Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation

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Scientific summary

FC testing for differentiating IBS and non-IBS

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Scientific summary

Background

Lower abdominal symptoms – such as pain, diarrhoea and bloating – are common and are usually due to irritable bowel syndrome (IBS), a troublesome condition that interferes with activities of daily life but which does not have serious consequences. Around 10% of the population have symptoms suggestive of IBS, although only about half consult their general practitioners (GPs).

The symptoms of IBS can resemble those of inflammatory bowel disease (IBD), mainly Crohn's disease (CD) and ulcerative colitis (UC). These diseases have serious complications, including a high risk of complications requiring surgery and an increased risk of colorectal cancer.

However, the symptoms of IBD can be different in children, many of whom present with non-specific symptoms, such as mild abdominal discomfort, lethargy, weight loss or growth impairment. In a large UK and Ireland study, only 25% of children with CD presented with the usual triad of diarrhoea, abdominal pain and weight loss. Delays in diagnosis were common, with over one-quarter of patients with CD taking over 1 year to be diagnosed. About 25% of people with IBD develop it under the age of 17 years.

Irritable bowel syndrome is often diagnosed on the basis of signs and symptoms, without a need for further investigations, but distinction from IBD on clinical grounds is often not possible. Distinguishing between IBD and IBS has often required referral to specialist care for colonoscopy, an invasive and unpleasant investigation requiring sedation, usually carried out on a day case basis, at a cost of around £650 (including specialist referral and day case endoscopy). Some centres have reported that > 60% of colonoscopies in younger patients have been normal, and in retrospect, not necessary.

Calprotectin is a protein released by the white blood cells involved in inflammation of the bowel. It is stable in faeces and can be measured by laboratory tests, and more recently by 'point-of-care testing' (POCT). It indicates inflammation in the bowel.

This review examines the clinical effectiveness and cost-effectiveness of FC testing in helping to distinguish between 'functional' disorders, such as IBS and 'organic' disorders, such as IBD. In adults, the differentiation is most often between IBS and IBD. In children, there is a different range of conditions.

Perspectives on the use of calprotectin testing will vary with setting. GPs will see far more cases of IBS than IBD, and for them calprotectin testing offers evidence to rule out IBD. A negative calprotectin will imply IBS. So GPs will be looking for parameters such as sensitivity (for IBD) and negative predictive value (NPV), to provide a basis for a decision not to refer. Gastroenterologists in adult clinics will be seeing a selected group of patients, referred by GPs, with a suspicion of IBD. Gastroenterologists will be looking for positive evidence of IBD in order to decide whether to proceed to further investigations, including colonoscopy and biopsy, and possibly also gastroscopy and other tests. They may find a positive predictive value or a positive diagnostic odds ratio more useful.

It should be noted that diagnosis will be made on the whole clinical picture, not on the basis of calprotectin results alone.

The same general principles will apply to the different case mix seen in paediatric gastroenterology. The proportion with IBD is higher, but a normal or near-normal calprotectin level may contribute to a decision not to proceed to invasive procedures such as endoscopy.

Methods

Systematic review and economic modelling. A broad search strategy was run in several databases. Studies that provided sufficient data for calculation of sensitivity, specificity and other diagnostic outcomes were identified. Review Manager (RevMan) version 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to generate paired forest plots and receiver operating characteristic (ROC) curves. Stata 12 (StataCorp LP, College Station, TX, USA) was used to produce likelihood ratios, areas under the curve (AUC) and nomograms. The quality of studies was assessed using Quality Assessment of Diagnostic Accuracy Studies. We sought studies in which the reference test was endoscopy with histology.

Results

Clinical effectiveness of calprotectin testing

The primary studies presented data for different groups of conditions, some providing a direct comparison of IBS and IBD, but others comparing a wider range of organic conditions.

Nearly all of the evidence comes from studies in specialist care.

Seven studies gave results that compared IBS and IBD, at eight cut-off levels, ranging from 8 to 150 µg/g, all in adults. Sensitivity was consistently high (usually 100% at levels of < 50 µg/g, ranging from 83% to 100% at a cut-off of 50 µg/g) but specificity was more varied (51% to 100%), especially at lower levels of FC.

Eleven studies, mostly from paediatrics, reported IBD versus non-IBD, with eight cut-off levels. They showed consistently high sensitivity at lower cut-offs: nearly all over 90%, with most at the 50 µg/g cut-off having sensitivities of 100%. Specificity was much more varied, ranging from 44% to 93% at a 50 µg/g cut-off.

