

Integrating faecal calprotectin testing into the diagnostic pathway for Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS)

Lower gastrointestinal symptoms present commonly in primary care and differentiating between a diagnosis of IBD and IBS can sometimes be difficult. Clearly distinguishing between these conditions is clinically important, as the prognosis and management of IBD and IBS are extremely different. Currently, many patients who ultimately receive a diagnosis of IBS are referred to specialist services as a result of diagnostic uncertainty, and may unnecessarily undergo an invasive colonoscopy.

Faecal calprotectin (fCal) testing can help to discriminate between organic and functional bowel disorders; therefore integrating fCal testing into IBD and IBS diagnostic pathways has the potential to reduce the number of referrals for colonoscopy, as well as fast-track referrals of those who have a high risk of IBD (potentially reducing the risk of admission).

Clinical presentation of IBD and IBS

IBD, comprising mainly of Crohn's disease (CD) and Ulcerative Colitis (UC), arises due to inflammation of the bowel. In some cases the features are more typical or severe (such as blood stained stool >3 times per day with urgency for over 2 weeks in the absence of infection, or , anaemia or raised inflammatory markers) and the diagnosis is confirmed straightforwardly following urgent referral; other cases present with milder symptoms that overlap with those of IBS. IBD is a relapsing condition; therefore diagnoses can be missed if tests are carried out during remission (mean time to diagnosis in CD is 13 monthsⁱ), and patients can even suffer severe relapses requiring admission before they are diagnosed (44% have a mean of 1.5 hospitalizations leading up to diagnosisⁱ).

IBS is a functional bowel disorder that typically presents with chronic abdominal discomfort associated with a change in the stools. Some cases are classical and a positive diagnosis can be made in primary care (e.g. using the Rome III criteriaⁱⁱⁱ), but IBS may also present with symptoms similar to those of IBD (such as pain/diarrhoea) and these cases can cause diagnostic confusion.

Morbidity of IBD and IBS

Both IBD and IBS significantly reduce quality of life (26% reduction in IBSⁱⁱ, 16% and 23% in UC and CD respectivelyⁱⁱⁱ); early clinical distinction between IBD and IBS is important in optimising care of these patients.

IBS is not associated with inflammation or increased risk of comorbidities, and treatment involves education, dietary manipulation, lifestyle changes and symptom relief from medication. In contrast, IBD requires immunosuppression, lifetime follow up, and carries a high risk of bowel surgery (50-70% of CD patients require surgery within 5 years of diagnosis^{iv}) and increased risk of colorectal cancer (relative risk of IBD patients is two to five times higher^v).

Current pathway for referral to specialist services

IBS is often diagnosed clinically with or without the aid of routine blood tests, as recommended by the National Institute for Health and Care Excellence (NICE)^{vi}, but sometimes it is a 'diagnosis of exclusion' after IBD has been ruled out. A diagnosis of IBD relies on secondary care investigations with the gold standard being colonoscopy and histology of biopsied bowel tissue.

Younger patients (< age 40) presenting with refractory lower gastrointestinal symptoms are usually referred urgently if they have features suggestive of severe disease: 'red flag'^{vii} symptoms' such as unintentional and unexplained weight loss, rectal bleeding (bloody diarrhoea), persistent fever; abdominal or rectal mass; or raised C-reactive protein (CRP), raised erythrocyte sedimentation rate (ESR) or low haemoglobin (Hb). Locally however ESR is being discouraged as it is not felt to add anything to CRP alone. Older patients (> age 40) have a lower threshold for colonoscopy referral due to the increased risk of colorectal cancer.

Diagnostic uncertainty arises in patients with a low-risk for IBD who also do not exhibit typical symptoms of IBS, i.e. young patients without 'red flag symptoms' who experience persistent lower bowel symptoms. Patients in this group most commonly have IBS but are often referred for colonoscopy; the NICE External Assessment Group suggests that whilst GPs are good at suspecting IBD and referring patients, this "results in a somewhat larger number of false positives being referred for unnecessary colonoscopies: 19.8% of the total patient population or 21.2% of those with IBS, as would be anticipated from the 78.8% specificity"^{viii}. Furthermore, studies have shown that 33% of adults (age range 16-45) with rectal bleeding have a normal colonoscopy; this percentage increases to 50% in patients with non-bleeding symptoms such as diarrhoea, abdominal pain and weight loss^{ix}.

