Point-of-care Calprotectin Tests

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Clinical Question:

In patients presenting to Primary Care with bowel symptoms, can a point-of-care calprotectin test differentiate between Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS)?

Background and Advantages over Existing Technology:

In primary care a common diagnostic challenge is the management of the patient with chronic intestinal symptoms, in particular the differentiation of IBD, which includes both Crohn's Disease (CD) and Ulcerative Colitis (UC), from IBS. Evidence from the literature suggests a need for a simple, accurate and differentiating test, to aid in management and referral decisions for such patients. Referral to secondary care is straightforward in patients with acute symptoms or "red flag" features, (such as blood in stool, nocturnal symptoms, weight loss, family history of colon cancer or presence of clinical signs). However, the majority comprise a mixed group with both identifiable pathologies and "functional" conditions.

Current NICE guidelines on IBS in 2008 recommend assessment using the "Rome I" criteria (see appendix) for patients with symptoms for more than 6 months, which is an evidence-based symptom assessment tool evaluating the likelihood of IBS (1). After exclusion of "red flag" symptoms, blood tests to exclude inflammation are recommended, including a full blood count (FBC), erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP) and endomysial or tissue transglutaminase antibody testing for coeliac disease. A trial of dietary exclusions for other food intolerances is also recommended.

The diagnostic accuracy of clinical criteria is low, with sensitivities and specificities in the range of 30-50%, and newer updated combined symptom predictors such as "Rome II" only modestly increase the specificity to 60% (2). The gold standard investigation to differentiate IBD from IBS is endoscopy with biopsy, but this is an invasive test limited to secondary care, requiring referral and incurring

cost and inconvenience (3). A recent study of 630 consecutive referrals to a gastroenterology unit in the UK, revealed an eventual organic diagnosis in only 17% of cases (4). The lack of accurate diagnostics in primary care contributes to such referrals.

Calprotectin, first described in 1980, forms one of the S100 group of intracellular proteins and is released from activated granulocytes, particularly neutrophils as part of the inflammatory response, and has been proposed as a potential diagnostic marker for IBD (5). Found in plasma, tissue and faeces, it resists degradation for up to 1 week after release. High levels are associated with the inflammation found in IBD, but also colorectal cancer and infection, and levels correlate well with severity of IBD (3). Conventional testing of calprotectin involves a laboratory ELISA test. However, recently point-of-care (or "rapid") stool tests have become available, which can be performed in clinic within 15 minutes. Only a few grams of stool are required, and testing is possible on samples stored at room temperature for up to 1 week. This enables the patient to bring a sample from home and get a test result within a single consultation.

Details of Technology:

We identified three rapid calprotectin tests; Quantum Blue®, PreventID by CalDetect® and Calpro® all of which are based on a chromatographic immunoassay technique. The faecal sample is prepared for testing by first dissolving into solution. This involves inserting a smear sample of stool into an extraction device which is a prepared tube/pipette containing buffer solution, and mixing. The test kit itself is a plastic cassette or lateral flow device, with a window displaying a test line and control line. The test line contains anti-calprotectin monoclonal antibodies and the control line contains anti-immunoglobulin antibodies, both dried into bands on the device membrane. The density of colour reaction in the test band correlates to the calprotectin concentration in the sample. This produces a light, medium or dense reaction, indicating low, medium and high concentrations, respectively. Alternatively it can be "read" more accurately by digital scanning. The control band reaction is used to indicate that sufficient fluid has soaked up the membrane for a valid test result and that the reagents involved have not degraded in storage.

The PreventID CalDetect kit comprises only the sample extraction device and cassette. The cassette displays the control band and 3 test bands. The sample well requires only 3 drops of extracted sample and the result is read at 10minutes. The number of test bands that appear provide an indication of the calprotectin concentration. Only one band appearing indicates <15 μg/g, while three bands indicates > 60 μg/g (6). This therefore provides a semi-quantitative result.

The Quantum Blue kit is a lateral flow device but includes a separate scanning device providing a quantitative result by densitometry of the colour band with a lot-specific calibration curve to calculate the calprotectin concentration. A minimum concentration of 30 μg/g is detectable and linearity maintained up to 300 μg/g.

