NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel

This document is a summary of the scope of the assessment and evidence/views submitted by the External Assessment Group in the diagnostics assessment report. It highlights key issues for discussion at the first Diagnostics Advisory Committee meeting. NICE prepares the overview before it receives stakeholder comments on the diagnostics assessment report. The sources used in the preparation of this document are given in appendix A.

The overview document seeks to bring together the aims of the evaluation as identified in the scope with the approach and outcomes of the assessment conducted by the External Assessment Group. There are a range of considerations surrounding the aim of faecal calprotectin testing in different populations, how test results should be interpreted, evidence identified in the systematic review and how the evidence translates into the model. Sections 1 – 5 provide the necessary details for these considerations and section 6 summarises important questions with notes for Committee discussion.

1. Background

The Medical Technologies Advisory Committee identified the EK-CAL calprotectin ELISA test (manufacturer: Buhlmann Laboratories AG), the LF-CAL25 Quantum Blue calprotectin test (manufacturer: Buhlmann Laboratories AG) and the KST11005 CalDetect Calprotectin Rapid test (alternative name: PreventID Caldetect, manufacturer: Immundiagnostik), as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of two briefing notes. These technologies are designed to detect intestinal inflammation by measuring levels of faecal calprotectin (FC). FC is a protein that correlates well with neutrophilic infiltration of the intestinal mucosa. FC is excreted in excess into the intestinal lumen during the inflammatory process and, therefore, can act as a surrogate marker for inflammatory disease of the

lower gastrointestinal tract. The tests are intended to aid in discriminating diseases characterised by inflammation of the bowel from non-inflammatory diseases of the bowel.

The scope of the evaluation was extended to include other FC tests in addition to those included in the briefing notes, and outlines the approach for assessing the clinical and cost effectiveness components for faecal calprotectin diagnostic tests to distinguish **inflammatory** from **non-inflammatory** diseases of the bowel in both primary and secondary care.

Inflammatory bowel disease (IBD) encompasses multiple inflammatory conditions of the colon and small intestine. The key types of IBD are Crohn's disease and ulcerative colitis. Feedback during scoping suggested that given the potential severity and chronic nature of IBD compared with non-inflammatory diseases of the bowel, such as irritable bowel syndrome (IBS), an important role is envisaged for FC testing to aid in the discrimination of IBD from non-inflammatory diseases of the bowel. The diagnostics assessment report compiled by the External Assessment Group echoes the importance of FC tests to distinguish between IBD and IBS, therefore, section 1 focuses on the background, diagnosis and care pathways for IBS and IBD.

Other terms used to describe inflammatory and non-inflammatory diseases of the bowel include; "organic" disease – formally defined as a condition in which there is an observable and measurable disease process (for example, inflammation) and, "functional" disease – formally defined as a condition in which there is no observable disease process. Organic disease includes inflammatory diseases (although there are non-inflammatory organic diseases) and functional disease includes IBS.

FC has also been shown to correlate well with IBD activity and, consequently, may have a role in patient monitoring, by indicating levels of lower gastrointestinal inflammation. However, clinical experts suggest that this is a relatively new development with an emerging evidence base. Therefore, given the low levels of evidence, the role of FC tests in patient monitoring in IBD is not included in the scope.

1.1. The conditions

Chronic abdominal pain or discomfort, accompanied by diarrhoea or constipation, is common. The symptoms can be due to a number of different conditions, some more serious than others. The conditions include irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). The commonest forms of the latter are ulcerative colitis and Crohn's disease.

Lower bowel symptoms are very common in general practice. Most patients have IBS, a troublesome and painful condition that reduces quality of life, but which does not have serious effects in terms of structural damage to the bowel. However, some patients have IBD, which can lead to serious complications. For example, in Crohn's disease, 50% of people will require surgery within 10 years of diagnosis. It is important to distinguish IBD from IBS so that patients with the former can be appropriately managed and monitored. IBD is characterised by inflammation of the bowel, which is not seen in most patients with IBS.

1.1.1. Irritable bowel syndrome (IBS)

IBS is an unexplained bowel disorder, characterised by frequent bouts of bowel disturbance and abdominal discomfort. There is no clear cause, no distinctive pathology and no definitive treatment. Exacerbations may be triggered by diet or stress. Physiological studies often show an increase in bowel sensitivity, and it may be associated with abnormal muscle activity in the wall of the bowel. It is a troublesome condition that interferes with activities of daily life although it does not usually have serious consequences.

Lower abdominal symptoms such as pain, diarrhoea and bloating are very common in the population, and are usually due to irritable bowel syndrome. NICE Clinical Guideline 61 (Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care) suggests the prevalence of the condition in the general population is between 10 and 20%. It is understood that prevalence figures can vary depending on the diagnostic criteria used and may account for the range of reported values. The true prevalence of IBS in the whole population may be higher than estimated, because many people with IBS symptoms do not seek medical advice; NHS Direct online data suggest that 75% of people using this service rely on self-care (NICE CG61). IBS most commonly affects people between the ages of 20 and 30 years and is twice as common in women as in men. Recent evidence indicates that there is also a significant prevalence of IBS in older people.

Although IBS does not lead to serious adverse events, the fact that it can be painful and disruptive of normal activities means that people with IBS often have a reduced quality of life. Akehurst et al (2002) report that in the Trent region, people with IBS had reduced quality of life compared with people who are not affected by IBS, based on an analysis of age, sex and socially matched populations. In this analysis, the lower quality of life in people with IBS was reflected in every dimension of both SF36 and EQ-5D instruments which was used to measure health outcomes. The population affected with

IBS also had more time off work, and imposed £123 more costs per year on the NHS.

1.1.2. Inflammatory bowel disease (IBD)

IBD is the term normally applied to a group of conditions, comprising mainly Crohn's disease and ulcerative colitis. These are diseases with serious complications, including a high risk of presentations requiring surgery, and an increased risk of colorectal cancer. In both ulcerative colitis and Crohn's disease, some people have active disease but no symptoms.

Ulcerative colitis and Crohn's disease, are the two most common forms of IBD that involve chronic inflammation of the gastrointestinal tract. The incidence of ulcerative colitis is approximately 10–20 per 100,000 per year with a reported prevalence of 100–200 per 100,000. The incidence of Crohn's disease is around 5–10 per 100 000 per year (and thought to be increasing) with a prevalence of 50–100 per 100,000. There is no significant gender difference in the prevalence of inflammatory bowel disease. IBD is more common in Caucasian people than in Afro-Caribbean people or those of Asian origin. The condition is most prevalent among Jewish people of European origin. The ratio of Crohn's disease to ulcerative colitis varies between adults and children. In adults the ratio of Crohn's Disease to ulcerative colitis is 2:3, whereas in children the ratio is much higher (2.3:1).

Ulcerative colitis: is a relapsing and remitting disease characterised by inflammation of the colon, sometimes intense, with bloody diarrhoea, but is often much milder. The cause is not known, but it appears that some people are more genetically susceptible than others. Around 10% of people with ulcerative colitis have a first degree relative with the condition. There may be an abnormal immune response to the bacteria that normally live in the gut, known as commensals. Ulcerative colitis is sometimes triggered by episodes of gastroenteritis caused by organisms such as Salmonella, Shigella and Campylobacter, but more commonly by changes in the natural gut flora than direct effects of these organisms.

Crohn's disease: can present in different ways, depending on which part of the intestinal tract is affected. Like ulcerative colitis, it is a relapsing and remitting inflammatory disease. However, it is a much more extensive disease and can affect any part of the gastrointestinal tract. Similarly to ulcerative colitis, there is a genetic susceptibility. The cause is unknown, but it appears to be commoner in those with a "westernised" lifestyle. Like ulcerative colitis, it can occur after infectious gastroenteritis and is associated with disturbances in the usual gut flora. The histological features include those similar to

tuberculosis but no mycobacteria have been shown to be responsible. There are around 60,000 people with Crohn's disease in the UK, of whom 20-30% are aged under 20. The incidence is highest in the age range of 15 to 30 years. About 25% of cases have onsets under age 17.