Using colonoscopy as a tool for IBD exclusion in these low-risk patients may unnecessarily subject them to an invasive, unpleasant investigation that has potential risks^x (including perforation in the order of 0.028%, bleeding, abdominal pain and further risks from intravenous sedation). Despite these side effects being rare, reducing them may still have a positive impact on patient quality-adjusted life years (QALY), as well as saving colonoscopy costs of over £700 per patient^{xi}. Hence there are both clinical and financial incentives to optimise colonoscopy referrals within this patient population.

Faecal calprotectin

Faecal calprotectin is a protein originating from the cytosol of neutrophils, which can be detected in faeces where it is a stable compound. It has been shown to be a more sensitive and specific biomarker of intestinal inflammation than ESR or CRP^{xii}. Calprotectin is significantly raised in IBD (as well as in other conditions such as colorectal cancer and bowel infection) but is not elevated in IBS. Therefore fCal may help clinicians to differentiate IBD and IBS – therefore fCal can identify patients who are most likely to benefit from endoscopy for suspected IBD and thus improve the cost-effectiveness of colonoscopy referrals. Such patients could be fast tracked (e.g. seen in hospital within 4 weeks of fax/email referral).

Existing recommendations

Many organisations already support the use of fCal to stratify patients' risk of IBD and their need for a colonoscopy. For example, the British Society of Gastroenterology (BSG) guidelines on IBD (2011)^{xiii} state that 'faecal calprotectin is accurate in detecting colonic inflammation and can help identify functional diarrhoea'. Of particular importance, NICE published diagnostic guidance on 'Faecal calprotectin diagnostic tests for inflammatory disease of the bowel'^{xiv} in October 2013 stating that:

'Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:

- *cancer is not suspected, having considered the risk factors (for example, age) – described in Referral guidelines for suspected cancer (NICE clinical guideline 27), **and***
- *appropriate quality assurance processes and locally agreed pathways are in place for testing.'*

Technologies available

The main categories of faecal calprotectin tests available to the NHS are:

- 1) *quantitative* laboratory-based technologies using an enzyme-linked immunosorbent assay (ELISA) platform, and
- 2) *semi-quantitative* point-of-care tests (POCTs).

ELISA tests for fCal are considered more suitable for ruling out IBD as they provide a range of numerical values instead of binary outcome, allowing the clinician to monitor change in values and consider the entire clinical picture when interpreting the result, also permitting a range of actions rather than a dichotomous pathway.

Within the range of ELISA tests available for fCal, monoclonal antibody testing has been shown to be superior to polyclonal tests^{xv}; at the JR, the EK-CAL monoclonal antibody fCal test (Bühlmann Laboratories) is expected to become available soon (early 2014), and is the assay preferred locally. A meta-analysis^{xvi} of 28 studies did not lead to a clear preference for any other assay.

Sensitivity and specificity of fCal testing

A meta-analysis^{xvii} of 6 studies has demonstrated that in a referred adult population, fCal tests perform well in differentiating IBS from IBD with overall sensitivity and specificity of 70-90%.

Recently, the performance of fCal in a UK primary care population has been studied^{xviii}. Data was collected from the Brighton and Hove Clinical Commissioning Group (CCG) (serving a population approximately 250,000). 962 patients (aged 18-45) received fCal testing after presenting to their general practitioner with persistent gastrointestinal symptoms. Suitable thresholds for the EK-CAL fCal test (same technology as that planned for Oxford) were investigated.

As expected, patients with organic disease had a significantly higher fCal level compared to those with non-organic disease (median fCal organic vs non-organic, 334 vs 24 mg/g, $p < 0.0001$). At a 50mcg/g cut-off for fCal, the sensitivity of the test for organic disease was 82% and the specificity was 77% with negative predictive value (NPV) and positive predictive value (PPV) of 98% and 28%, respectively. Increasing the fCal cut-off to 150mcg/g increased the specificity to 97% but at the cost of sensitivity which was reduced to 69% (NPV reduced to 97% whilst PPV increased to 71%) – this higher fCal cut-off would have led to an additional 4 missed IBD cases but also 23 fewer invasive procedures, 140 fewer referrals to secondary care and potential endoscopic and specialist referral savings of over £36,000 and £26,000 per year respectively.

Some of the false positives for fCal are attributable to campylobacter enteritis, alcohol or NSAID use. Stool culture may detect cases of campylobacter, yet this was not a requirement of the Brighton pathway; but the Brighton pathway did require avoidance of regular NSAIDs for 4 weeks prior to fCal testing.

