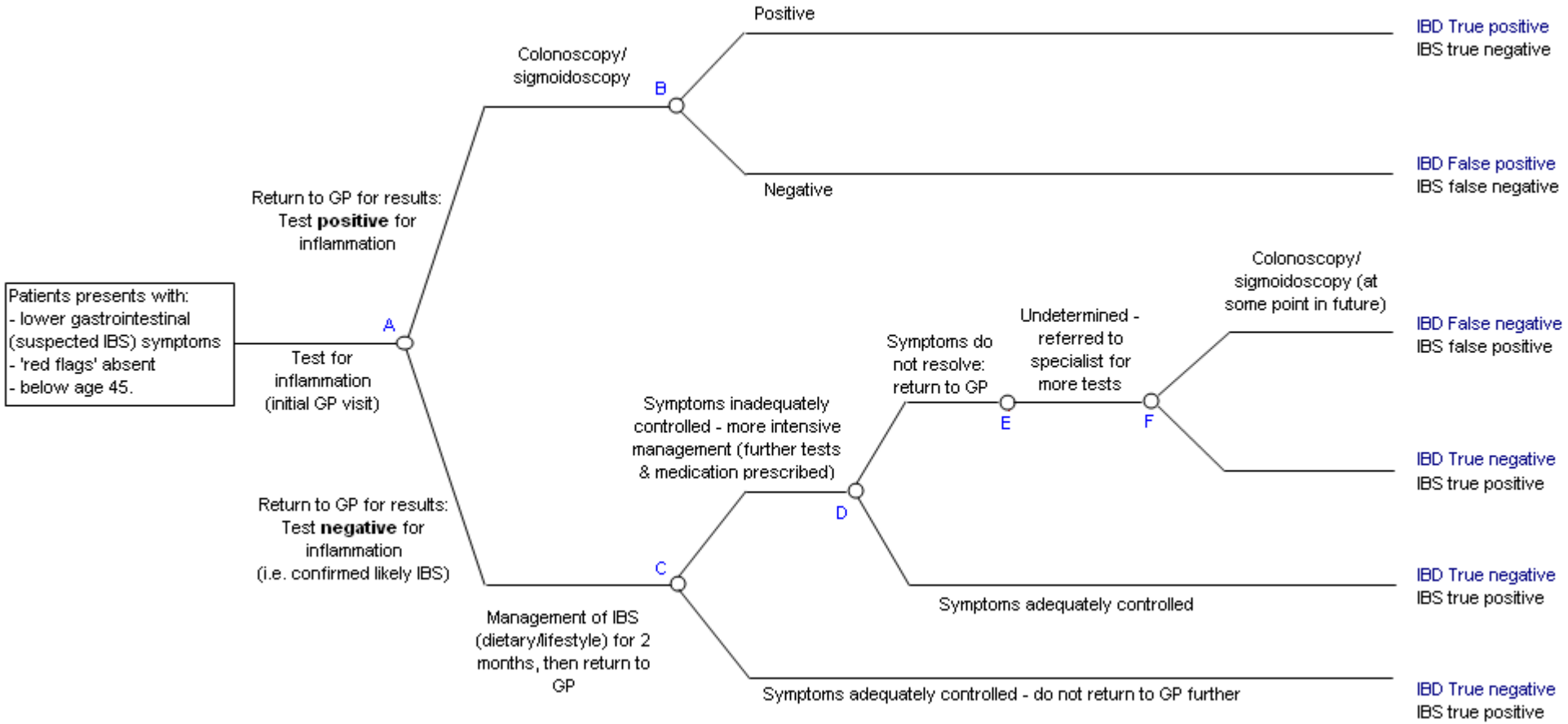
- At node E, patients who continue to have inadequate control of symptoms will be referred to a specialist in secondary care for further investigation, assumed to involve further tests including an endoscopy. Node F then indicates where the endoscopy identifies inflammation of the bowel (IBD false negatives) or does not (IBD true negatives). Note that all patients at node F would receive an endoscopy.

A separate decision tree was developed for each of the test strategies:

- calprotectin
- ESR and CRP
- laboratory calprotectin
- point-of-care calprotectin.

Methods

Figure 1. Model schematic



Economic evaluation

Cost-effectiveness models are used to assess the relative benefits of a given intervention or strategy using patient outcomes and the costs incurred in achieving those outcomes. The additional cost per unit of benefit gained is of key interest to policy and decision makers. This is known as incremental (marginal) analysis and results are presented as incremental cost-effectiveness ratios (ICERs).

The ICER for comparing two testing strategies can be calculated using the formula below, which divides the difference in the costs of the two strategies by the difference in the effectiveness of the strategies:

$$ICER = \frac{Cost_{Strategy1} - Cost_{Strategy2}}{Effect_{Strategy1} - Effect_{Strategy2}}$$

The model generates the total expected costs and effectiveness in order to estimate incremental cost-effectiveness ratios using the number of correctly identified IBS patients and the number of correctly identified IBD patients. This information can be used in decision-making, in order to identify an optimal testing strategy for distinguishing IBS from IBD.

Costs

Since the analysis was taken from the perspective of the NHS, the costs included in the model were limited to direct costs. That is, the analysis included health care costs that were incurred as a direct consequence of the diagnostic strategies for distinguishing IBS from IBD. Indirect costs such as travel time and lost productivity due to symptom-related work absence were not included given the payer perspective of the analysis. All costs are evaluated in 2008/09 pounds (£).

For each test strategy (*eg* ESR + CRP), total costs were calculated by assigning costs to the corresponding numbers of patients who were at the end of each pathway in the model. The relevant costs comprised the costs of the tests or endoscopic procedures, medication and the associated resource use, such as GP visits. The total costs include the costs associated with the different pathways followed by patients in order to reach a correct diagnosis, using endoscopy as necessary.

Outcomes

The outcomes included in the analysis comprise the number of correctly diagnosed cases of IBS and the number of correctly diagnosed cases of IBD from the initial use of each diagnostic method. For each comparison, the total numbers of correctly diagnosed IBS and IBD cases were calculated for both strategies under consideration and compared to demonstrate the associated incrementals.

For each strategy, the number of correctly identified IBS patients was derived from the number of IBD true negatives, *ie* the number of patients that were correctly identified by the initial test as being truly negative for IBD, and therefore positive for IBS.

The number of correctly identified IBD patients was derived from the number of IBD true positives in the model for each strategy. That is, the number of patients whom the initial test correctly identified as truly having IBD.

As the model followed each patient through to a final correct diagnosis (assuming endoscopy to be the gold standard) the initial success rates act as a proxy for the clinical benefit of faster diagnosis and institution of therapy.

Incremental cost-effectiveness ratios

The results from the analysis are displayed in terms of the incremental cost-effectiveness ratio, specifically:

- the incremental cost per correctly diagnosed IBS patient
- the incremental cost per correctly diagnosed IBD patient.

For example, for the comparison of calprotectin alone versus ESR plus CRP, the incremental cost per correctly diagnosed IBS patient can be calculated using the following formula, where 'effect' represents the number of correctly diagnosed IBS patients:

$$ICER = \frac{Cost_{Calprotectin} - Cost_{ESR+CRP}}{Effect_{Calprotectin} - Effect_{ESR+CRP}}$$

Data

The data used in the model were sourced from published studies where possible, identified from the literature reviews. Expert clinical consultation was undertaken in order to validate the model structure and to provide estimates where the necessary data were absent. The final model structure therefore reflects the views of clinical experts and the availability of good quality data.

Clinical data
Accuracy of tests

Clinical data on the accuracy of the various diagnostic techniques were sourced from published studies identified in CEP's evidence review (table 2).

Table 2. Diagnostic accuracy values used in model

Test	Sensitivity (%)	Specificity (%)	Reference
Calprotectin	90	80	Tibble *et al* 2002 [3]
ESR + CRP	35	73	Tibble *et al* 2002 [3]
Calprotectin (Lab)	96	87	Otten *et al* 2008 [10]
Calprotectin (POC)	61	98	Otten *et al* 2008 [10]

For each comparison, the accuracy values for both strategies were drawn from the same study. This was to ensure that the specificities and sensitivities were calculated using the same patient population and study conditions in order to minimise bias which would arise from combining diagnostic accuracy values from different studies.