The pattern of symptoms in children is different. A prospective survey was carried out in the UK and Ireland by the British Paediatric Surveillance Unit, the British Society of Gastroenterology Research Unit and the Paediatric Register of IBD. 739 cases under the age of 16 were reported, making it the largest such study. The commonest presenting symptoms of Crohn's disease were abdominal pain, weight loss and diarrhoea, but 44% did not report diarrhoea, and only 25% reported the classical triad of abdominal pain, diarrhoea and weight loss. Other symptoms at presentation included lethargy and anorexia. Paediatric IBD is often more extensive at diagnosis than in adults.

1.2. Prognosis

1.2.1. IBS

IBS has not been shown to be associated with the development of serious co-morbidities and there is no indication that the disease is linked with a worse prognosis compared with the general population (British Society of Gastroenterology (BSG), Guidelines on the irritable bowel syndrome, 2007).

However, IBS can be painful and disruptive of normal activities, and people with IBS have a reduced quality of life. For example, Spiegel et al (2009) reported quality of life in people with IBS to be reduced by 26% on average and 30% if severe when compared with an individual at full health. Quality of life is reduced because of disturbed work and sleep, and anxiety. People with IBS can have symptoms for many years.

1.2.2. IBD

As with IBS, IBD can be painful and disruptive of normal activities, and people with IBD have a reduced quality of life – particularly during periods of active disease. For example, Stark et al. (2010) reported quality of life to be reduced by an average of 16% (9% for those in remission and 29% for those with active disease) in people with ulcerative colitis and reduced by an average of 23% (11% for those in remission and 39% for those with active disease) in people with Crohn's disease when compared with an individual at full health.

Ulcerative colitis: at first presentation, most patients have mild disease, and only 10% have severe disease. About half will continue to have mild disease

or remission, but in about one fifth of patients, ulcerative colitis will be chronic and continuous, and more likely to become extensive, throughout the colon. One review, Ordas et al. (2012), noted that 10 years after onset, 20-30% of patients will have required removal of the colon (colectomy). Another review, Ford and Talley (2013), estimated that the colectomy rate was less than that – around 10%. The risk of mortality does not seem to be raised in people with ulcerative colitis compared with the general population.

Crohn's disease: the outlook in Crohn's disease is worse than in ulcerative colitis. Only 10% of people with this condition have prolonged remission. Ford and Talley (2013) estimated that approximately 20% require hospital admission each year, and half will require surgery within 10 years of diagnosis. Life expectancy is shown to be slightly decreased in people with Crohn's disease compared with the general population (Baumgart and Sandborn [2012]).

There are three main serious intestinal complications of Crohn's disease. The first is stricture (narrowing) of the bowel. This can lead to intestinal obstruction, and Crohn's disease can present as an "acute abdomen" requiring surgery, sometimes mimicking appendicitis. The second is fistulas, which are abnormal connections between sections of bowel, or between bowel and bladder. The third is colorectal cancer, and surveillance is required.

British Society of Gastroenterology (BSG) guidelines for the management of inflammatory bowel disease in adults (2011) state: 'Most patients are referred to hospital clinics for evaluation, and approximately 30% of patients are under regular hospital follow-up. About 2000 people undergo colectomy for IBD each year. The lifetime risk for surgery may be as high as 70 - 80% for Crohn's disease and 20 - 30% for ulcerative colitis, depending on disease severity and location. Costs of caring for patients with IBD in UK hospitals have recently been assessed. Lifetime costs for IBD are comparable to a number of major diseases, including heart disease and cancer. This implies a substantial burden of disease...'

Newer drugs such as the biological agents infliximab and adalimumab may reduce admission rates and the need for surgery.

1.3. Diagnostic and care pathways

1.3.1. Diagnosis of IBS and IBD

Primary care

The symptoms of lower gastrointestinal disorders (including IBD and IBS) can be sufficiently similar to make diagnosis difficult. Tests are often carried out to exclude conditions rather than to diagnose, leading to repeat visits and investigations.

In the majority of cases the diagnosis of IBS can be made on the basis of clinical history alone. NICE Clinical Guideline 61 'Irritable Bowel Syndrome' recommends that people presenting with abdominal pain or discomfort, bloating or change in bowel habit for at least six months should be asked if they have any red flag indicators such as unexplained weight loss. They should also be clinically tested for red flag indicators including anaemia, rectal masses, inflammatory biomarkers for IBD (FC is not specifically mentioned) and late onset (greater than 60 years) change in bowel habits. Presence of any of these indicators should result in a referral to secondary care for further investigation. Therefore, patients presenting with symptoms/test results indicative of IBD are referred to secondary care for specialist investigation (most likely to a gastroenterology clinic).

If there are no red flag indicators to cause concern, the guidelines state that patients who meet the IBS diagnostic criteria should receive the following laboratory tests to exclude other diagnoses:

- Full blood count
- Erythrocyte sedimentation rate or plasma viscosity
- C-reactive protein
- Antibody testing for coeliac disease (endomysial antibodies or tissue transglutaminase).

Of these, the two main tests for inflammation are erythrocyte sedimentation rate and C-reactive protein. However, these tests are not a direct indication of bowel inflammation, because they can be influenced by non-intestinal diseases, and can lack diagnostic accuracy. Therefore, these two tests can identify inflammation but cannot localise it. As a result, many patients are referred for further investigation involving endoscopy, which may not be required. CG61 states that an endoscopy (and a range of other tests) is not needed to confirm the diagnosis of IBS.

The majority of individuals diagnosed with IBS at this stage are managed in primary care.

Secondary care

Existing diagnostic criteria for IBS have been derived from the characteristics of patients presenting in secondary care. Physicians may diagnose IBS in some patients following a thorough clinical history and application of diagnostic criteria, such as Rome III. Many patients with IBS and IBD, however, are likely to be referred to secondary care when there is uncertainty about the diagnosis or a high clinical suspicion of IBD and will require further investigation.

BSG guidelines on IBS suggest that tests conducted in secondary care are largely based on the likely differential diagnosis. Following initial laboratory tests (full blood count, erythrocyte sedimentation rate, C-reactive protein, endomysial antibodies and tissue transglutaminase – as in primary care), which may be repeated in secondary care, the next level of investigation involves endoscopy and imaging.

BSG guidelines on IBD state 'the diagnosis of IBD is confirmed by clinical evaluation and a combination of biochemical, endoscopic, radiological, histological, or nuclear medicine based investigations'. Initial laboratory investigations in common practice include full blood count, erythrocyte sedimentation rate, C-reactive protein and other tests (such as kidney function tests). With regards to FC the guidelines state 'Faecal calprotectin is accurate in detecting colonic inflammation and can help identify functional diarrhoea'. The next level of investigation involves endoscopy (with or without a biopsy), histology and imaging.

Endoscopy can be: 1) colonoscopy, involving inspection of the whole colon, 2) sigmoidoscopy, inspection of only the distal part of the bowel (the sigmoid colon), or 3) gastroscopy, visualising oesophagus, stomach and upper part of the small bowel. There are some sections of the small bowel that cannot currently be reached by widely available forms of endoscopy. In those situations, options include capsule camera endoscopy (the "camera pill"), and imaging methods including ultrasound and MRI.

Therefore, clinical guidelines suggest that patients with symptoms indicative of IBD/IBS presenting in secondary care follow a similar diagnostic pathway of initial investigations prior to receiving endoscopy (second level of testing). As in primary care, erythrocyte sedimentation rate and C-reactive protein are the main markers used to measure intestinal inflammation.

A UK and Ireland survey found that delays in diagnosis of Crohn's disease in children were common; 18% had a pre-diagnosis duration of symptoms of 1 to 3 years, and 9% of more than 3 years. Only 9% had isolated small bowel

disease. In addition, both within the UK and internationally the incidence of Crohn's disease has been increasing.

Differential diagnosis

IBS 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. Blood tests that indicate the presence of inflammation (erythrocyte sedimentation rate and C-reactive protein) have been used as an aid to diagnosis, but may be abnormal because of other, non-gastrointestinal conditions, and can be normal in people with IBD. Until recently, 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. In younger patients, over 60% of colonoscopies have been normal.