The trade-off between sensitivity and specificity makes choosing a threshold for primary care a difficult decision for a CCG. Given the low prevalence of organic disease in primary care, it is difficult to determine whether the increase in missed IBD cases as a result of a higher cut-off is significant enough to be of concern. Missing IBD is a serious consideration, as IBD is a more severe condition than IBS, although cases with lower fCal may be “milder” cases of IBD. This must also be balanced against the patients’ burden of investigations and the consumption of finite resources which could be used to treat other conditions. A safer approach to reduce the risk of missing IBD could be to re-test patients with fCal values between 50-150mcg/g who experience persistent symptoms, and to refer if their fCal values remain >50mcg/g. However, without fCal testing, GPs base referral decisions on clinical grounds and non-specific blood tests (Hb, CRP & previously also ESR), a method shown to be inferior to fCal testing, regardless of the cut-off.^{xix}

Cost analyses

Cost analyses^{xx} have shown that within primary care, different fCal tests are at least as cost-effective as current GP practice: the total cost of current management of IBD and IBS combined is approximately £3297 (per patient) and the cost of using ELISA fCal tests in addition to this current practice is estimated to reduce it to £3215. This does not include any assessment of the impact on GP consultation rates, and assumes that fCal testing will not be extended to other groups.

Taking into account costs incurred within secondary care, fCal testing should improve cost-effectiveness by reducing the number of colonoscopies (costs of colonoscopy and in-house ELISA fCal test were estimated at £741.68 and £22.79 respectively^{xxi}), and as demonstrated in the Brighton and Hove study^{xxii}, fCal testing (at a cut-off of 150mcg/g) in primary care has the potential to reduce secondary care costs (including endoscopy and specialist referral fees) by approximately £62,000 per year (for a base population of 250,000).

Integrating faecal calprotectin into pathways within the Oxford City locality

Progress so far

To initiate the establishment of a local fCal pathway in Oxford, a preliminary meeting between a biochemist, gastroenterologist (both from the JR) and GP was arranged in January 2014. The meeting discussed various aspects of the pathway – such as eligibility criteria for fCal testing and types of fCal immunoassays suitable for use in Oxford.

It was agreed that fCal testing should only be used to rule out IBD in a low risk population (i.e. young patients presenting with symptoms lasting over 6 weeks, with no clinical or biochemical indication of inflammation, where the main differential diagnosis is between IBS and IBD).

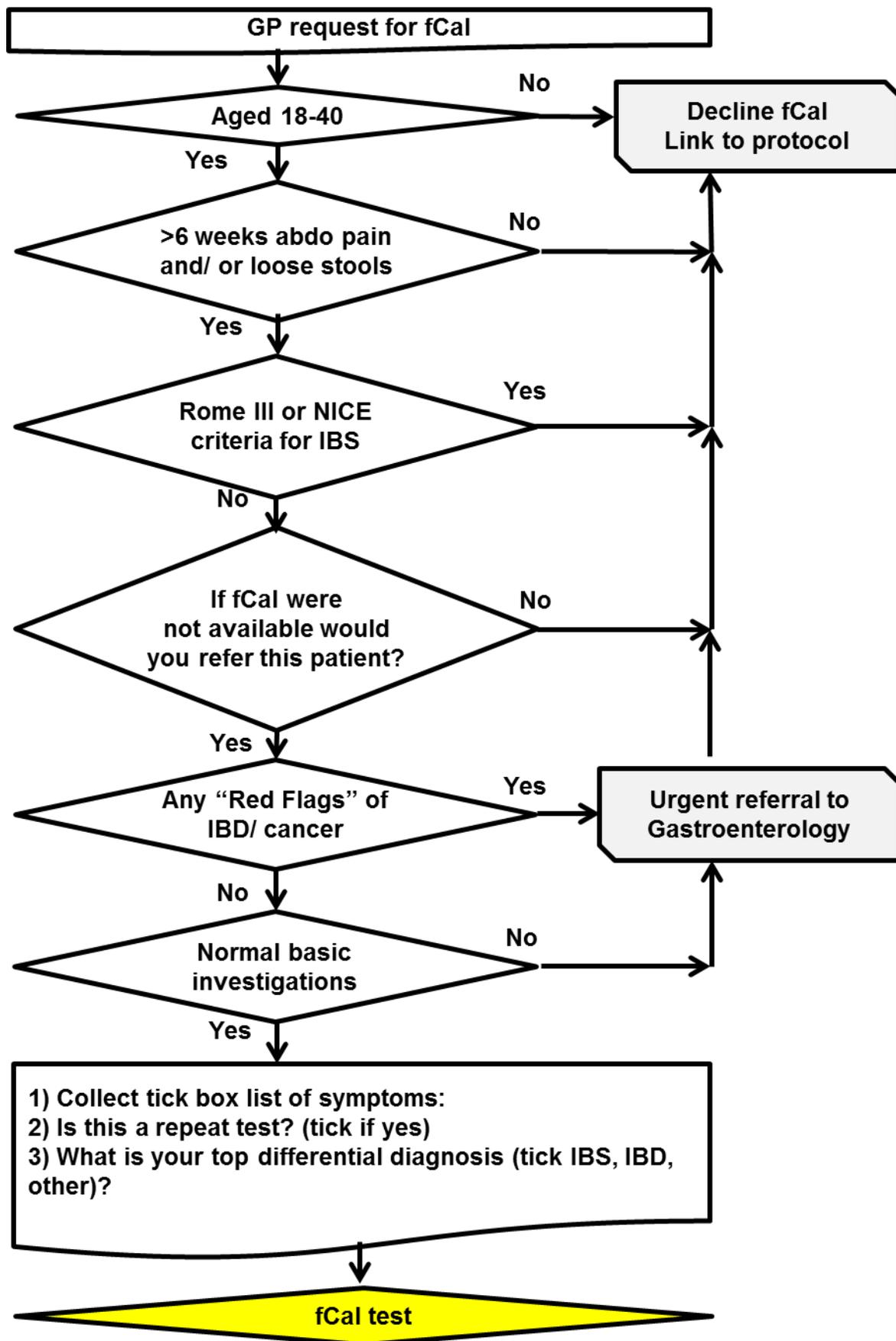
The meeting shared the view that using fCal in primary care should reduce the rate of colonoscopy referrals in Oxford, as well as expedite diagnoses of IBD and IBS. Based on figures from one consultant gastroenterologist’s clinic at the JR (seeing approximately 2,500 IBD patients per year) it was estimated that introducing fCal testing in primary care could reduce up to 400 colonoscopies per year across the whole department, requiring approx. 1500 fCal tests. This estimate does not include the Horton General Hospital in Banbury.