The cut-off value for calprotectin tests that is most frequently used, and recommended by manufacturers, is 50 µg/g, with similar cut-off points used in the studies from which the diagnostic values for the model were drawn. Faecal calprotectin results below 50 µg/g indicate the patient is negative for inflammation, whereas results above 50 µg/g indicate there is inflammation of the bowel. A high faecal calprotectin concentration is a strong indicator that an endoscopy should be undertaken in order to rule out IBD or other organic pathologies [11].

The specificity and sensitivity values for calprotectin and ESR plus CRP were taken from the study by Tibble *et al* 2002 [3], which assessed the diagnostic accuracy of several markers of inflammation for distinguishing between IBS and organic bowel disease. The patients included in the study had been referred to a gastroenterology clinic for symptoms suggestive of IBS or organic intestinal disease. The values used for the model were based on the results for a subset of patients in the study, who were positive for Rome criteria and negative for 'red flags', *ie* for 281 patients at low risk of organic disease.

Diagnostic accuracy values for the comparison of laboratory-based calprotectin and point-of-care calprotectin were drawn from the study by Otten *et al* 2008 [10]. The diagnostic performance of the two types of calprotectin tests were assessed in terms of their ability to differentiate IBD from IBS in 114 patients who were referred to hospital with chronic abdominal complaints. The specificity and sensitivity for the

rapid calprotectin test relate to a cut-off value of 60 µg/g being used. The study also included diagnostic accuracy values for a lower cut-off of 15 µg/g.

The model assumed that the endoscopic procedures were 100% accurate.

Resource use pathway data

The literature review helped to guide the pathways and resource use included in the model. More detailed information on current resource use patterns in the NHS was sought from clinical experts, such as the proportion of patients who would have adequate control of symptoms following dietary and lifestyle IBS management. In combining the estimates from experts, average values were taken. The resource use data used in the model can be seen in table 3.

Table 3. Resource use data used in model

Resource	Value	Reference
True negatives return with persistent symptoms due to inadequate control using dietary/lifestyle advice (node C)	50%	Expert clinical opinion
True negatives' symptoms do not resolve - *ie* require further investigation (node D)	5%	Expert clinical opinion
Proportion given colonoscopy, as opposed to sigmoidoscopy	100%	Current policy, expert clinical opinion
Average number of calprotectin tests taken	1.16	Unpublished data, clinical opinion

For patients who are referred to secondary care for further investigation via endoscopy, the model allows for a certain proportion being given a colonoscopy and the remainder being given a sigmoidoscopy. In the base case all patients are given a colonoscopy, in line with policies that are currently in place at certain hospitals in the UK (expert opinion). However this proportion is varied using sensitivity analysis to investigate the impact on the overall results. We understand that when sent for further investigation patients may have an alternative to endoscopy such as a barium enema, but there is little published evidence on this and, for simplicity. we have assumed that patients in the model would be sent for an endoscopy.

Based on clinical expert opinion, after following dietary and lifestyle advice, 50% of the true negative patients do not return to the GP; their symptoms are adequately controlled. Of the remaining 50% who do seek additional advice from their GP (involving repeat tests) and move onto a second level of IBS management using medication, 5% will return a further time to the GP (based on expert opinion).

When patients in the negative arm of the decision tree return to the GP due to their symptoms being inadequately controlled, further tests are undertaken (according to

expert opinion). The further tests that are given are assumed to comprise the same tests as those undertaken in the first instance. For example, when considering the calprotectin alone strategy, the further tests undertaken were repeat calprotectin tests. Similarly for patients in the ESR plus CRP decision tree, the repeat tests comprised ESR and CRP.

Based on clinical expert opinion, it was ascertained that a positive calprotectin result would not necessarily indicate that a patient should be sent straight for endoscopy. Calprotectin results have different levels of positivity due to the quantitative nature of the test. Those who have values over 250 µg/g would be sent for endoscopy immediately. However, for those who have an 'intermediate' positive result, within a 'grey zone' between 50 µg/g and approximately 250 µg/g, it is probable that another calprotectin test would be conducted before making a decision about referral for endoscopy. Hence it may be necessary for more than one calprotectin test to be undertaken in order to make a decision as to whether to send the patient for endoscopy.

In order to capture the costs associated with such additional calprotectin tests, the proportion of test results that fall within the 'grey zone' (50-250 µg/g), and therefore lead to an extra test, was sourced from unpublished data for over 2,700 calprotectin results. The results were for patients under 45 years of age who were referred to hospital with lower gastrointestinal symptoms, excluded for IBD before this point, over a period of five years [12]. The data indicate that 16% of patients had results which fell in the 'grey zone', hence an average of 1.16 calprotectin tests was assigned per patient. This was built into the cost calculations of the model, for both laboratory and point-of-care calprotectin tests.

Cost data

Cost data were obtained from standard national sources such as the NHS National Tariff [13], the British National Formulary (BNF) [14] and the PSSRU Unit Costs of Health and Social Care [15] in the first instance. Where data were not available from these sources, such as for point-of-care (rapid) calprotectin tests, supplier websites were used. Table 4 provides a summary of the cost data used in the model.

The laboratory calprotectin test cost was obtained from KingsPath Clinical Diagnostic Pathology Services [16]; the comprehensive cost for a Buhlmann calprotectin ELISA test including kit and materials, staff input and overheads was £25 in total. The cost of the calprotectin point-of-care rapid test (£27,68) similarly comprises the cost of the test kit (based on £145 for 10 tests, excluding VAT, sourced from Alpha Laboratories [17]), labour (nurse consultation cost of £11[15]) and overheads. For point-of-care calprotectin testing, the model incorporates the test being conducted by a nurse on a separate occasion to the initial GP visit, since it is unlikely that the patient will be able to produce a stool sample at that time. After the point-of-care test has been carried

out by the nurse, the patient is seen by a GP to discuss next steps. For the laboratory-based calprotectin test, the sample is returned to the surgery without need for consultation with a nurse or GP (expert opinion).

The costs for ESR and CRP tests were drawn from the Indicative Tariff 2008/09 [18]. In line with the NICE costing report, the CRP cost is based on a biochemistry test and the ESR cost is based on a haematology test. The costs were inflated by the national average market forces factor, as were all costs from the National Tariff [13].

Endoscopy costs were obtained from the National Tariff 2008/09 [13]. The sigmoidoscopy cost relates to a flexible sigmoidoscopy, and the colonoscopy cost is based on a the cost for endoscopic or intermediate procedure, relating to the large intestine.

The costs for a nurse visit and GP visit were derived from the PSSRU Unit Costs for Health and Social Care [15]: £11 per nurse consultation, and £36 per GP consultation, lasting 12 minutes on average. For patients who are referred to a specialist in secondary care for further investigation, the cost was derived from the cost of a gastroenterology outpatient visit (£189), from the National Tariff 2008/09 [13].

For patients who required medication for control of IBS symptoms, the cost of mebeverine (an antispasmodic agent licensed for use in the UK [7]) use was included, in order to represent the cost incurred by a typical IBS patient according to medical opinion & IBS guidelines. We are aware that the medication prescribed to IBS patients will vary depending on the predominant symptoms experienced, however the cost included in the model aims to provide an example of the possible costs such patients would incur. Based on expert opinion, the IBS medication cost is based on two months of mebeverine tablets, which can be used on an as required basis (*ie* before meals). The cost for two months of mebeverine used in the model is £17.22 in total; 100-tablet pack of mebeverine = £9.43, assumed to be taken 3 times a day [14].

Table 4. Costs used in the model

Test/Resource	Cost	Reference
Calprotectin (Lab) [a]	£25.00	KingsPath [16]
Calprotectin (POC) [a]	£27.68	Alpha Labs [17]; PSSRU Unit Costs [15] [b]
CRP	£1.60	Indicative tariff [18]
ESR	£3.04	Indicative tariff [18]
Colonoscopy	£544.45	National tariff [13]
Sigmoidoscopy	£365.59	National tariff [13]
GP visit	£36.00	PSSRU Unit Costs [15]
Specialist visit	£188.81	National tariff [13]
IBS medication (mebeverine, 100-tablet pack)	£9.43	British National Formulary [14]

[a] The calprotectin test cost comprises the test kit, labour and overheads; [b] nurse consultation cost of £11 was included.