The Calpro rapid test prepares the solute in the same way and uses an almost identical lateral flow device. However, the bands are read by a non-dedicated ordinary office scanner and then fed into proprietary software Calproscan®, to produce a quantitative result.

Table 1. Point-of-care Calprotectin tests available and features:

Product	Volume of Faeces Required	Volume of test fluid	Test time (min)	Nature of device	Result format	CE approval	FDA approval
Quantum Blue® POC test (Buhlmann, Germany)	Smear from a collection stick	1-2 drops	30	Cassette encased test strip with dedicated digital scanner	Quantitative	Yes	No
PreventID® CalDetect® (Preventis GmbH, Germany)	Smear from a collection stick	3 drops	10	Cassette encased test strip	Semi-quantitative	Yes	No
Calpro Rapid Test® Calpro Inc, Oslo Norway	Smear from a collection stick	1-2 drops	30	Cassette encased test strip	Quantitative	Yes	No

Patient Group and Use:

The strongest evidence for use, (in conjunction with the Rome criteria), is in excluding organic disease in patients between 20 and 40 years of age presenting with non-acute abdominal symptoms, suggestive of IBS, with no "Red flag" symptoms

Exclusions:

- Recent ingestion of anti-inflammatory medications (within previous 48hrs).
- Recent nosebleeds, menses or episodes of gastrointestinal bleeding e.g. severe gastritis
- Symptoms associated with recent history of foreign travel or suggestive of infection
- Patients in whom colonoscopy or referral is otherwise indicated

Patients being tested must be screened for evidence of recent nosebleeds, menses or other blood in the GI tract as the test will detect the calprotectin in blood cells (7). Recent NSAID or anticoagulation medication can cause an enteropathy and should be discontinued 48hrs before testing (8). Husebye et al demonstrated variable levels of calprotectin within each stool, indicating a possible need for

multiple sampling on each patient, or employing an automatic preprocessing system for samples, similar to that used in ELISA (9).

A negative result would indicate a high likelihood of IBS and enable the patient to be further managed within primary care, pending review if the symptoms change. A positive result indicating a raised level of faecal calprotectin is present in IBD, but can occur with numerous other conditions, and would therefore prompt further investigation and/or referral. These include coeliac disease, upper gastrointestinal bleed, rectal polyps (including colorectal cancer), cholecystitis, appendicitis, gastroenteritis, diverticulitis, bacterial overgrowth. Therefore there are significant consequences to a false positive test.

Importance:

IBS is a common condition within the population, with an average prevalence of between 4.4% and 13.6% depending on the criteria and the symptom scoring system used (Rome I and Manning, respectively) (10). A large UK study found a prevalence of 6.6% in men and 14% of women in 2004 (11). The incidence is similar between countries despite differences of lifestyle. In contrast, the prevalence of IBD in Europe is approximately 527/100,000 population (12). Combined, the two groups plus other categories of bowel disease represent a significant draw on primary care resources in terms of time and cost, often passed on and repeated in secondary care. There is currently enormous variability in referral rates between GPs, and patients with more IBS-like symptoms tend to wait longer for referrals (13). Differentiating IBS from IBD at an early stage could potentially improve clinical management and optimise referral decisions.

Previous Research:

Accuracy compared to existing technology

<u>Calprotectin ELISA compared to existing methods of diagnosis:</u>

Calprotectin testing by laboratory ELISA compares similarly to other predictors of IBD (ESR and C-reactive protein blood tests and “Rome II” scoring). One study of faecal calprotectin in 602 consecutive referrals to endoscopy from primary care in the UK showed that with a cut-off level of 10 mg/L, the sensitivity and specificity of ELISA for organic disease was 89% and 79% respectively, comparing with the Rome criteria (for IBS) of 85% and 71%. The sensitivity and specificity for CRP >5.0mg/L was 50% and 81% and for ESR >10mm/h this was 58% and 72%, respectively. However in combination the predictive value of the tests increased, particularly with negative calprotectin results (PPV = 0.97) This would indicate a role for calprotectin in diagnosing IBS and hence ruling out IBD (14,15).