The cost-effectiveness of fCal testing in Oxford was also discussed; there are some fixed costs for training, staffing and equipment and then costs involved in providing reagents and staff time: the number of tests per year needs to be sufficient to make the initial investment and fixed costs worthwhile. It was estimated that the investigation would prove most cost-effective if approximately 2000 patients were tested for fCal per year, providing all these tests were conducted as part of the approved pathway. In the past, the test has been available to hospital patients in Oxford only by sending samples to King’s College Hospital at a cost of around £50; if the test is provided in Oxford at a volume of around 2,000 tests per year then the cost should be more similar

to the costs used by NICE (i.e. up to £25).

Implementing fCal testing in Oxford would be relatively straightforward, as the JR expects to acquire equipment for in-house testing by early 2014, and technicians are already trained to perform fCal. Consultants have been anticipating the introduction of fCal for some time.

Safety was a principal consideration, so every effort has been made to reduce the risks of false negative results and to respect other pathways for detecting colorectal cancer (hence the age range is <40, not <45). The pathway should be viewed as a rational way to use fCal; it is not a compulsory route for all eligible patients as there will always be cases for whom referral is indicated for other reasons.



Red Flags:

- Weight loss
- Fever
- Vomiting
- Blood in stool
- Abnormal rectal exam

Basic investigations:

- CRP <20
- Hb >10
- EMA -ve
- Stool culture -ve (if indicated)