Prevalence data

The model considers a population of patients who have lower gastrointestinal symptoms suggestive of IBS, with no 'red flags' present. The prevalence data required for the model therefore comprise the proportions of IBD and IBS patients within this population who present in primary care. Hence the proportions of IBD and IBS patients are assumed to sum to 100%.

Data on the prevalence of IBS and IBD patients in primary care have not been identified. The majority of studies relating to such patients are based in secondary care, where the patients tend to have more severe symptoms than those of patients presenting in primary care. Therefore, prevalence data were derived from clinical expert opinion; 90% of the patient population had IBS and the remaining 10% had IBD. Due to the paucity of evidence relating to IBS and IBD prevalence, sensitivity analysis was undertaken.

Base case analysis (Comparison 1)

For the comparison of calprotectin alone against ESR plus CRP, calprotectin was found to be the dominant diagnostic strategy for all outcomes explored in the analysis. The use of calprotectin compared with ESR plus CRP resulted in an additional 63 correctly diagnosed IBS cases and an additional 55 correctly diagnosed IBD cases, in the hypothetical cohort of 1,000 patients. The base case results can be seen in tables 5 and 6.

The total costs were estimated to be £312,143 for the cohort tested with calprotectin, compared with £325,606 for the ESR plus CRP cohort. The strategy involving calprotectin was therefore associated with a reduction in costs of £13,464 when compared with the use of ESR plus CRP. The calprotectin strategy is therefore considered to be cost-saving.

Table 5. Results of calprotectin versus ESR + CRP

Test strategy	Correctly diagnosed IBS cases	Correctly diagnosed IBD cases	Total costs
Calprotectin alone	720	90	£312,143
ESR + CRP	657	35	£325,606

Table 6. Incremental analysis: calprotectin versus ESR + CRP

Incremental cost	Additional correctly diagnosed IBS cases	Cost per correctly diagnosed IBS case	Additional correctly diagnosed IBD cases	Cost per correctly diagnosed IBD case
-£13,464	63	Dominant	55	Dominant

Comparison 2

The use of laboratory-based calprotectin tests generated additional costs for the patient cohort compared with the use of point-of-care calprotectin tests; total costs were £36,167 higher for the laboratory calprotectin testing. The laboratory-based calprotectin test generated additional correctly diagnosed IBD cases but resulted in fewer correctly diagnosed IBS cases and hence additional unnecessary endoscopies. In terms of identifying IBS, point-of-care calprotectin testing was therefore the dominant strategy, when compared with laboratory-based calprotectin testing due to correctly identifying more IBS patients, avoiding unnecessary endoscopies and having lower total costs for the cohort. The incremental cost per correctly identified IBD patient for laboratory calprotectin was £1,030. The corresponding results are shown in tables 7 and 8.

Table 7. Results of calprotectin (Lab) versus calprotectin (POC)

Test strategy	Correctly diagnosed IBS cases	Correctly diagnosed IBD cases	Total costs
Calprotectin (Lab)	781	96	£281,663
Calprotectin (POC)	880	61	£245,496

Table 8. Incremental analysis: calprotectin (Lab) versus calprotectin (POC)

Incremental cost	Additional correctly diagnosed IBS cases	Cost per correctly diagnosed IBS case	Additional correctly diagnosed IBD cases	Cost per correctly diagnosed IBD case
£36,167	-99	No benefit	35	£1,030

Sensitivity analysis

Extensive sensitivity analyses were conducted to determine the key inputs which drive the results of the model. One-way sensitivity analyses were undertaken, meaning that one parameter was varied whilst the remaining parameters in the model were held constant. Sensitivity analysis was conducted for the following inputs, with the results shown in terms of the impact on the incremental costs[4]:

- sensitivity and specificity of the inflammatory tests
- cost of the tests
- prevalence of IBS/IBD
- cost of colonoscopy
- proportion of patients sent for colonoscopy compared with sigmoidoscopy.

Base case

The impact of endoscopy costs can be seen in figures 2 and 3. By varying the ratio of colonoscopy to sigmoidoscopy procedures it is evident that when the proportion of patients given a colonoscopy reduces (*ie* proportion given a sigmoidoscopy increases), the average cost of endoscopy is lower as a result (figure 2). The calprotectin strategy is cost-saving for all colonoscopy to sigmoidoscopy ratios, *ie* even when all patients receive an endoscopy, costs remain lower under the

[4] Sensitivity analysis was displayed in terms of the impact on incremental costs rather than the ICER due to more meaningful results able to be displayed.

calprotectin strategy. Varying the cost of a colonoscopy investigates this further, for the base case; as the cost reduces to below approximately £340, the calprotectin strategy involves incremental costs compared with the ESR plus CRP strategy, as displayed in figure 3.

For all IBD prevalence values, the calprotectin strategy had associated cost-savings (figure 4). The impact of varying the cost of calprotectin and ESR tests can be seen in figures 5 and 6; the calprotectin results remain dominant for all costs of an ESR test that were explored, however as the cost of a calprotectin test exceeds approximately £33, incremental costs are incurred for the calprotectin strategy.

The sensitivity of a test is linked to the specificity of a test. Hence, when varying the sensitivity and specificity values of calprotectin, the receiver operator curve (ROC) from the Tibble *et al* study[5] was used in order to indicate how the two are likely to be related. Different scenarios were investigated, as shown in table 9.

Table 9. Sensitivity and specificity scenarios for calprotectin

Scenario	Sensitivity (%)	Specificity (%)	Incremental Cost
Base case	90	80	-£13,464
Scenario 1	100	50	£109,476
Scenario 2	84	90	-£53,569
Scenario 3	80	93	-£64,879

Scenarios where the sensitivity was lowered and specificity was increased (scenarios 2 and 3) demonstrated additional cost savings compared with those generated in the base case. Where sensitivity was increased, at the expense of a loss in specificity, incremental costs were incurred, as shown by scenario 1.
The impact of using accuracy values from an alternative study was explored. The study by Dolwani *et al* 2004 [19] contained a smaller patient group but used a more recent calprotectin test. As a consequence, the base case results were altered quite considerably, due to the ESR plus CRP tests being more specific than the calprotectin test. Higher numbers of false positive patients in the calprotectin arm result in extra expense through additional endoscopies being performed unnecessarily. However, it is worthwhile to note that the cut-off for a positive test tends to be user-definable where the test is quantitative, such as for a calprotectin test. An increase in the cut-off value would reduce the number of false positives (*ie*

[5] The ROC curve in the Tibble *et al* study relates to the identification of patients with organic and non-organic disease using calprotectin, for all patients, rather than the subset that our analysis was based on. However, the purpose of the ROC curve here is to give an indication of the likely movement of the specificity in relation to the sensitivity.

increase specificity). The results presented in table 10 suggest that there is the potential for the specificity of calprotectin to be increased through a small increase in the cut-off used, whilst maintaining higher sensitivity than ESR plus CRP.

Table 10 displays the diagnostic accuracy values from the alternative study. Under this scenario, there are 45 fewer correctly diagnosed IBS patients under the calprotectin strategy, and therefore additional unnecessary endoscopies. There are additional correctly diagnosed IBD patients, but at increased total costs of £39,112 for the cohort.