Two reports by the York Health Economics Consortium (YHEC) were very useful. The first, from 2010, concluded that FC was a reliable marker of inflammation of the bowel, that high sensitivity was very important and that false positives were preferable to false negatives, that the cut-off should be 50 µg/g, and, in economic terms, that calprotectin dominated (more correct diagnoses at less cost) blood tests such as erythrocyte sedimentation rate and C-reactive protein.

The second YHEC report provided data on the use of calprotectin testing in routine care and on how it contributed to final diagnosis. One finding was that when GPs were sure a patient had IBS, they were usually right – 95% of such patients had normal calprotectin levels.

Choice of cut-off levels

The commonest level for defining normality was 50 µg/g. If sensitivity was deemed of paramount importance (in order not to miss any cases of IBD), that level could be used. Some adults with IBS have raised calprotectin levels and would be 'false positives', who might be referred for endoscopy as '?IBD'. However, there is some evidence that organic pathology is rare with levels of < 150 µg/g, and clinical consensus is that if there are adults with IBD but calprotectin levels of < 150 µg/g, they are likely to have low-grade IBD and would come to no harm if simply monitored by repeated calprotectins, with referral if the level rose.

In theory, a very sensitive approach might lead to people with IBS being false positives and undergoing endoscopy, and a less sensitive approach might mean missing a few people with IBD, with more serious consequences. In practice, clinicians will apply clinical nous and observation, and that will reduce colonoscopies in false positives. Decisions will not be made purely on FC results.

In paediatric age groups, with a different spectrum of conditions, a cut-off level of 50 µg/g gives almost 100% sensitivity but specificity varying from 44% to 94%. One study reported that a cut-off level of 100 µg/g gave sensitivity of only 86%, specificity 91%. Another study recommended a cut-off level of 200 µg/g as being most useful in routine practice.

Cost-effectiveness

NHS Technology Adoption Centre pilot study

Results from the pilot project show that calprotectin testing could reduce costs of referral and investigation of patients under 60 years with chronic diarrhoea by over 60%, if all patients with negative tests are managed in primary care as IBS, with those with borderline and positive tests being referred to gastroenterology.

This reduction is similar to the proportions of colonoscopies reported as normal from some other UK centres.

Review of previous studies

Previous economic analyses have typically concluded that calprotectin testing is cost saving compared with the situation without it. Given test specificities and the assumed prevalences of IBD in the presenting population, the additional cost of the calprotectin testing is more than offset by the reduction in the cost of unnecessary colonoscopies.

External Assessment Group: primary care

The External Assessment Group (EAG) developed a de novo cost-effectiveness model for the use of calprotectin testing for distinguishing between IBS and IBD in the primary care setting. This had an initial sequence of tests, with associated sensitivities and specificities, with positive results being referred to outpatient assessment and colonoscopy. Those testing positive were assumed to go on to an outpatient appointment and colonoscopy. Colonoscopy was associated with a slight risk of bleeds and perforation, with the latter having a very small mortality risk.

Subsequent to testing, patients could receive induction and maintenance treatment for IBS, CD and UC. False negatives could spend a period of time being unsuccessfully treated for IBS before re-presenting for testing.

A key uncertainty in the modelling was whether calprotectin testing would result in a wider group of patients being considered for testing than in the absence of calprotectin testing. This was explored through an alternative presenting population scenario analysis that doubled the number who would be tested compared with the number who would have been previously considered for referral in the absence of calprotectin testing.

The base case of the modelling assumed that without calprotectin testing all of those referred from primary care would go through an outpatient assessment and on to receive a colonoscopy.

Without calprotectin testing, GP clinical assessment can be highly sensitive in referring IBD. However, this may be at the cost of low specificity, with many ‘false positives’ (people with IBS) referred to gastroenterology. GPs without calprotectin testing might refer about 20%, most without IBD. The rates of false positives referred after calprotectin testing would be much lower: 5.1% and 5.6%, respectively.