Calprotectin ELISA compared to point of care Calprotection tests:

Calprotectin point-of-care (POC) testing compares well with the laboratory ELISA method (gold standard) across a range of calprotectin levels. The ELISA test can detect levels down to 10 µg/g of stool (16), and organic disease is associated with levels of the order of 100-300 µg/g. There is debate around the threshold level for defining positive results, but many studies consider 50 µg/g as their limit of normal. A POC test therefore would need an accuracy of around +/- 5µg to be able to accurately detect cases near the cut-off, and therefore be clinically useful. Several studies have compared the different POC tests against ELISA, however all were performed in the setting of a hospital trial or research unit, and not exclusively within primary care on initial presentation of symptoms. Studies varied in their objective, with some comparing both tests against control patients and those with IBD, while others compare POC and ELISA test performance.

1. PreventID CalDetect Test

A study of 140 patients compared the Prevent ID CalDetect test against ELISA for the diagnosis of IBD and malignancy in those referred for colonoscopy with symptoms. Patients with co-existent disease or on anti-inflammatory drugs were excluded. Taking a cut-off of above 50 µg/g to indicate active IBD, the ELISA sensitivity of 100% compared with the rapid test of 89%, although the negative predictive value (NPV) was 100%. (17).

A second study investigated the use of this rapid test to exclude disease in 114 consecutive patients referred for endoscopy with final diagnoses of IBS (80%) and IBD (20%). At a cut-off point ≥15 mg/kg, the sensitivity and NPV of the rapid test were both 100% and compared well with ELISA values ($p<0.05$). The specificity was 94% and the PPV was 82%. As the NPV was higher than the positive predictive value (PPV) they suggested that the rapid test would be better used in excluding disease than in diagnosis (18).

A Danish hospital study compared the rapid test with laboratory ELISA in 95 samples from patients with clinical symptoms and 5 samples from healthy volunteers. With calprotectin values <15 µg/g, the sensitivity and specificity of the rapid test was 96% (95% confidence interval (CI), 87–100%) and 70% (CI, 55–83%), respectively, with a negative predictive value of 94% (CI, 81–99 %), however with values >15 µg/g, the rapid test was less accurate (19).

2. Quantum Blue Rapid Test

A study of 47 samples from patients presenting with gastrointestinal symptoms compared the Quantum Blue kit to ELISA in a laboratory setting (20). Linearity of the POC kit results against ELISA was confirmed by serial dilution of faeces (n=4) in the range 30-300µg/g (r=0.76). Interestingly, repeat extractions from the same stool (n=3) showed a variation of -31.3 and +31.5%, and similar variation occurred with ELISA ($p > 0.05$). In 10% of clinical results the ELISA and rapid test were on different sides of the 50µg/g cut-off from each other. There was a 5% variation of results of reading the cartridge at -2 to +4 minutes around the recommended 12 minute time.

A study of 50 samples taken from healthy controls and patients with known UC, CD or IBS, also compared Quantum Blue against ELISA, but for differentiating CD and UC against IBS. Results are summarised in Table 2 (21).

3. Calpro Rapid Test

Only one study was identified involving this kit. 404 samples from known UC patients were tested using ELISA as a control and the rapid test, with the intensity of the test line read by laptop and office scanner .The same tests were also photographed by mobile phone for comparison. The office scanner image was analysed by Calproscan software, and the mobile phone image was sent by internet to a server in Oslo, which relayed back the result, automatically ("Home Test photo"). The scanning test results correlated with ELISA significantly (r=0.954, p<0.001) as did the photo results (r=0.939, p <0.001), and when compared against each other (r=0.961, p<0.001). Taking cut-off values as 50 µg/g the NPV of the scanning and photo methods was 97% (93%-99%) and 96% (92%-98%), respectively (22).