Table 10. Alternative diagnostic accuracy values

Test	Sensitivity (%)	Specificity (%)	Reference
Calprotectin	100	79	Dolwani *et al* 2004 [19]
ESR + CRP	50	84	Dolwani *et al* 2004 [19]

Figure 2. Sensitivity analysis: colonoscopy to sigmoidoscopy ratio

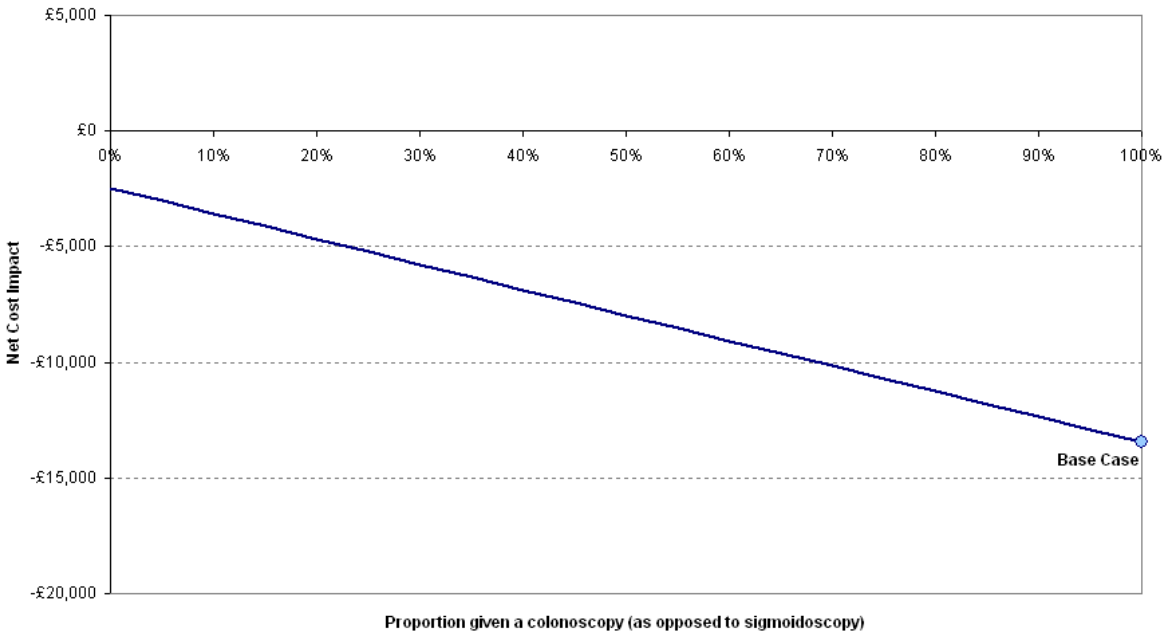


Figure 3. Sensitivity analysis: cost of colonoscopy

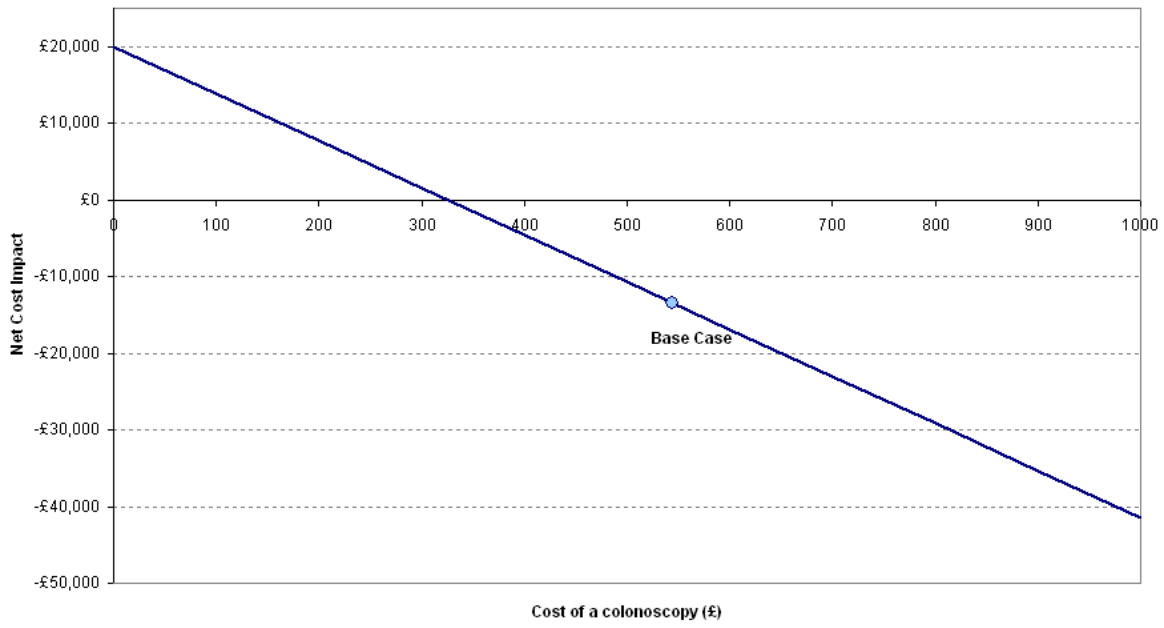


Figure 4. Sensitivity analysis: prevalence of IBD

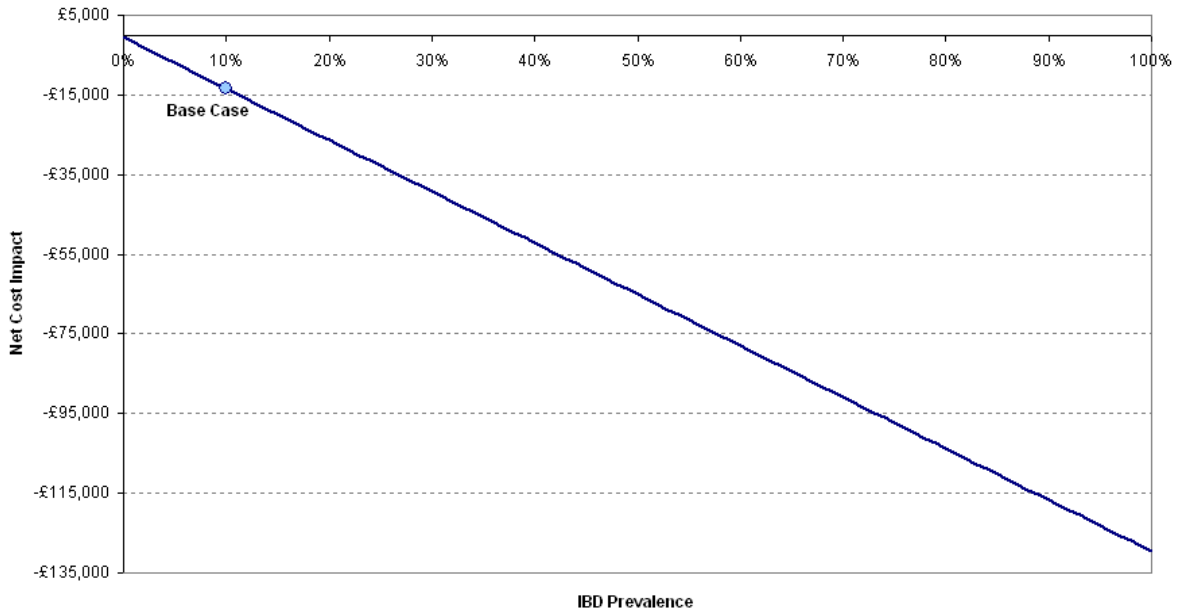


Figure 5. Sensitivity analysis: calprotectin test cost

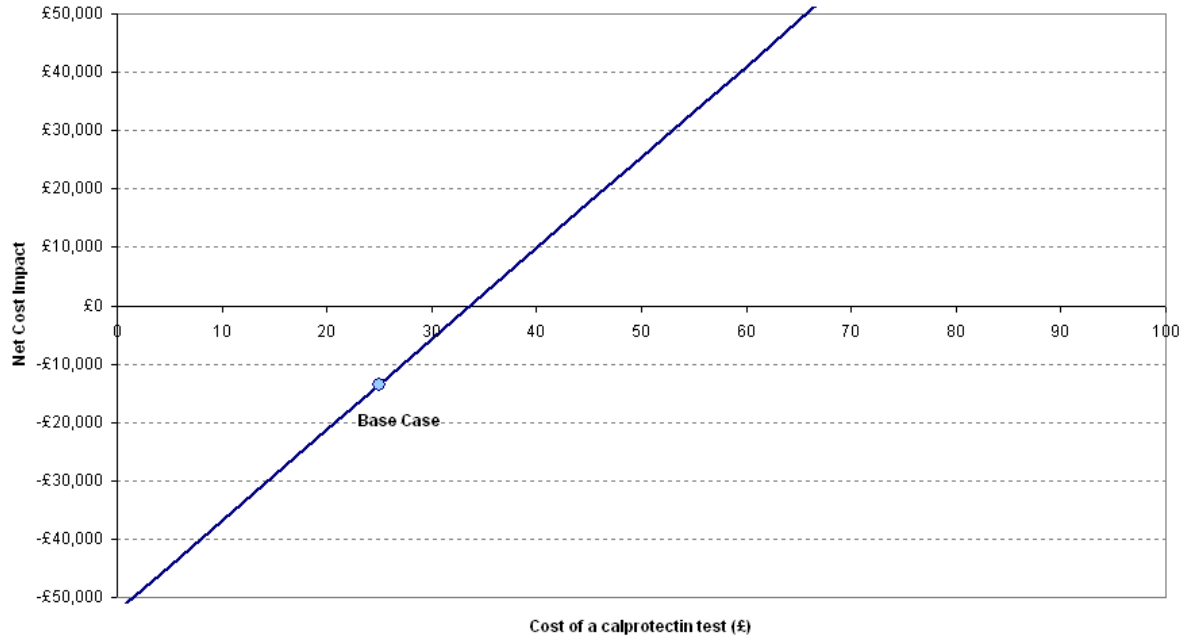
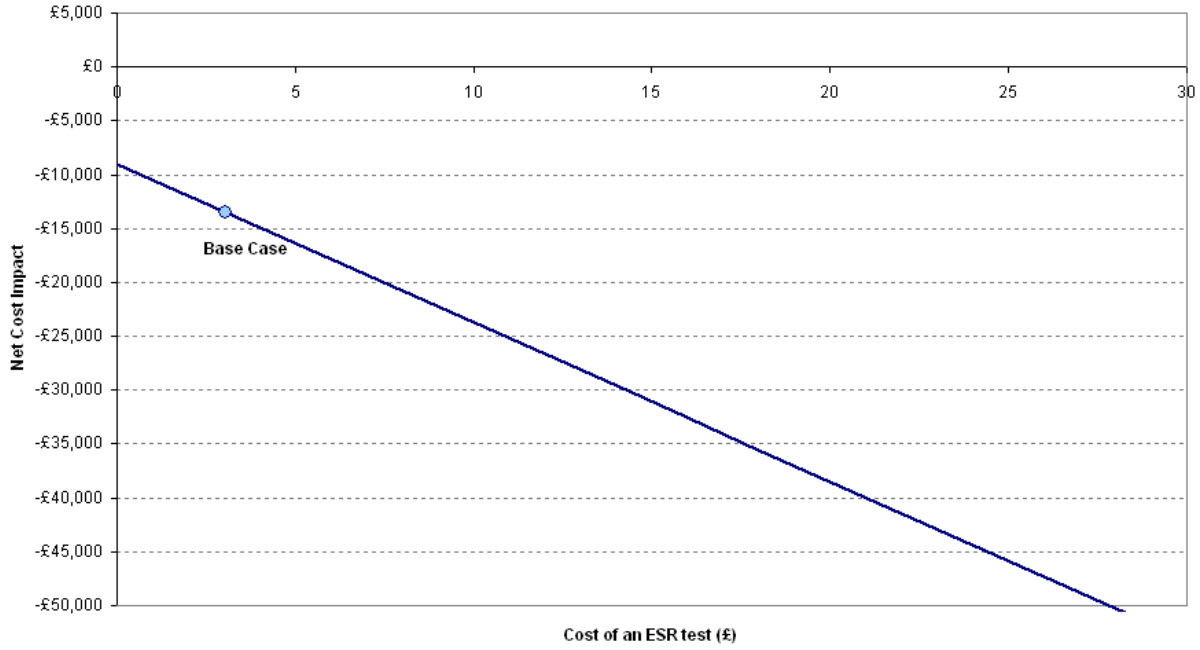


Figure 6. Sensitivity analysis: ESR test cost



Comparison 2

Alternative study

Due to the lack of evidence surrounding the point-of-care tests due to the tests being relatively new, the diagnostic accuracy of such tests compared with the laboratory-based tests as found by Damms and Bischoff 2008 [20] was also investigated (table 11).

Table 11. Alternative diagnostic accuracy values

Test	Sensitivity (%)	Specificity (%)	Reference
Calprotectin (Lab)	100	79	Damms & Bischoff 2008 [20]
Calprotectin (POC)	89	80	Damms & Bischoff 2008 [20]

The corresponding results can be seen in tables 12 and 13, which indicate point-of-care calprotectin remains the less costly option, although marginally, with the differences in initial accuracy being much less.

Table 12. Results of calprotectin (Lab) versus calprotectin (POC)

Test strategy	Correctly diagnosed IBS cases	Correctly diagnosed IBD cases	Total costs
Calprotectin (Lab)	711	100	£313,070
Calprotectin (POC)	720	89	£312,244

Table 13. Incremental analysis: calprotectin (Lab) versus calprotectin (POC)

Incremental cost	Additional correctly diagnosed IBS cases	Cost per correctly diagnosed IBS case	Additional correctly diagnosed IBD cases	Cost per correctly diagnosed IBD case
£826	-9	No benefit	11	£75

Alternative cut-off

In addition to the 60 µg/g cut-off used for the POC calprotectin test in the study by Otten *et al[10]* a 15 µg/g cut-off was also considered. The associated specificity and sensitivity values are displayed in table 14. When compared with the original comparison 2 diagnostic accuracy values, the 15 µg/g cut-off was associated with a higher sensitivity of 100% and a slightly lower specificity of 95%.

Table 14. Diagnostic accuracy values associated with POC calprotectin test: 15 µg/g cut-off

Test	Sensitivity (%)	Specificity (%)	Reference
Calprotectin (POC)	100	95	Otten *et al* 2008 [10]