1.3.2. Management

IBS

The aetiology of IBS has not yet been established and as a result management focuses on the relief of symptoms. The symptom profile can vary and can require a combination of different interventions to achieve effective relief. These include watchful waiting, diet and lifestyle interventions, patient education and self-help, pharmacological interventions, behavioural and psychological therapies, complementary and alternative therapies. Pharmacological intervention includes antispasmodic agents, laxatives, antimotility agents (such as loperamide) and antidepressants or SSRIs (both as second-line treatment).

IBD

The treatments and the aims of treatments have changed in recent times for IBD. Schoepfer et al. (2012) comment that the aims of management have evolved from relieving symptoms towards mucosal healing. They consider that this shift has been driven by the arrival of new medications such as the anti-tumour necrosis factor (anti-TNF) drugs that can induce and maintain mucosal healing.

The aim of treatment in active disease is to secure a remission, and maintain it. The management of IBD involves diet and lifestyle interventions, pharmacological intervention and surgery to induce, and then maintain, remission. Pharmacological intervention includes aminosalicylates, corticosteroids, thiopurines, disease-modifying anti-rheumatic drugs (methotrexate), immunosuppresants (for example, cyclosporine) and anti-TNF

drugs (such as, infliximab). There is an increased risk of colorectal cancer, so surveillance for that is part of care.

The arrival of more effective new drugs increases the importance of prompt diagnosis of IBD, particularly in Crohn's disease. Achieving earlier diagnosis may impact the treatment pathway that follows. NICE has issued guidance on the use of the anti-TNF drugs, infliximab and adalimumab, in Crohn's disease(TA 187).

1.4. Faecal calprotectin (FC)

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 tests" (POCT). It indicates inflammation in the bowel, but cannot identify the cause of the inflammation.

It should be noted that the diagnosis of any inflammatory or non-inflammatory disease would not be made on the basis of FC results alone, but rather on the basis of history, symptoms (gastrointestinal and other) and absence of weight loss. However, GPs may find FC useful to confirm a diagnosis of IBS based on clinical assessment.

Potentially different aims of FC testing in primary and secondary are discussed below. Although FC testing is specifically discussed, the principles are equally applicable to the entire diagnostic strategy used in either setting.

Adults

Perspectives on the use of FC testing will vary with setting. In primary care, GPs see far more cases of IBS than IBD, and for them FC testing offers evidence to rule out IBD and, therefore, rule in IBS. A negative FC result (normal levels of FC) will imply IBS. GPs are therefore likely to look for a high negative predictive value (or specificity), to provide a basis for a decision not to refer into secondary care for further tests.

Gastroenterologists in adult clinics see a selected group of patients referred by GPs with a suspicion of IBD. In this setting the utility of an FC test would arise from its ability to provide positive evidence of IBD which could help gastroenterologists decide whether to proceed to further investigations, including colonoscopy, biopsy and other tests. In this context, a high positive predictive value (or sensitivity) may be sought, because clinicians will wish to avoid unnecessary invasive investigations in people who have IBS.

Children

The same general principles will apply to the different case mix seen in paediatric gastroenterology. For the GP, a high negative predictive value from a normal FC level would lead to a decision not to refer to paediatric gastroenterology. In secondary care the proportion with IBD is higher, but a normal or near normal FC level may contribute to a decision not to proceed to invasive procedures such as endoscopy, which in children requires either deep sedation or a general anaesthetic.

2. Decision-problem

The aim of this evaluation is to examine the clinical effectiveness and cost-effectiveness of faecal calprotectin testing in distinguishing between non-inflammatory disorders such as IBS, where sufferers will not come to serious harm, and inflammatory disorders, such as IBD, that require referral to specialist care for further investigation, in individuals aged up to 60 years presenting with any of the following lower gastrointestinal symptoms for at least 6 weeks - abdominal pain or discomfort, bloating or change in bowel habit.

The External Assessment Group suggests that in adults presenting with these symptoms, the distinction likely to be most clinically useful is that between IBS and IBD. They also suggest that children presenting with these symptoms can have a different range of conditions, making the role of faecal calprotectin testing in this group potentially less clear, that said, the External Assessment Group believes the most clinically useful distinction in children is likely to be between IBD and non-IBD.

3. Scope of the assessment

The scope of the assessment as identified in the scope document is outlined below.

3.1. Population

Primary care: individuals aged up to 60 years presenting to their GP with any of the following lower gastrointestinal symptoms for at least 6 weeks - abdominal pain or discomfort, bloating or change in bowel habit.

Secondary care: individuals aged up to 60 years presenting with any of the following lower gastrointestinal symptoms - abdominal pain or discomfort, bloating or change in bowel habit that have been referred for assessment.

3.2. The technologies

Several FC tests designed for use as quantitative laboratory-based technologies (many of which use an enzyme-linked immunosorbent assay [ELISA] platform), quantitative rapid tests and as semi-quantitative point of care tests (POCTs), are available to the NHS in England. In principle, all technologies may be used to provide an FC testing service in either primary or secondary care.

The POC and rapid tests can give faster results, within about 30 minutes (which may be quite slow in the context of the pressure of work in general practice). Extraction of the faecal sample is always manual so some time costs are irreducible.

During scoping, it was suggested that some of these tests may perform similarly and, therefore, may be assessed as a group of tests by the External Assessment Group. For example, ELISA tests may be assessed as a group of technologies.

Technologies included in the scope are summarised in Table 1.

Table 1 Technologies included in the scope

Manufacturer	**Test**	**Platform**	**Included in the External Assessment Group assessment?**
Buhlmann	EK-CAL calprotectin ELISA test *Referred to as the 'EK-CAL' test in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: 10-600µg/g	Yes
Buhlmann	EK-CAL calprotectin ELISA test *Referred to as the 'EK-CAL' test in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: 30-1800µg/g	Yes

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?
Buhlmann	LF-CAL25 Quantum Blue calprotectin test *Referred to as the 'Quantum Blue' test in table 2 of the diagnostics assessment report*	Rapid test - Immunoassay designed for the quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. Range: 30-300µg/g	Yes
Buhlmann	LF-CHR 25 Quantum Blue calprotectin test *Referred to as the 'Quantum Blue' test in table 2 of the diagnostics assessment report*	Rapid test - Immunoassay designed for the quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. Range: 100 - 1800µg/g	Yes

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?
Calpro	CALPRO CALPROTECTIN ELISA TEST (ALP) – formerly known as the Phical test CAL0100 *Referred to as the 'CALPRO Calprotectin ELISA test (ALP)' in table 2 of the diagnostics assessment report* *Table 2 of the diagnostics assessment report also refers to the 'Phical ELISA kit' test which is believed to be the same test as the 'CALPRO Calprotectin ELISA test (ALP)'. Therefore, studies of the 'Phical ELISA kit' test are also summarised here*	ELISA – quantitative Range: up to 1250mg/kg	Yes
Calpro	CALPROLAB CALPROTECTIN ELISA (ALP) – formerly known as the Phical test CALP0170 *Referred to as the 'CALPRO Calprotectin ELISA test (ALP)' in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: up to 2500mg/kg	Yes

Manufacturer	**Test**	**Platform**	**Included in the External Assessment Group assessment?**
Eurospital	Calprest *Referred to as the 'Calprest' test in table 2 of the diagnostics assessment report*	ELISA – quantitative	Yes
Eurospital	CalFast *This test is not referred to in table 2 of the diagnostics assessment report*	Rapid test - Quantitative determination of FC in combination with a dedicated reader	Yes
Immundiagnostik	ELISA (K6927) *Referred to as the 'PhiCal Calprotectin ELISA kit' in table 2 of the diagnostics assessment report*	ELISA – quantitative	Yes
Immundiagnostik	ELISA (K6937)	ELISA – quantitative	No – superseded.
Immundiagnostik	ELISA (K6967)	ELISA – quantitative	No - variant of K6927
Thermo Fisher Scientific	EliA Calprotectin *Referred to as the 'EliA platform)' in table 2 of the diagnostics assessment report*	EliA – quantitative In contrast to ELISA, EliA measures the presence of target antibodies by fluorescence signal detection.	Yes

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?
Preventis (sister company to Immundiagnostik)	KST11005 CalDetect Calprotectin Rapid test (version 1 - Caldetect) *Referred to as the 'Prevent ID Caldetect' test in table 2 of the diagnostics assessment report*	POCT – immunochromatographic rapid test. A semi-quantitative test with 3 lines corresponding to: Calprotectin "negative", Calprotectin ≤ 15µg/g, Calprotectin 15-60µg/g and Calprotectin > 60µg/g stool	Yes
Preventis (sister company to Immundiagnostik)	CalDetect Calprotectin Rapid test (version 3 – CalScreen) *This test is not referred to in table 2 of the diagnostics assessment report*	POCT – immunochromatographic rapid test. A yes-no test with only 1 Test-Line corresponding to the cut-off value of 50µg/g stool (no inflammation = <50µg/g and inflammation present = ≥50µg/g)	Yes

Of the 14 tests included in the scope, 12 are quantitative tests that require a cut-off to be set which provides the appropriate context for interpreting the results.