Faecal calprotectin testing is estimated to result in cost savings. In theory, small quality-adjusted life-year (QALY) gains could accrue but these are too small to be significant, because of the low prevalence of IBD and the high sensitivities of all the tests, resulting in few false negatives with IBD. Sensitivity analyses suggest that calprotectin testing results in patient gains and remains cost saving compared with GP assessment without calprotectin testing, up to an IBD prevalence of 25%. At this point,

the less-than-perfect sensitivity ELISA testing results in very slight QALY losses compared with GP assessment without calprotectin testing, although cost savings of around £63 per patient on average remain.

The cost savings from calprotectin testing would be much reduced if the numbers tested were double those referred in the absence of calprotectin testing, resulting in slight cost savings or broad cost neutrality. Increases beyond a doubling would be likely to result in additional costs from calprotectin testing.

The savings from increased specificity of GP referral when given access to calprotectin testing depend largely on reduced colonoscopies. Scenario analysis shows that increasing the specificity of specialist assessment reduces the number of colonoscopies, with the cost savings from calprotectin testing falling. With a 95% specificity for outpatient assessment, the cost savings fell to around £10. Given lack of data, no modelling of repeat testing after indeterminate results was done. The impact of this on costs would mainly be determined by the calprotectin levels among patients with IBS who had an indeterminate result from their first test. If levels fell, the second test would result in fewer referrals and so could result in cost savings.

Secondary care

The model developed was also applied to differentiating IBD from non-IBD in the mainly paediatric secondary care setting.

Despite the higher IBD prevalence in the paediatric population, the main test differences still lie in the number of colonoscopies. Without calprotectin testing, all 52.1% of non-IBD patients receive a colonoscopy compared with 13.5% for the ELISA with the 50 µg/g cut-off, and only 9.4% for ELISA with the 100 µg/g cut-off.

The additional ELISA test costs are more than offset by the savings from reduced colonoscopies. Compared with all having a colonoscopy, ELISA with the 50 µg/g cut-off is estimated to save £205 on average, whereas ELISA with the 100 µg/g cut-off is estimated to save £240. Trivial QALY gains of around 0.001 QALYs may occur with ELISA compared with universal colonoscopy, these being slightly larger the 50 µg/g cut-off owing to its better sensitivity. But given the additional average £35 cost, the cost-effectiveness estimate using the 50 µg/g cut-off compared with the 100 µg/g cut-off is £35,000 per QALY. It should be stressed that the QALY differences between the strategies are very small and they may be better considered as equivalent.

Research needs

There is a lack of studies in primary care populations, and on the proportion of patients with lower bowel symptoms that would be tested if FC testing was available to GPs.

Many people have intermediate calprotectin levels (50–150 µg/g) and follow-up studies are required to determine the most useful cut-off level.

Some people with IBS have raised calprotectin levels. The reasons for that are not clear.

Conclusions

The National Institute for Health and Care Excellence (NICE) scope raised questions, abbreviated in italic text below:

Is calprotectin testing a reliable way of differentiating inflammatory diseases of the bowel from non-inflammatory ones?

Yes. The majority of younger adult patients seen with lower abdominal symptoms in general practice have IBS, and the absence of inflammation as indicated by a negative calprotectin test means that IBD is very unlikely. They could be managed in primary care and spared further investigations.

What are the optimal cut-offs for use in primary and secondary care?

The same cut-off should be used in primary and secondary care – currently 50 µg/g for ELISA tests but needing to be reviewed as evidence accumulates. This is based on ensuring high sensitivity, and not missing people with IBD. People with borderline levels of 50–150 µg/g could be monitored initially, with repeat calprotectin testing but some of this group will progress to definite IBD.

How do the rapid point-of-care tests compare with the laboratory tests?

There is currently insufficient evidence on either diagnostic reliability or cost-effectiveness considerations for preferring one test over another.

How will calprotectin testing perform in primary care?

Sensitivity and specificity will be as good in primary care but the lower prevalence will increase the NPV. The main benefit would be to confirm the clinical diagnosis of IBS by GPs. Making calprotectin testing available to GPs could reduce the number of younger adults referred to specialist care, and the need for unpleasant invasive investigations, such as colonoscopy.

Impact in secondary care?

In secondary care, calprotectin testing could considerably reduce the number of colonoscopies required. In various studies, over 60% of colonoscopies in this group of adult patients have been normal.

Calprotectin testing can also reduce the need for colonoscopy in children who do not have IBD, and could reduce diagnostic delays in those who do. It could also reduce loss of work time for parents and loss of school time for children.

Study registration

This study is registered as PROSPERO CRD 42012003287.

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