The results associated with the use of a lower cut-off value of 15 µg/g can be seen in tables 15 and 16. Laboratory-based calprotectin testing resulted in fewer correctly diagnosed IBS and IBD patients than POC calprotectin testing. This is in contrast to the original comparison which found that the laboratory-based calprotectin strategy led to additional correctly diagnosed IBD patients when compared with POC calprotectin.

Table 15. Results of calprotectin (Lab) versus calprotectin (POC: 15 µg/g cut-off)

Test strategy	Correctly diagnosed IBS cases	Correctly diagnosed IBD cases	Total costs
Calprotectin (Lab)	781	96	£281,663
Calprotectin (POC)	851	100	£247,242

Table 16. Incremental analysis: calprotectin (Lab) versus calprotectin (POC: 15 µg/g cut-off)

Incremental cost	Additional correctly diagnosed IBS cases	Cost per correctly diagnosed IBS case	Additional correctly diagnosed IBD cases	Cost per correctly diagnosed IBD case
£34,421	-69	No benefit	-4	No benefit

Discussion

The base case analysis indicates that calprotectin will result in more correct diagnoses than the current practice of ESR and CRP tests being used. In addition, fewer unnecessary colonoscopies occur when calprotectin is used to distinguish IBS from IBD, at reduced cost. Sensitivity analysis has demonstrated that the calprotectin strategy remains dominant for certain scenarios. The key drivers of the results were identified as being the accuracy values, endoscopy costs and the calprotectin test cost.

The cut-off point used for the tests under analysis is vital in order to generate efficient and cost-effective use of tests. The cut-off values for the tests included in the evaluations were based on those recommended by the manufacturer. The assumption that all patients who have a calprotectin result over 50 µg/g (*ie* the threshold for positive and negative results) receive an endoscopy is not likely to arise in practice. It is probable that patients who had an initial intermediate test result, ranging from 50 µg/g to 250 µg/g, would be re-tested and subsequently the second test may find that an endoscopy is not needed. The cost of re-testing the 'intermediate' patients is included in the model. Hence, by incorporating these costs and by assuming all positive IBD patients in the calprotectin strategy would receive an endoscopy, the cost savings demonstrated through the use of calprotectin may actually be underestimated. A conservative approach has therefore been taken in the absence of data relating to the specificity and sensitivity of repeat calprotectin tests being conducted. The collection of such accuracy values for additional tests undertaken for the patients who initially fall in the 'grey zone' would aid more realistic pathways to be modelled for calprotectin testing strategies.