Of the 12 quantitative tests, 8 are based on the traditional ELISA method. Two of the 8, (Immunodiagnostik test K6937 and K6967) were not included in the assessment conducted by the External Assessment Group because one is a variant and the other was superseded by another Immunodiagnostik test (K6927) that is included in the assessment. Of the 6 ELISA tests included in the assessment, some are included as multiple entries because the measurable range of the test varied between versions. Accounting for multiple entries for individual tests, there are four manufacturers of different ELISA

tests. Three of the 12 quantitative tests are 'rapid tests' that reduce the time it takes to run the test when compared with the traditional ELISA method (these rapid tests have not been formally classed as POCTs in this assessment because they require a dedicated reader to process the test). Accounting for multiple entries, there are 2 manufacturers of different rapid tests. One of the 12 quantitative tests is based on the EliA method and is a fully automated test (in contrast to ELISA, EliA measures the presence of target antibodies by fluorescence signal detection).

Two of the 14 tests, by Preventis, are semi-quantitative POCTs that report results at predetermined cut-offs without the need for a reader.

In total, 12 tests were included in the assessment conducted by the External Assessment Group. Accounting for multiple entries of different versions of the same test, there are 4 manufacturers of different ELISA tests, 2 manufacturers of different rapid tests, 1 manufacturer of the EliA test and 1 manufacturer of the POCTs.

Table 2 of the diagnostics assessment report also refers to the 'Prevista' POCT. Data was noted on the Prevista test but this test was not identified for inclusion in the scope for the assessment and, subsequently to compiling the assessment report the External Assessment Group believes this test is not available to the NHS in England and may be out of production. Therefore, the Prevista POCT will not be the subject of the NICE assessment.

Reference standard: histology after endoscopy was taken to be the definitive reference standard.

Interpreting FC tests: because FC correlates with the level of bowel inflammation, test results need to be interpreted in the context of a cut-off value, below which is deemed negative and above which is positive. In the context of distinguishing between IBS and IBD, this would mean a negative result would indicate IBS (a disease not characterised by inflammation) and positive result would indicate IBD (a disease characterised by inflammation). For an ELISA test the output is a single number representing micrograms of FC per gram of stool sample, for example 15µg/g. If the cut-off value is selected as 50 µg/g for distinguishing between IBS and IBD then a person with an FC level of 15µg/g would be classified as negative (indicating IBS). The cut-off value selected influences the diagnostic accuracy of the tests under consideration and different cut-off values may be selected for different purposes (for example, distinguishing between different diseases). Cut-off values can include a middle range in which results are considered indeterminate, below which are deemed negative and above which are

positive. Although a cut-off value needs to be selected for interpreting results of an ELISA test, the cut-offs for a POCT may be pre-specified in the design of the test For example, Caldetect reports 1 of 4 results when the test runs correctly; 1) negative – FC not detectable, 2) negative - FC ≤ 15µg/g, 3) positive - FC 15 – 60µg/g and, 4) positive - FC > 60µg/g. Users may apply local cut-offs for interpreting the results of POCTs, for example, a cut-off of 60µg/g may be applied, test results below which are deemed negative and above which are positive.

3.3. Comparators

The main comparator is clinical assessment. The main tests currently used to measure inflammation are erythrocyte sedimentation rate and C-reactive protein, which can indicate inflammation, but not localise it.

3.4. Outcomes

Depending on data availability, these may include:

- Referral rates
- Numbers of colonoscopies with/without FC testing
- Proportion of colonoscopies with no abnormal findings
- Duration from onset of symptoms to definite diagnosis of IBD – late diagnosis of Crohn's disease
- Cost
- Adverse events such as complications of colonoscopy
- Quality of life and hence quality adjusted life years.

4. The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group.

4.1. Clinical effectiveness

The systematic review identified a total of 1308 references of which, following de-duplication and assessment of eligibility, 28 were included in the

quantitative synthesis, with other studies being used for comparing different tests.

Section 2.1 of the Diagnostics Assessment Report highlights issues experienced in the systematic review. These included the reference standard used in the studies (in particular, the ability of the reference standard to provide a definitive diagnosis and verification bias), patient groups (in particular, different study populations may make FC testing appear more or less attractive), data on cut-off values (in particular, much of the data focused on one cut-off value) and spectrum bias (in particular, most of the evidence is from secondary care). On an individual study level, it is likely that most if not all of these issues are captured in the quality assessment using the quality assessment tool for diagnostic accuracy studies (QUADAS) tool.

4.1.1. Previous systematic reviews

Five previously conducted systematic reviews of FC testing have been quality assessed and summarised by the External Assessment Group. Please refer to section 2.2 of the Diagnostics Assessment Report for further information.

In summary, reviews conducted recently (published in 2010 or onwards) and judged to be medium or high quality by the External Assessment Group concluded that FC testing is a useful tool. For example, the Centre for Evidence-based Purchasing (2010) review focusing on FC for distinguishing between IBS and IBD concluded that FC performs well in distinguishing organic bowel disease from functional bowel disease (organic disease includes inflammatory diseases and functional disease includes IBS); sensitivity and specificity are over 80% in most studies (at a 50µg/g cut-off) and, where calculated, most positive and negative predictive values were 70 to 90%.

4.1.2. Diagnostic accuracy - the comparisons

The External Assessment Group summarises the ability of FC tests to distinguish between 2 sets of conditions, and 4 sets of comparisons are made:

1. Organic vs. non-organic
2. IBS vs. IBD (most appropriate comparison for adults)
3. Organic vs. IBS
4. IBD vs. non-IBD (most appropriate comparison for paediatrics)

Organic disease includes inflammatory diseases. “Organic” disease is formally defined as a condition in which there is an observable and measurable disease process (for example, inflammation).

The decision-problem for this evaluation concerns the use of FC to help distinguish between inflammatory and non-inflammatory conditions of the bowel. However, as shown above, the External Assessment Group have summarised the evidence for a range of comparison

Comparison 1, organic vs. non-organic is the closest comparison to the decision-problem set out in the scope. However, the External Assessment Group asserts that in practice the most important distinction is between IBS vs. IBD (comparison 2) in the adult population and IBD vs. non-IBD (comparison 4) in the paediatric population because IBS is much less common than in the adult population. Comparison 3, organic vs. IBS, is another way of distinguishing between conditions because in adult medicine there are organic causes other than IBD that can cause symptoms.

Since comparisons 2 and 4 are deemed to provide a reasonable proxy for the decision problem at hand, the External Assessment Group’s economic analysis focuses on the cost effectiveness of FC within these applications of the test. Diagnostic accuracy data for FC testing in all four comparisons are summarised below.

Nearly all the evidence comes from studies in secondary care, with little data from primary care.

Organic vs. non-organic

Ten studies gave results that compared organic and non-organic bowel disease, at 8 cut-off levels, ranging from 10 to 217µg/g, mostly in adults in secondary care. The majority of studies used ELISA tests, and 2 studies reported results for the rapid quantitative test Quantum Blue LF-CAL25 and the POCT Prevent ID CalDetect [redacted].

Figure 1 (updated) shows the diagnostic performance of different FC tests in organic vs. non-organic disease using different cut-offs. Of the 10 studies, 3 had samples sizes of less than 100 patients and 2 studies employed a sample size of over 600 patients. Studies were of mixed quality with Dolwani et al. (2004) and Kok et al. (2012) assessed as having the least risk of bias when compared with the other studies.