NICE diagnostic criteria for IBS

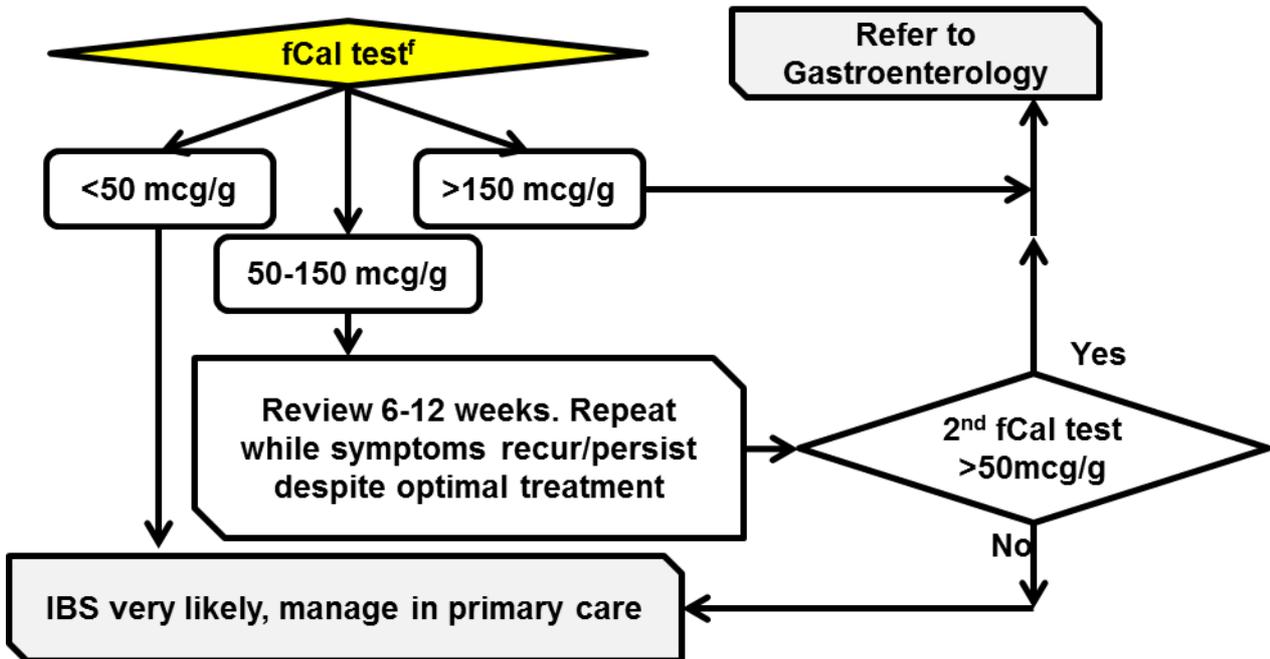
- abdominal pain or discomfort that is:
- relieved by defaecation, or
 - associated with altered bowel frequency or stool form
- and at least two of the following:
- altered stool passage (straining, urgency, incomplete evacuation)
 - abdominal bloating (more common in women than men), distension, tension or hardness
 - symptoms made worse by eating
 - passage of mucus

Rome III criteria:

- Symptoms for ≥3 days per month for ≥ 6 months, plus 2 of:
- 1) Relief from defaecation
 - 2) Pain relates to change in stool frequency
 - 3) Pain related to change in stool appearance

list of symptoms to evaluate compliance with protocol:

Diarrhoea; Constipation; Bloating; Nausea; Gas; Incomplete evacuation; Passing mucus; nocturnal symptoms



Issues for further discussion

Integrating fCal into local diagnostic pathways for IBD and IBS could significantly reduce colonoscopy rates and save costs; but importantly, use of fCal has the potential to aid earlier diagnoses of both these conditions and improve patient outcomes. Despite the strong rationale for using fCal, a few issues remain that require further discussion.

As discussed previously, there is controversy over optimal cut-off values for fCal. Physicians will need to discuss whether they feel able to accept the trade-off between NPV and PPV of the test at the 150mcg/g cut-off, and whether re-testing those between 50-150mcg/g is a good enough compromise.

Many different methods of laboratory fCal testing exist, and commissioners will need to evaluate which tests they are willing to support. The Bühlmann EK-CAL has good evidence and is preferred by the local consultants. Whichever test and threshold are preferred, the high NPV of fCal testing at all cut-off levels make it an appealing tool for screening when compared to CRP (with or without ESR).

Integrating fCal testing into primary care seems likely to create a minimal additional workload for general practitioners; as the cost-effectiveness of the test is dependent on overall uptake within general practice, it is important to ensure GPs have sufficient support and funded training to engage with any new pathway: while some GPs will welcome this improvement in the care of patients, others may struggle with even a small increase in workload. It is possible that earlier diagnosis may ultimately reduce the number of GP consultations (including chasing referrals or dealing with patient anxiety while awaiting a diagnosis) but this has not been studied. Such issues were discussed with GPs at the City Locality meeting in February 2014.

Furthermore, auditing processes will need to be established, as the pathway is implemented, to evaluate the specific predictive values of fCal testing in the Oxford primary care setting. Such audit may be easier if information is collected prospectively through data selection from drop-down menus on requesting software (known locally as "ICE"), completed at the time of the request- such menus have been developed (in approx. May 2014) as far as ICE can be programmed to allow this. There is a chance that the test may also be used outside the intended pathway, which may increase costs with uncertain health benefits (for example a GP who would previously have made a confident positive diagnosis of IBS may use the test to confirm the diagnosis in a particular case- which might not be a cost effective use of resources); but there may also be other valuable roles for fCal in future, such as for the follow-up of proven IBD.

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Based on a very similar paper coauthored with Lucia Chen (medical student) presented in Feb 2014

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