Table 2. Summary of accuracy studies

Test used	Population	Final diagnosis	Threshold	POCT sens/spec	ELISA sens/spec	Ref.
Prevent ID CalDetect test	140 patients referred for colonoscopy	56 control group; 18 diverticulosis; 29 colorectal adenoma; 8 colorectal carcinoma; 18 active IBD; 11 intestinal infections	50 µg/g	89%/80%	100%/79%	17
	114 consecutive referrals for colonoscopy	IBS 80%, IBD 20%	≥15 µg/g	100/94	?/?	18
	95 samples from patients with clinical symptoms, 5 healthy controls	Not reported	15 µg/g 60 µg/g	96/70 66/100	96/69 67/100	19
Quantum Blue rapid test	47 samples from patients with gastrointestinal symptoms	Not reported	50 µg/g	Not reported	Not reported	20
	50 patient samples	16 IBD 9 UC 7 CD 7 IBS 19 controls	150 µg/g	UC versus IBS: 55%/100% CD versus IBS: 71%/100%	Not reported	21
Calpro rapid test	404 samples from UC patients	Ulcerative colitis	50 µg/g	Rapid test (RT scanning): 97%/88% Home test (HT photo): 96%/90%	Not reported	22

Impact compared to existing technology

We did not identify any studies assessing the performance of the calprotectin rapid tests in a primary care setting, or POC testing against current clinical strategies for diagnosing (or ruling out) IBD. Potential benefits of using calprotectin as a "rule out" test for organic gastrointestinal disorders could include reduction of the proportion of patients with non-specific (and no "red flag") symptoms referred to gastroenterology, reduced time to diagnosis of organic disease and a change in the referral behaviour of GPs (13). One study calculated that screening (by calprotectin testing), could result in a 67% reduction in the number of adults requiring referral for endoscopy (23). Approximately 10% of those undergoing endoscopy would have a calprotectin positive condition other than IBD. The average time to diagnosis could be significantly reduced in IBD patients with more subtle symptoms. Countering this is the delayed diagnosis of the 6% of patients with IBD but false negative calprotectin results, although they may have other signs provoking referral (23). In practice, even a diagnosis of functional disease sometimes still requires referral to dieticians, psychology and IBS specialist nurses, and therefore can still be resource demanding, so the effect on referral behaviour is difficult to predict (4).

The rapid test kits could enable the use of calprotectin as a first line diagnostic aid in determining the presence or absence of gastrointestinal pathology, in combination with traditional methods. Patients presenting to primary care with non-acute intestinal symptoms and no “red flag” features would potentially be suitable candidates for faecal calprotectin testing. As some studies suggest a high negative predictive value (NPV) for POC calprotectin tests there may be a better role in excluding disease, as a screening-out tool. A negative result, possibly repeated, could indicate subsequent management within primary care, rather than referral for colonoscopy. However, it is unclear what the added value of point of care testing would be over sending stool specimens to a laboratory for the ELISA testing, given that management and referral deisions for non-acute gastrointestinatl conditions are unlikely to need immediate answers from a calprotectin test.

A recent meta-analysis of studies in all age groups showed a drop in calprotectin specificity for IBD from adults (96%) to children and teenagers (76%). In patients over 50, the increased incidence of bowel cancer and other pathology reduces calprotectin’s specificity for IBD, indicating that the optimum age group for testing would be young adults under 50. (22). One other possible use could be in monitoring disease activity or treatment response in patients with known IBD or for early detection of relapse (22).

Guidelines and Recommendations

Calprotectin has not so far been included in guidelines for the management of IBS. The last Primary Care Society for Gastroenterology guidelines are from 2001 (24). The 2008 NICE guidelines acknowledge faecal calprotectin as a new biomarker (25). The NICE Diagnostics Assessment

Programme is currently assessing SeHCAT (Tauroselcholic selenium 75 acid testing) as a secondary care investigation.

In the British Society for Gastroenterology (BSG) guidelines for IBD 2010 faecal calprotectin is described as "accurate in detecting colonic inflammation and can help identify functional diarrhoea" (26). However, in the 2007 BSG guidelines for IBS there is no reference to calprotectin. (27).

The NHS Centre for Evidence Base Purchasing published a "Review on Calprotectin in screening out IBS" in 2010. This concluded that the calprotectin laboratory ELISA test was sufficiently accurate in screening out IBD but that research in primary care and on point-of-care tests was needed (28).