Sensitivity ranged from 43% - 100% but specificity was more varied (50% - 98%) for ELISA tests used in a secondary care adult population. For ELISA tests used in a secondary care paediatric population, the range of sensitivity figures reported is narrower than that seen in adults (57% - 100%) and specificity ranged from 43% - 100%.

A non-UK study by Kok et al. (2012) assessed the Buhlmann ELISA (EK-CAL) and the rapid quantitative test Quantum Blue LF-CAL25 in a primary care adult population of 382 patients when using a cut-off of 50µg/g. The ELISA test demonstrated a sensitivity of 74% and specificity of 47% whilst the rapid test had a lower sensitivity of 64% but slightly higher specificity of 53% when compared with the ELISA.

[redacted]

Figure 1 Diagnostic performance of FC testing in organic vs non-organic bowel disease (updated Diagnostics Assessment Report Figure 19)

Given the number of results reported at the 50µg/g cut-off it may have been possible for the External Assessment Group to combine these individual estimates into combined summary estimates of sensitivity and specificity. However, such a meta-analysis has not been conducted here. This may be because the External Assessment Group suggests that the use of FC testing to distinguish between organic and non-organic disease is not the most relevant comparison for this assessment.

The term organic covers a range of conditions and the range varies amongst studies. Some of these conditions would not normally be regarded as inflammatory. Inflammation implies the presence of white blood cells, and one would not expect these in lesions such as colonic polyps. However, FC is often raised in patients with larger polyps, (please refer to **Error! Reference source not found.** of the Diagnostics Assessment Report for further information). FC may indicate the presence of conditions other than IBD, such as some colorectal cancers and large adenomas, but results are more variable than with IBD. It is noteworthy that some organic conditions are not obviously inflammatory, so studies where the organic group included a mixture of conditions could make FC testing look less useful. FC testing will therefore appear most beneficial in studies that include only people with IBS and IBD.

FC testing for distinguishing between organic and non-organic diseases is not included in the economic analysis conducted by the External Assessment Group.

IBS vs. IBD

Seven studies gave results that compared IBS and IBD, at 8 cut-off levels, ranging from 8 to 150µg/g, all in adults in secondary care. All studies assessed ELISA tests, and one also assessed the performance of the POCT Prevent ID CalDetect. As expected, low cut-offs gave high sensitivity for IBD but poor specificity. Sensitivity was consistently high (usually 100% at levels under 50µg/g; ranging from 83% to 100% at a cut-off of 50µg/g), but specificity was more varied (51% to 100%). It is noteworthy that different studies of the Phical (Calpro [ALP]) ELISA test when used at the 50µg/g cut-off reported different estimates of test performance, sensitivities ranged from 83% to 96% and specificities ranged from 87% - 100%.

Figure 2 shows the diagnostic performance of different FC tests in IBS vs. IBD using different cut-offs. Many of the studies had a small sample size; the largest study was by Li et al. (2006) who employed a sample of 240 patients (refer to Diagnostics Assessment Report table 9 for further details). Studies are of mixed quality. Schroder et al. (2007) and Schoepfer et al. (2008) were

assessed as having the least risk of bias (refer to table 10 of the Diagnostics Assessment Report for further details).

[redacted]

Five studies (4 on the Phical test (Calpro [ALP]) and 1 on the Immunodiagnostik test) reported data for FC testing with ELISA when a cut-off of 50µg/g was applied. This allows for the meta-analysis of such studies to provide an overall combined estimate of sensitivity and specificity (figure 3). The combined estimates for ELISA tests, at a 50µg/g cut-off, are a sensitivity of 93% and a specificity of 94%. The meta-analysis estimates are informed by a pool of 596 people of which 40% are from the Li et al. (2006) study. The mean age of people in these studies, where reported, ranged from 40 – 52 in people with IBS and 34 – 45 in people with IBD. However, the age of people in the Schoepfer et al. (2008) study went as high as 78 years.

The only study using a POCT was Otten et al. (2008), which assessed the Prevent ID CalDetect test in a sample of 114 people. CalDetect produces 1 of 4 results when the test has run correctly; 1) negative – FC not detectable, 2) negative - FC ≤ 15µg/g, 3) positive - FC 15 – 60µg/g and, 4) positive - FC > 60µg/g. Otten et al. showed that the test performed well at a cut-off of 15µg/g with a sensitivity of 100% and a specificity of 95%. At a cut-off of 60µg/g, although specificity improved slightly to 98%, sensitivity was only 61%, which the External Assessment Group considered to be unlikely to be acceptable in clinical practice given the importance of not missing people with IBD. The average age of people in the Otten et al. study is 52 in people with IBS and 45 in people with IBD.

The cost effectiveness of FC testing for distinguishing between IBS and IBD in an adult population in primary care is assessed in the economic evaluation conducted by the External Assessment Group.

[redacted]

(The confidence contour shows the confidence interval or region for the summary point. The prediction contour outlines the prediction region for the true sensitivity and specificity in a future study)

Organic vs. IBS

The term organic covers a range of conditions and the range varies amongst studies. Some of these conditions would not normally be regarded as inflammatory. Inflammation implies the presence of white blood cells, and one would not expect these in lesions such as colonic polyps. However, FC is often raised in patients with larger polyps, (please refer to **Error! Reference source not found.** of the Diagnostics Assessment Report for further information).

FC may flag up the presence of conditions other than IBD, such as some colorectal cancers and large adenomas, but results are more variable than with IBD. Therefore in studies with a mix of organic conditions, FC may not appear as reliable. However, this should not detract from what appears to be its good performance in detecting IBD and excluding IBS.

Two studies reported results for “organic bowel disorders” versus IBS for FC testing with ELISA at different cut-offs, mostly in adults and all in secondary care (figure 4).

[redacted]

FC testing for distinguishing between organic diseases and IBS is not included in the economic analysis conducted by the External Assessment Group.

[redacted]

IBD vs. non-IBD

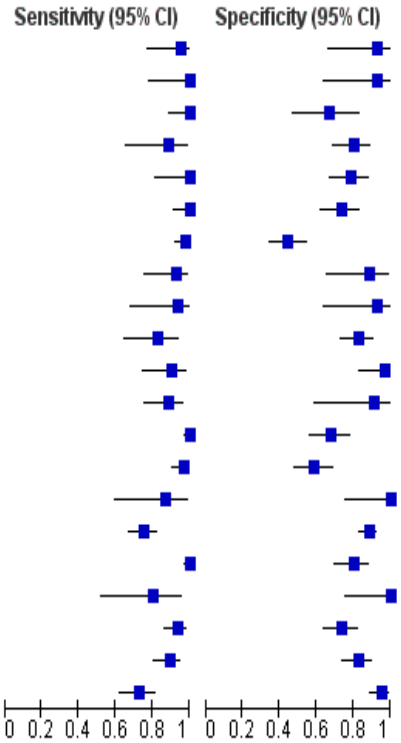
Eleven studies reported IBD versus non-IBD, at 8 cut-off levels (figure 5). Eight studies were conducted in paediatrics and 3 in adults. All used ELISA tests, and one (Damms and Bischoff [2008]) also assessed the Prevista POCT. Data was noted on the Prevista test but this test was not identified for inclusion in the scope for the assessment and, subsequently to compiling the assessment report the External Assessment Group believes this test is not available to the NHS in England and may be out of production. Therefore, the Prevista POCT will not be the subject of NICE guidance.

The studies showed consistently high sensitivity at lower cut-offs, nearly all over 90%, with most at the 50µg/g cut-off having sensitivities of 100%. Specificity was much more varied, ranging from 44% to 93% at a 50µg/g cut-off. Most of these results were in paediatric groups. Most studies reported results at only 1 cut-off, but 1 study reported 5 cut-offs and another 4, both in paediatric populations. Studies are of mixed quality with Canini et al. (2006), Diamanti et al. (2010), Fagerberg et al. (2005) and van de Vijver et al. (2012) assessed as having the least risk of bias compared with the other studies.

It should be borne in mind that symptoms of IBD in children may be “subtle and atypical” (Sidler and Leach [2008]) rather than the typical diarrhoea, abdominal pain and weight loss. Impaired growth can be one presentation.