The choice of the cut-off point is influenced by whether, in the particular circumstance for the test, the specificity is more important than the sensitivity, or vice-versa. Factors to be considered are the costs involved and the next steps, *ie* repeat tests, invasive procedures *etc*. For example, if an invasive procedure is the next step, it may be more important to maximise specificity rather than sensitivity, and in reality the cut-off may be adjusted to meet particular criteria. The impact of varying specificity and sensitivity can be seen in table 9.

The patients included in a study will influence the specificity and sensitivity of the corresponding tests. The impact of using accuracy values from different studies has been investigated in sensitivity analysis, which found the inputs to be key drivers of the results. The diagnostic accuracy parameters used in the model were sourced from studies relating to secondary care settings. Ideally the parameters would relate to those patients seen in the primary care setting in order to be directly relevant for the analysis. However in the absence of such studies, the specificity and sensitivity values were drawn from studies which were deemed to include patients who were most relevant for our analysis, *ie* patients from Tibble *et al* who had symptoms

suggestive of IBS and no red flags. Future studies which focus on a primary care patient population would be useful.

The use of calprotectin in combination with ESR and CRP was considered for inclusion in the analysis. However, the diagnostic accuracy of using calprotectin in combination with ESR and CRP tests was not available and was, therefore, excluded from the report. It will be useful to investigate this combination of tests when future data become available.

Assumptions have been made relating to those patients who were initially found to be negative for inflammation and subsequently return to health care professionals and thus incur repeat tests; the diagnostic accuracy values included in the model are based on the test being undertaken only once. This is not representative of the situation in reality but the accuracy of multiple tests has not been incorporated due to data being unavailable.

The model has been developed to represent actual clinical practice as far as is possible given the data that are available. Due to the absence of information relating to certain points in the diagnostic pathway, assumptions have been made which may simplify the situation that occurs in reality. These have been highlighted throughout the report and efforts have been made to take a conservative approach wherever possible. The cost of calprotectin tests may fall if they are more widely adopted within the NHS.

It must be remembered that any economic model should be regarded as a simplified representation of the real world, which aims to inform decision-makers about resource allocation by providing estimates of expected costs and effects for different strategies under evaluation, based on currently available data. The best available evidence and expert opinion have been incorporated, hence the results reported from the economic model aim to provide information on the cost-effectiveness of calprotectin for the screening out of IBS in primary care.

Conclusions

The analysis has evaluated the benefit of using calprotectin in terms of its potential for screening out more cases of IBS in primary care than other tests for inflammation, and therefore reducing the number of unnecessary referrals to secondary care for endoscopy.

Calprotectin has a higher diagnostic accuracy than ESR and CRP tests for distinguishing IBS from IBD. The specificity and sensitivity values were of key importance for the model results, in addition to the cost of endoscopy being a key driver.

This analysis has demonstrated that faecal calprotectin is less costly and more effective, in terms of diagnostic accuracy, than the standard tests currently used for distinguishing IBS from IBD. Due to the overall diagnostic cost being lower for the strategy involving calprotectin compared with the tests currently used (ESR plus CRP), calprotectin was found to be the dominant diagnostic option. When comparing laboratory-based calprotectin with point-of-care calprotectin, point-of-care calprotectin was the dominant strategy for identifying IBS, due to correctly identifying more IBS patients, avoiding unnecessary endoscopies and having lower total costs for the cohort, although fewer IBD cases were correctly identified.

The use of calprotectin for the detection of inflammation of the bowel would enable improved management of IBS patients in primary care due to it being possible for GPs to be more confident about their diagnosis by excluding the possibility of inflammation. This would reduce the need for referral to secondary care and therefore reduce health care resource utilisation and ultimately result in cost savings, as demonstrated by the economic evaluation.

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1. Economic/cost searches

NHS EED (Cochrane Library). 2009:Issue 3. 11th September 2009

123 records were retrieved.

#1 MeSH descriptor Irritable Bowel Syndrome explode all trees
#2 "irritable bowel" NEAR/2 syndrome*:ti,ab,kw
#3 (irritable NEAR/2 colon):ti,ab,kw
#4 (mucous NEAR/2 colit*):ti,ab,kw
#5 MeSH descriptor Inflammatory Bowel Diseases explode all trees
#6 (inflammatory or irritable) NEAR/2 "bowel disease":ti,ab,kw
#7 MeSH descriptor Crohn Disease explode all trees
#8 "crohn* disease" or ileocolitis:ti,ab,kw
#9 (ileitis NEAR/2 (terminal or regional)):ti,ab,kw
#10 (colitis or enteritis) NEAR/2 (granulomatous or regional):ti,ab,kw
#11 MeSH descriptor Colitis, Ulcerative explode all trees
#12 (ulcerative NEAR/2 colitis):ti,ab,kw
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Leukocyte L1 Antigen Complex explode all trees
#15 (calprotectin or calgranulin):ti,ab,kw
#16 (leukocyte or antigen) NEAR/2 L1:ti,ab,kw
#17 (#14 OR #15 OR #16)
#18 MeSH descriptor Blood Sedimentation explode all trees
#19 (erythrocyte NEAR/2 sedimentation):ti,ab,kw
#20 (blood NEAR/2 sedimentation):ti,ab,kw
#21 (#18 OR #19 OR #20)
#22 MeSH descriptor C-Reactive Protein explode all trees
#23 "c reactive" NEAR/2 protein:ti,ab,kw
#24 (#22 OR #23)
#25 (#13 OR #17 OR #21 OR #24), from 1999 to 2009

HEED (Wiley online). 1999-2009/August. 11th September 2009

144 records were retrieved.

AX=(irritable bowel syndrome)
AX=(inflammatory bowel disease)
AX=(irritable bowel disease)
AX=(crohn disease) or (crohns disease) or (ileocolitis)
AX=(ulcerative colitis)
CS=(1 OR 2 OR 3 OR 4 OR 5)
AX=(calprotectin) or (calgranulin) or (leukocyte L1) or (antigen L1)
AX=(erythrocyte sedimentation) or (blood sedimentation)
AX=(c reactive protein) or (c-reactive protein)

CS=(7 OR 8 OR 9)
CS=(6 OR 10)
JD>=1999
CS=(11 AND 12)

Cost-Effectiveness Analysis (CEA) Registry. (Tufts Medical Center. https://research.tufts-nemc.org/cear/search/search.aspx). 1999-2009/August. 11th September 2009

7 records were retrieved.

Each line was searched separately; results were then browsed and potentially relevant records retrieved.

irritable bowel
inflammatory bowel
calprotectin
erythrocyte
c reactive

IDEAS (RePeC website). 11h September 2009

10 records were retrieved.

Each line searched separately

irritable bowel
inflammatory bowel
calprotectin
erythrocyte
c reactive

HTA (Cochrane Library). 2009:Issue 3. 11th September 2009

44 records were retrieved.

#1 MeSH descriptor Irritable Bowel Syndrome explode all trees
#2 "irritable bowel" NEAR/2 syndrome*:ti,ab,kw
#3 (irritable NEAR/2 colon):ti,ab,kw
#4 (mucous NEAR/2 colit*):ti,ab,kw
#5 MeSH descriptor Inflammatory Bowel Diseases explode all trees
#6 (inflammatory or irritable) NEAR/2 "bowel disease":ti,ab,kw
#7 MeSH descriptor Crohn Disease explode all trees
#8 "crohn* disease" or ileocolitis:ti,ab,kw
#9 (ileitis NEAR/2 (terminal or regional)):ti,ab,kw

#10 (colitis or enteritis) NEAR/2 (granulomatous or regional):ti,ab,kw
#11 MeSH descriptor Colitis, Ulcerative explode all trees
#12 (ulcerative NEAR/2 colitis):ti,ab,kw
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 MeSH descriptor Leukocyte L1 Antigen Complex explode all trees
#15 (calprotectin or calgranulin):ti,ab,kw
#16 (leukocyte or antigen) NEAR/2 L1:ti,ab,kw
#17 (#14 OR #15 OR #16)
#18 MeSH descriptor Blood Sedimentation explode all trees
#19 (erythrocyte NEAR/2 sedimentation):ti,ab,kw
#20 (blood NEAR/2 sedimentation):ti,ab,kw
#21 (#18 OR #19 OR #20)
#22 MeSH descriptor C-Reactive Protein explode all trees
#23 "c reactive" NEAR/2 protein:ti,ab,kw
#24 (#22 OR #23)
#25 (#13 OR #17 OR #21 OR #24), from 1999 to 2009

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP). 1999-2009/Sep wk 1. 11th September 2009

8 records were retrieved in MEDLINE and 0 in MEDLINE In-Process & Other Non-Indexed Citations.