Cost-effectiveness and economic impact:

The NHS CEBP report 2010 (CEP09041) has affirmed the economic cost effectiveness of both calprotectin as a biomarker and of the rapid test method (28). The rapid tests cost approximately £30 per sample comparing with £18 for ELISA. ELISA tests are labour intensive and being batch run have long turnaround times, making the rapid tests more cost effective, although sending a specimen to the local lab may actually be more time efficient for primary care.

Research Questions:

Due to the specificity of calprotectin being lowered by the presence of other organic diseases, calprotectin is more accurate for excluding than confirming IBD. Recent studies have examined this feature, but only in secondary care. Several studies also employed a case-control design, which is likely to inflate the accuracy results. Statistical extrapolation however would predict that the lower prevalence of disease in primary care will tend to increase the NPV and reduce the PPV of a test, further emphasising the role in "ruling out" disease (23). Trials based in secondary care will reflect the different clinical presentations, disease incidence and levels of specialisation, resources and time allocation. In addition, the economic assessments from hospital studies do not directly transfer to primary care. Research is therefore needed within primary care to address these factors. Also, in terms of practical application, patient selection criteria for trial entry are often strictly applied, and therefore it would be interesting to see how the test accuracy changes in everyday primary care use.

Future research would need to establish 4 questions:

1. What is the diagnostic accuracy of both the laboratory based ELISA test and the point of care tests in primary care?

2. What is the added diagnostic accuracy of calprotectin testing to existing diagnostic criteria for IBS in primary care?

3. What is the impact of the POC kit compared to the laboratory based ELISA test for patient management decisions in primary care?

4. Comparative accuracy of the 3 point of care devices?

5. What is the cost effectiveness of POC testing for calprotectin in primary care as compared to sending samples away for ELISA testing?

Suggested methods of approach might be:

1. A randomized trial of calprotectin -guided management or standard practice in a primary care setting

2. Diagnostic accuracy study of calprotectin testing (both laboratory and point of care) with reference standard including follow up and/or referral/endoscopy where appropriate.

3. Pre-post study of referral and investigation rates before and after incorporation of testing into local policy.

Outside the remit of this review, there may also be addition uses of calprotectin in known IBD patients, for example in treatment monitoring, early detection of relapse, and screening for occult disease in relatives.

Suggested next step:

Future research needs to assess the performance of the POC test in a primary care context. Trials would need to compare POC test performance against the ELISA standard and both results against the final diagnosis (by endoscopy). The resulting test sensitivities and specificities may alter as a result of the lowered disease prevalence in a primary care setting from which the negative predictive value can be determined in the case of a "ruling out" test.

Expected outcomes:

With disease prevalence affecting test accuracy and differing between primary and secondary care, it is not possible to recommend calprotectin testing until primary care populations have been studied. There is some evidence to suggest that point of care calprotectin testing as a "ruling out" test could make a significant impact on the current volume of referrals of intestinal symptoms to secondary care. However numerous questions remain regarding cost/time efficiency when compared with sending samples to the local pathology lab and the performance of the POC technology in a primary care setting.

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Appendix

Details of Rome criteria

Rome I criteria

At least three months of recurrent symptoms of:
(1) Abdominal pain or discomfort relieved with defecation, or associated with a change in stool frequency, or associated with a change in stool consistency and
(2) Two or more of the following on at least 25% of occasions or days:
Altered stool frequency
Altered stool form
Altered stool passage
Passage of mucus
Bloating or distension
It should be recognised that these criteria were drawn up with the support of the pharmaceutical industry to allow greater comparability between studies of drug effects. They are a consensus, however many patients with abdominal pain and disturbed bowel habit do not exactly fit these criteria, yet their clinical course is similar. The Rome criteria have recently been revised (see Rome II).

Rome II criteria

12 weeks or more in the last 12 months of abdominal discomfort or pain that has two of the following three features:
(1) Relieved by defecation
(2) Associated with a change in frequency of stool
(3) Associated with a change in consistency of stool
The second group of criteria included in Rome I are now considered supportive rather than mandatory in the diagnosis.

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