Figure 5 Diagnostic performance of FC testing in IBD vs. non-IBD (Diagnostics Assessment Report Figure 12)

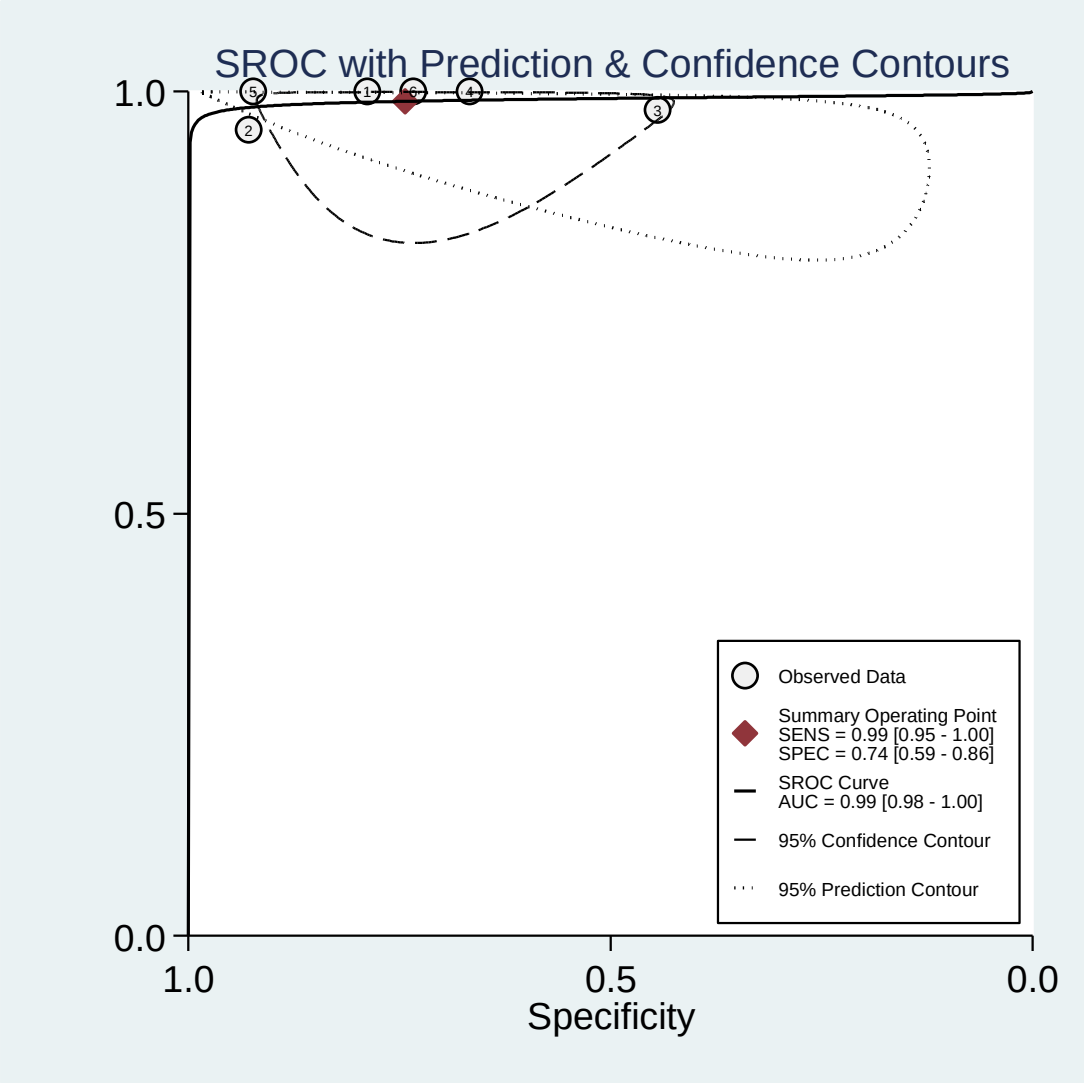
Study	TP	FP	FN	TN	Cut-off level	Make of test	Age	Primary of secondary care	ELISA or POCT	Sensitivity (95% CI)	Specificity (95% CI)
Fagerberg 2005	21	1	1	13	50.0	Calprest	Paediatric	Secondary	ELISA	0.95 [0.77, 1.00]	0.93 [0.66, 1.00]
Tomas 2007a	15	1	0	12	50.0	Calprest	Paediatric	Secondary	ELISA	1.00 [0.78, 1.00]	0.92 [0.64, 1.00]
Sidler 2008	31	10	0	20	50.0	PhiCal	Paediatric	Secondary	ELISA	1.00 [0.89, 1.00]	0.67 [0.47, 0.83]
Damms 2008b	16	13	2	53	50.0	Prevista	Adult	Secondary	POCT	0.89 [0.65, 0.99]	0.80 [0.69, 0.89]
Damms 2008a	18	14	0	52	50.0	EK-CAL	Adult	Secondary	ELISA	1.00 [0.81, 1.00]	0.79 [0.67, 0.88]
Van de Vijver 2012a	42	20	0	55	50.0	CALPRO	Paediatric	Secondary	ELISA	1.00 [0.92, 1.00]	0.73 [0.62, 0.83]
Henderson 2012a	89	55	2	44	50.0	PhiCal	Paediatric	Secondary	ELISA	0.98 [0.92, 1.00]	0.44 [0.34, 0.55]
Canani 2006	25	2	2	16	93.5	Calprest	Paediatric	Secondary	ELISA	0.93 [0.76, 0.99]	0.89 [0.65, 0.99]
Tomas 2007b	14	1	1	12	100.0	Calprest	Paediatric	Secondary	ELISA	0.93 [0.68, 1.00]	0.92 [0.64, 1.00]
Limburg 2000	24	14	5	67	100.0	PhiCal	Adult	Secondary	ELISA	0.83 [0.64, 0.94]	0.83 [0.73, 0.90]
Sidler 2008b	28	1	3	29	100.0	PhiCal	Paediatric	Secondary	ELISA	0.90 [0.74, 0.98]	0.97 [0.83, 1.00]
Ashorn 2009	39	1	5	10	100.0	PhiCal	Paediatric	Secondary	ELISA	0.89 [0.75, 0.96]	0.91 [0.59, 1.00]
Diamanti 2010a	117	26	0	54	100.0	Calprest	Paediatric	Secondary	ELISA	1.00 [0.97, 1.00]	0.68 [0.56, 0.78]
Henderson 2012b	88	41	3	58	100.0	PhiCal	Paediatric	Secondary	ELISA	0.97 [0.91, 0.99]	0.59 [0.48, 0.68]
Tomas 2007c	13	0	2	13	150.0	Calprest	Paediatric	Secondary	ELISA	0.87 [0.60, 0.98]	1.00 [0.75, 1.00]
Licata 2012	107	24	35	180	150.0	Calprest	Adult	Secondary	ELISA	0.75 [0.67, 0.82]	0.88 [0.83, 0.92]
Diamanti 2010b	117	16	0	64	160.0	Calprest	Paediatric	Secondary	ELISA	1.00 [0.97, 1.00]	0.80 [0.70, 0.88]
Tomas 2007d	12	0	3	13	200.0	Calprest	Paediatric	Secondary	ELISA	0.80 [0.52, 0.96]	1.00 [0.75, 1.00]
Henderson 2012c	85	26	6	73	200.0	PhiCal	Paediatric	Secondary	ELISA	0.93 [0.86, 0.98]	0.74 [0.64, 0.82]
Henderson 2012d	81	17	10	82	300.0	PhiCal	Paediatric	Secondary	ELISA	0.89 [0.81, 0.95]	0.83 [0.74, 0.90]
Henderson 2012e	66	5	25	94	800.0	PhiCal	Paediatric	Secondary	ELISA	0.73 [0.62, 0.81]	0.95 [0.89, 0.98]



Six separate estimates of sensitivity and specificity are available at a cut-off of 50µg/g (2 from Calprest, 3 from Phical (Calpro [ALP]), 1 from the EK-CAL) and another 6 estimates at 100µg/g (2 from Calprest and 4 from Phical (Calpro [ALP])) which allows the individual estimates to be meta-analysed into combined overall estimates of sensitivity and specificity for ELISA tests. The overall pooled results for IBD versus non-IBD, show very high sensitivity of 99% but a moderate specificity of 74% at a cut-off of 50µg/g (figure 6). These estimates are informed by a pool of 531 people with the majority of these studies including patients up to the age of 18 years. At a cut-off of 100µg/g, sensitivity falls to 94% but specificity improves to 82% (figure 7). These estimates are informed by a pool of 656 people, however, the upper age limit varied in these studies. Two studies recruited patient up to the age of approximately 15 years, 2 studies up to the age of 18 years and 1 study of to an age of 20 years. The age limit was not reported in the sixth study.