1. Irritable Bowel Syndrome/
2. (irritable bowel adj2 syndrome$).ti,ab.
3. (irritable adj2 colon).ti,ab.
4. (mucous adj2 colit$).ti,ab.
5. Inflammatory Bowel Diseases/
6. ((inflammatory or irritable) adj2 bowel disease$).ti,ab.
7. Crohn Disease/
8. (crohn$ disease or ileocolitis).ti,ab.
9. (ileitis adj2 (terminal or regional)).ti,ab.
10. ((colitis or enteritis) adj2 (granulomatous or regional)).ti,ab.
11. Colitis, Ulcerative/
12. (ulcerative adj2 colitis).ti,ab.
13. or/1-12
14. Leukocyte L1 Antigen Complex/
15. calprotectin.ti,ab.
16. calgranulin.ti,ab.
17. ((leukocyte or antigen) adj2 L1).ti,ab.
18. or/14-17
19. Blood Sedimentation/
20. (erythrocyte adj2 sedimentation).ti,ab.

21. (blood adj2 sedimentation).ti,ab.
22. or/19-21
23. C-Reactive Protein/
24. (c reactive adj2 protein).ti,ab.
25. 23 or 24
26. economics/
27. exp "costs and cost analysis"/
28. economics, dental/
29. exp "economics, hospital"/
30. economics, medical/
31. economics, nursing/
32. economics, pharmaceutical/
33. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
34. (expenditure$ not energy).ti,ab.
35. (value adj1 money).ti,ab.
36. budget$.ti,ab.
37. or/26-36
38. ((energy or oxygen) adj cost).ti,ab.
39. (metabolic adj cost).ti,ab.
40. ((energy or oxygen) adj expenditure).ti,ab.
41. or/38-40
42. 37 not 41
43. 42 and 13 and (18 or 22 or 25)
44. animals/ not (animals/ and humans/)
45. (editorial or letter or comment).pt.
46. 43 not (44 or 45)
47. limit 46 to (english language and yr="1999 - 2009")

EMBASE (OvidSP). 1999-2009/wk 36. 11th September 2009

44 records were retrieved.

1. exp irritable colon/
2. (irritable bowel adj2 syndrome$).ti,ab.
3. (irritable adj2 colon).ti,ab.
4. (mucous adj2 colit$).ti,ab.
5. enteritis/
6. ((inflammatory or irritable) adj2 bowel disease$).ti,ab.
7. Crohn disease/
8. (crohn$ disease or ileocolitis).ti,ab.
9. (ileitis adj2 (terminal or regional)).ti,ab.
10. ((colitis or enteritis) adj2 (granulomatous or regional)).ti,ab.
11. ulcerative colitis/
12. (ulcerative adj2 colitis).ti,ab.
13. or/1-12

14. calgranulin/
15. calprotectin.ti,ab.
16. calgranulin.ti,ab.
17. ((leukocyte or antigen) adj2 L1).ti,ab.
18. or/14-17
19. erythrocyte sedimentation rate/
20. (erythrocyte adj2 sedimentation).ti,ab.
21. (blood adj2 sedimentation).ti,ab.
22. or/19-21
23. C reactive protein/
24. (c reactive adj2 protein).ti,ab.
25. 23 or 24
26. Health Economics/
27. exp Economic Evaluation/
28. exp Health Care Cost/
29. exp PHARMACOECONOMICS/
30. or/26-29
31. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
32. (expenditure$ not energy).ti,ab.
33. (value adj2 money).ti,ab.
34. budget$.ti,ab.
35. or/31-34
36. 30 or 35
37. (metabolic adj cost).ti,ab.
38. ((energy or oxygen) adj cost).ti,ab.
39. ((energy or oxygen) adj expenditure).ti,ab.
40. or/37-39
41. 36 not 40
42. editorial.pt.
43. note.pt.
44. letter.pt.
45. or/42-44
46. 41 not 45
47. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
48. exp animal/
49. Nonhuman/
50. or/47-49
51. exp human/
52. exp human experiment/
53. 51 or 52
54. 50 not (50 and 53)
55. 46 not 54
56. 55 and 13 and (18 or 22 or 25)

57. limit 56 to (english language and yr="1999 - 2009")

2. Sensitivity/specificity/predictive value of calprotectin/ESR/CRP

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP). 1999-2009/Sep wk 1. 11th September 2009

163 records were retrieved in MEDLINE and 9 in MEDLINE In-Process & Other Non-Indexed Citations.

1. Irritable Bowel Syndrome/
2. (irritable bowel adj2 syndrome$).ti,ab.
3. (irritable adj2 colon).ti,ab.
4. (mucous adj2 colit$).ti,ab.
5. Inflammatory Bowel Diseases/
6. ((inflammatory or irritable) adj2 bowel disease$).ti,ab.
7. Crohn Disease/
8. (crohn$ disease or ileocolitis).ti,ab.
9. (ileitis adj2 (terminal or regional)).ti,ab.
10. ((colitis or enteritis) adj2 (granulomatous or regional)).ti,ab.
11. Colitis, Ulcerative/
12. (ulcerative adj2 colitis).ti,ab.
13. or/1-12
14. Leukocyte L1 Antigen Complex/
15. calprotectin.ti,ab.
16. calgranulin.ti,ab.
17. ((leukocyte or antigen) adj2 L1).ti,ab.
18. or/14-17
19. Blood Sedimentation/
20. (erythrocyte adj2 sedimentation).ti,ab.
21. (blood adj2 sedimentation).ti,ab.
22. or/19-21
23. C-Reactive Protein/
24. (c reactive adj2 protein).ti,ab.
25. 23 or 24
26. exp "sensitivity and specificity"/
27. predictive value of tests/
28. (sensitivity or specificity).ti,ab.
29. (predictive value$ or reproducibility or logistic regression).ti,ab.
30. (ability adj3 predict$).ti,ab.
31. (diagnos$ adj3 (efficen$ or efficac$ or effectiv$ or accura$ or correct$ or reliable or reliability or error$ or mistake$ or inaccura$ or incorrect or unreliable)).ti,ab.
32. (reference test or reference tests or reference testing).ti,ab.
33. (predictive standard$ or predictive value$ or predictive model$ or predictive factor$).ti,ab.

34. (sroc or srocs or roc or rocs).ti,ab.
35. (receiver operat$ curve$ or receiver operat$ character$).ti,ab.
36. likelihood ratio$.ti,ab.
37. (false positive$ or false negative$).ti,ab.
38. (true negative$ or true positive$).ti,ab.
39. (positive rate$ or negative rate$).ti,ab.
40. (accura$ adj2 (test or tests or testing or standard$ or score$ or aid or aids)).ti,ab.
41. (reliable adj2 (test or tests or testing or standard$)).ti,ab.
42. (reliability adj2 (test or tests or testing or standard$)).ti,ab.
43. (performance adj2 (test or tests or testing or standard$)).ti,ab.
44. misdiagnos$.ti,ab.
45. or/26-44
46. 45 and 13 and (18 or 22 or 25)
47. animals/ not (animals/ and humans/)
48. (editorial or letter or comment).pt.
49. 46 not (47 or 48)
50. limit 49 to (english language and yr="1999 - 2009")

EMBASE (OvidSP). 1999-2009/wk 36. 11th September 2009

124 records were retrieved.