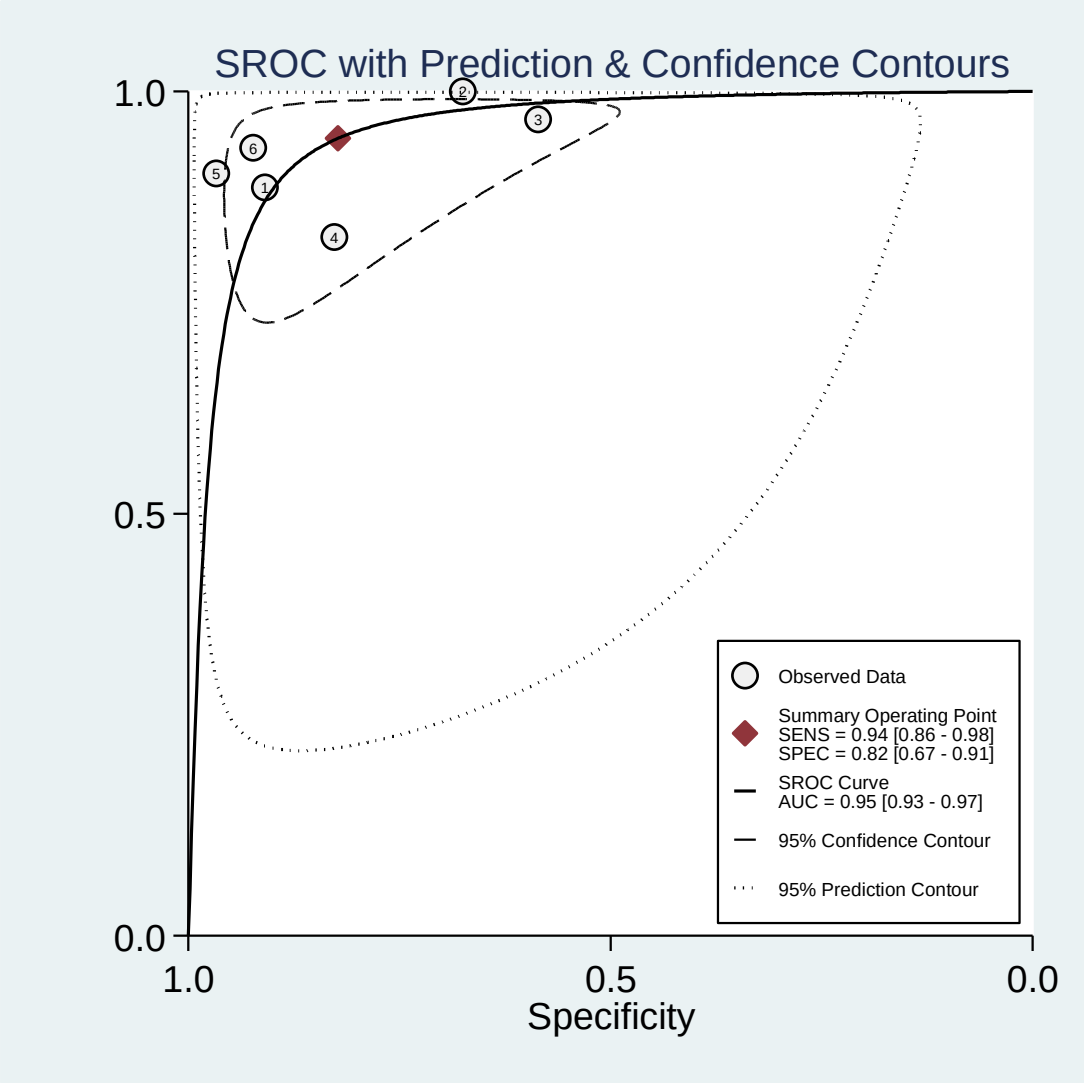
The cost effectiveness of FC testing for distinguishing between IBD and non-IBD in a paediatric population in secondary care is assessed in the economic evaluation conducted by the External Assessment Group.

Figure 6 Summary receiver-operating characteristic (sROC) curve for FC testing with ELISA in the diagnosis of IBD versus non-IBD at a cut-off level of 50 µg/g (Diagnostics Assessment Report figure 13)



(The confidence contour shows the confidence interval or region for the summary point. The prediction contour outlines the prediction region for the true sensitivity and specificity in a future study)

Figure 7 Summary receiver-operating characteristic (sROC) curve for FC testing with ELISA in the diagnosis of IBD versus non-IBD at a cut-off level of 100 µg/g (Diagnostics Assessment Report figure 16)



(The confidence contour shows the confidence interval or region for the summary point. The prediction contour outlines the prediction region for the true sensitivity and specificity in a future study)

4.1.3. Primary care pilot data on FC testing

4.1.3.1. Adults

As noted previously, there is a lack of published data on the use of FC testing in primary care. However unpublished results from the NHS Technology Adoption Centre (NTAC) implementation/pilot projects provide data on referral patterns by GPs in the UK (assuming that those in the North-East are representative).

Implementation projects for FC testing in two North East Clinical Commissioning Groups within Northumberland and Durham Dales during 2011/12 were undertaken by NTAC. The Durham Dale project provides data on GP referrals using current practice (with no FC testing), and the effect of introducing FC testing in primary care. The data allowed the External Assessment Group to explore what might happen if FC testing is made available and is used to inform the economic analysis.

The diagnosis and management pathway used in Durham Dales suggests that erythrocyte sedimentation rate and C-reactive protein blood tests, suggested initial laboratory tests in the BSG guidelines for IBS and IBD, may or may not be used be used for distinguishing IBS from IBD depending on individual physician preferences. Erythrocyte sedimentation rate and C-reactive protein may be used to exclude other diagnoses. Therefore, GP current practice may be based on clinical assessment without testing for these inflammatory markers.

The test used was the POCT Prevevnt ID CalDetect, which divides people into 3 groups;

1. Negative < 15µg/g (negative – FC not detectable and negative - FC ≤ 15 µg/g test results are grouped together)

2. Positive (deemed to be an intermediate/indeterminate level of FC in the project) 15 - 60µg/g

3. Positive > 60µg/g.

GPs made referral decisions based on clinical assessment without knowledge of the FC test result. They referred those that they thought might have IBD, and managed those that they thought had IBS in primary care.

A final consultant diagnosis was made, based on FC test results and clinical data including colonoscopy. The clinical data came from GP and outpatient data, where patients were referred, or just from GP data, when patients were not referred. Note that those diagnosed as having IBS did not have colonoscopy so it is not possible to completely exclude false negatives (partial verification bias). These would have IBD but appear clinically to be IBS and have negative FC test results. Such false negatives are unlikely given the high sensitivity (100% see figure 2) of this POCT at the 15 µg/g cut-off. However, it should be noted that data on the performance of this test have been collected in secondary care (Otten et al. [2008]). The Durham Dale data could not be used to inform the estimates of test accuracy for the Prevent ID CalDetect test in the main economic analysis because of the partial verification bias.

For assessing the sensitivity and specificity of GP assessment, there are two options using the Durham Dale pilot data.

- Use FC as the reference test
- Use final consultant diagnosis as the reference test.

If we compare GP diagnosis with FC levels, and assume that a positive or intermediate FC test result implied IBD, then we have a 2x2 table as follows:

Table 2 GP diagnosis compared with FC level

	FC +ve	FC –ve	Total
GP IBD (no FC testing)	28	4	32
GP IBS (no FC testing)	6 (4 high, 2 indeterminate)	79	85
	34	83	117

Therefore, a sensitivity of 82% (28/34) and a specificity of 95% (79/83) is achieved. If the two patients with indeterminate levels of FC (who would be re-tested, rather than referred) are excluded, the sensitivity is 88%. Of the 83 patients diagnosed as having IBS by the GP, only 4 had high levels of FC, a 5% error rate giving a negative predictive value of 95% for a GP diagnosis. Note that the 4 diagnoses are not false negative in the sense of IBD being missed, but in the sense of being “false non-referrals”. It is possible that not all these patients would have IBD.