1. *irritable colon/
2. (irritable bowel adj2 syndrome$).ti,ab.
3. (irritable adj2 colon).ti,ab.
4. (mucous adj2 colit$).ti,ab.
5. *enteritis/
6. ((inflammatory or irritable) adj2 bowel disease$).ti,ab.
7. *Crohn disease/
8. (crohn$ disease or ileocolitis).ti,ab.
9. (ileitis adj2 (terminal or regional)).ti,ab.
10. ((colitis or enteritis) adj2 (granulomatous or regional)).ti,ab.
11. *ulcerative colitis/
12. (ulcerative adj2 colitis).ti,ab.
13. or/1-12
14. calgranulin/
15. calprotectin.ti,ab.
16. calgranulin.ti,ab.
17. ((leukocyte or antigen) adj2 L1).ti,ab.
18. or/14-17
19. *erythrocyte sedimentation rate/
20. (erythrocyte adj2 sedimentation).ti,ab.
21. (blood adj2 sedimentation).ti,ab.
22. or/19-21
23. *C reactive protein/
24. (c reactive adj2 protein).ti,ab.

25. 23 or 24
26. *"sensitivity and specificity"/
27. *"prediction and forecasting"/ or *predictive validity/
28. (sensitivity or specificity).ti,ab.
29. (predictive value$ or reproducibility or logistic regression).ti,ab.
30. (ability adj3 predict$).ti,ab.
31. (diagnos$ adj3 (efficen$ or efficac$ or effectiv$ or accura$ or correct$ or reliable or reliability or error$ or mistake$ or inaccura$ or incorrect or unreliable)).ti,ab.
32. (reference test or reference tests or reference testing).ti,ab.
33. (predictive standard$ or predictive value$ or predictive model$ or predictive factor$).ti,ab.
34. (sroc or srocs or roc or rocs).ti,ab.
35. (receiver operat$ curve$ or receiver operat$ character$).ti,ab.
36. likelihood ratio$.ti,ab.
37. (false positive$ or false negative$).ti,ab.
38. (true negative$ or true positive$).ti,ab.
39. (positive rate$ or negative rate$).ti,ab.
40. (accura$ adj2 (test or tests or testing or standard$ or score$ or aid or aids)).ti,ab.
41. (reliable adj2 (test or tests or testing or standard$)).ti,ab.
42. (reliability adj2 (test or tests or testing or standard$)).ti,ab.
43. (performance adj2 (test or tests or testing or standard$)).ti,ab.
44. misdiagnos$.ti,ab.
45. or/26-44
46. 45 and 13 and (18 or 22 or 25)
47. (editorial or note or letter).pt.
48. 46 not 47
49. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
50. exp animal/
51. Nonhuman/
52. or/49-51
53. exp human/
54. exp human experiment/
55. 53 or 54
56. 52 not (52 and 55)
57. 48 not 56
58. limit 57 to (english language and yr="1999 - 2009")

3. QALYs

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP). 1999-2009/Sep wk 1. 11th September 2009

88 records were retrieved in MEDLINE and 11 in MEDLINE In-Process & Other Non-Indexed Citations.

1. Irritable Bowel Syndrome/
2. (irritable bowel adj2 syndrome$).ti,ab.
3. (irritable adj2 colon).ti,ab.
4. (mucous adj2 colit$).ti,ab.
5. Inflammatory Bowel Diseases/
6. ((inflammatory or irritable) adj2 bowel disease$).ti,ab.
7. Crohn Disease/
8. (crohn$ disease or ileocolitis).ti,ab.
9. (ileitis adj2 (terminal or regional)).ti,ab.
10. ((colitis or enteritis) adj2 (granulomatous or regional)).ti,ab.
11. Colitis, Ulcerative/
12. (ulcerative adj2 colitis).ti,ab.
13. or/1-12
14. Leukocyte L1 Antigen Complex/
15. calprotectin.ti,ab.
16. calgranulin.ti,ab.
17. ((leukocyte or antigen) adj2 L1).ti,ab.
18. or/14-17
19. Blood Sedimentation/
20. (erythrocyte adj2 sedimentation).ti,ab.
21. (blood adj2 sedimentation).ti,ab.
22. or/19-21
23. C-Reactive Protein/
24. (c reactive adj2 protein).ti,ab.
25. 23 or 24
26. Quality-adjusted life years/
27. (qaly$ or qald$ or qale$ or qtime$).ti,ab.
28. (health utilit$ index or health utilit$ indices).ti,ab.
29. health state$ utilit$.ti,ab.
30. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
31. health utilit$ scale$.ti,ab.
32. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
33. Health Resources/
34. resource$.ti.
35. or/26-34
36. 35 and (13 or 18 or 22 or 25)
37. animals/ not (animals/ and humans/)
38. (editorial or letter or comment).pt.
39. 36 not (37 or 38)
40. limit 39 to (english language and yr="1999 - 2009")

EMBASE (OvidSP). 1999-2009/wk 36. 11th September 2009

73 records were retrieved.

1. *irritable colon/
2. (irritable bowel adj2 syndrome$).ti,ab.
3. (irritable adj2 colon).ti,ab.
4. (mucous adj2 colit$).ti,ab.
5. *enteritis/
6. ((inflammatory or irritable) adj2 bowel disease$).ti,ab.
7. *Crohn disease/
8. (crohn$ disease or ileocolitis).ti,ab.
9. (ileitis adj2 (terminal or regional)).ti,ab.
10. ((colitis or enteritis) adj2 (granulomatous or regional)).ti,ab.
11. *ulcerative colitis/
12. (ulcerative adj2 colitis).ti,ab.
13. or/1-12
14. calgranulin/
15. calprotectin.ti,ab.
16. calgranulin.ti,ab.
17. ((leukocyte or antigen) adj2 L1).ti,ab.
18. or/14-17
19. *erythrocyte sedimentation rate/
20. (erythrocyte adj2 sedimentation).ti,ab.
21. (blood adj2 sedimentation).ti,ab.
22. or/19-21
23. *C reactive protein/
24. (c reactive adj2 protein).ti,ab.
25. 23 or 24
26. *quality adjusted life year/
27. (qaly$ or qald$ or qale$ or qtime$).ti,ab.
28. (health utilit$ index or health utilit$ indices).ti,ab.
29. health state$ utilit$.ti,ab.
30. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
31. health utilit$ scale$.ti,ab.
32. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
33. *resource allocation/
34. resource$.ti.
35. or/26-34
36. 35 and (13 or 18 or 22 or 25)
37. (editorial or note or letter).pt.
38. 36 not 37
39. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
40. exp animal/
41. Nonhuman/
42. or/39-41
43. exp human/

44. exp human experiment/
45. 43 or 44
46. 42 not (42 and 45)
47. 38 not 46
48. limit 47 to (english language and yr="1999 - 2009")

4. Point-of-care/laboratory testing of calprotectin

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP). 1999-2009/Sep wk 1. 11th September 2009

25 records were retrieved in MEDLINE and 2 in MEDLINE In-Process & Other Non-Indexed Citations.

1. exp Point-of-Care Systems/
2. point of care.ti,ab.
3. "Laboratory Techniques and Procedures"/
4. laboratory.ti,ab.
5. or/1-4
6. Leukocyte L1 Antigen Complex/
7. calprotectin.ti,ab.
8. calgranulin.ti,ab.
9. ((leukocyte or antigen) adj2 L1).ti,ab.
10. or/6-9
11. 5 and 10
12. animals/ not (animals/ and humans/)
13. (editorial or letter or comment).pt.
14. 11 not (12 or 13)
15. limit 14 to (english language and yr="1999 - 2009")

EMBASE (OvidSP). 1999-2009/wk 36. 11th September 2009

34 records were retrieved.

1. *"point of care testing"/
2. point of care.ti,ab.
3. *laboratory test/
4. laboratory.ti,ab.
5. or/1-4
6. calgranulin/
7. calprotectin.ti,ab.
8. calgranulin.ti,ab.
9. ((leukocyte or antigen) adj2 L1).ti,ab.
10. or/6-9
11. 5 and 10

12. (editorial or note or letter).pt.
13. 11 not 12
14. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
15. exp animal/
16. Nonhuman/
17. or/14-16
18. exp human/
19. exp human experiment/
20. 18 or 19
21. 17 not (17 and 20)
22. 13 not 21
23. limit 22 to (english language and yr="1999 - 2009")

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Economic report:
Value of calprotectin in screening out irritable bowel syndrome

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