Therefore, without FC testing, GPs would not refer 4 of the 32 patients with high FC levels.

This means that the consultant diagnosis may be more useful for the External Assessment Group evaluation, and the next table compares the GP diagnosis (without knowledge of the FC test result) and the consultant diagnosis (with knowledge of the FC test result and of endoscopy where performed). Note that far more patients (22) had endoscopy than were found to have IBD.

Table 3 GP diagnosis compared with final consultant diagnosis

	Consultant IBD (including FC testing and, where performed, endoscopy)	Consultant IBS (including FC testing and, where performed, endoscopy)	Total
GP IBD (no FC testing)	7	22	29
GP IBS (no FC testing)	0	82	82
	7	104	111

Numbers are slightly less than in the previous table because some patients do not appear to have been followed up. No data are given in the NTAC report on the presumed diagnosis or FC test results in 5 missing cases. The sixth was found to have cancer.

These results show that the GPs referred all those diagnosed as having IBD, giving a "whole pathway" sensitivity of 100% (7/7). "Whole pathway" combines GP assessment, FC testing and consultant opinion, based on clinical data that included endoscopy (mainly colonoscopy but some flexible sigmoidoscopies).

However this is achieved at a specificity of 79% (82/104) for GP assessment without FC testing. Without FC testing, GPs refer a group of whom around 25% have IBD (7 of 29) and 75% have IBS. This is similar to results from routine care that over 60% of colonoscopies in young people are normal.

The External Assessment Group states that this implies that if GPs had access to FC testing, they might be able to reduce referrals by a considerable amount. The Durham Dale data suggest that GPs refer about a quarter of people presenting to them with gastrointestinal symptoms that could be due to IBS or IBD. The number of people in the study is quite small, but that proportion is similar to the figure of 29% reported in the BSG guideline on IBS, which increases confidence in the data.

The prevalence of IBD in the whole population was 6.3 % (7/111 with a standard error of 2.3%), but amongst those referred, it was almost 25% (7/29).

For modelling purposes, the External Assessment Group uses a prevalence of IBD of 6.3%, and in the absence of FC testing, a sensitivity of GP current practice of 100%, and 79% specificity.

Using the North European data from Shivananda et al. (2006), a ratio of ulcerative colitis to Crohn's disease of 3:2 (incidence of ulcerative colitis 12.9 in 15-44 age group, based on 539 cases; of Crohn's disease 8.7, based on 365 cases) is expected in this adult population.

4.1.3.1.1. Uptake of FC testing in primary care – hypothetical scenario

In the implementation project, a GP decision to refer a patient could lead to colonoscopy and possible other invasive investigations. This decision would not be taken lightly. However, if FC testing is introduced, the External Assessment Group suggests that GPs would consider testing in a wider patient group then they would consider for referral. They refer about 25% (29/111) of those that present to them with symptoms. A scenario analysis can be created, arbitrarily assuming that if FC testing becomes available, GPs will test twice as many (50%) as they would have referred in the absence of FC testing.

The External Assessment Group believes the 50% is a rather arbitrary assumption. The External Assessment Group has assumed that more patients with symptoms would have FC testing than were referred when testing was not available, but they cannot say if 50% is correct. Given that the Durham Dales suggests that GPs are generally good at diagnosing IBS, we would not expect 100% to be tested.

The External Assessment Groups notes from the Durham pilot data that if GPs thought a patient had IBS, only 5% had a positive FC test result. So a positive GP diagnosis of IBS was usually right, (a negative predictive value of 95%). Not all those with a positive FC test result would have organic disease – some would have IBS. But they would be referred or re-tested, so the 5% are false negatives in the sense of being "false non-referrals" rather than definite organic disease. But some could have IBD.

In the External Assessment Group's scenario analysis, it is assumed that all patients with IBD will be in the assumed larger group (50%, so 222 patients) that will have FC testing. If it is assume that 50% of patients with symptoms will be tested, this gives figures as shown in table 4.

If the FC test used by the GP is an ELISA FC test, this would result in 0.44 of people with IBD being missed in the overall population. The ELISA test has a sensitivity of 93% for distinguishing IBD from IBS (based on combined estimates in figure 3) so with overall prevalence of IBD 6.3%, then (6.3 x 0.07) = 0.44% people would be missed. The test accuracy estimates from ELISA testing have been used to hypothesise how any people with IBD may be missed with FC testing because data for Prevent ID CalDetect suggests the test has 100% sensitivity so no cases of IBD would be missed with this test.

The extra group of 25% of people with symptoms tested are those regarded by the GP as less likely to have IBD than the initial 25% (because the GP didn't refer them), and the GP is likely to be doing the test to confirm IBS. However it is unclear whether the number of false positives increases.

The External Assessment Group base case assumption is that doubling the number tested would not increase the number of false positives. Since the extra 25% tested would have less severe symptoms than the first 25% (referred), the External Assessment Group believe it may be reasonable to rule out a doubling of false positives. However assuming no increase may be too optimistic. When assuming 50% of presenting patients are tested with FC, as oppose to 25%, the figures change to;

Table 4 Expected GP diagnosis compared with final consultant diagnosis when assuming 50% of presenting patients are eligible for an FC test

	Consultant IBD (including FC testing and, where performed, endoscopy)	Consultant IBS (including FC testing and, where performed, endoscopy)	
GP IBD (no FC testing)	7	22	
GP IBS (no FC testing)	0.44	192.56	
	7.44	214.56	222

Using these figures the prevalence of IBD is now 3.3% (7/222) in the whole population. Since all those with IBD are tested, there are no false negatives

and sensitivity is 100% (if you take into account the 0.44 cases missed by the GP, sensitivity falls to 94%). Specificity is 90%. If it is assumed that there would be more false positives, specificity would be 80% if we double the false positives to 44 and 85% if we increased them to 33.

The 100% sensitivity for the POCT Prevent ID CalDetect test at 15ug/g is based on only one study (Otten et al [2008]) with not very large numbers in a secondary care setting, and the External Assessment Group suggest this needs to be replicated in a larger study. However, experts suggest that GPs would not simply rely on the results of an FC test alone, knowing that sensitivity for ELISA testing is not perfect, and some of the false negatives on ELISA testing might be referred based on clinical judgement.

If the performance of diagnostic testing when adding FC testing to GP current practice was the average estimates of using an ELISA test at a cut-off of 50ug/g, then a sensitivity of 93% and specificity of 94% would change the figures in table 4 to the figures in table 5;

Table 5 Expected GP diagnosis if an FC test was used in primary care compared with final consultant diagnosis when assuming 50% of presenting patients are eligible for an FC test (based on test accuracy data for ELISA testing from figure 3)

	Consultant IBD (including FC testing and, where performed, endoscopy)	Consultant IBS (including FC testing and, where performed, endoscopy)	
GP + FC IBD	6.51	13.19	
GP + FC IBS	0.49	201.51	
	7	215	222

Only 9% would be referred when a GP uses FC testing due to the greater specificity of ELISA when compared with GP current practice alone if 50% of people with symptoms were tested. This is compared with 25% when a GP does not have FC testing available (as seen from table 3).

4.1.3.2. [redacted]Children

Modelling requires different assumptions in children. Based on the recent UK study by Henderson et al. (2012), 48% of referred cases (91/190) had IBD. The ratio of Crohn's disease to ulcerative colitis is higher in children, at 2.3:1. The potential reduction in colonoscopies is therefore greater in children than adults.

4.1.4. Ranges of FC values and choice of test

Ranges

It is worth noting that notwithstanding the generally good performance of FC testing (as judged by the External Assessment Group) for differentiating IBD and IBS in adults, and IBD and non-IBD in children, the range of results can be wide, with some low levels in patients with IBD and raised levels in people with IBS/non-IBD.

In some studies, the ranges do not overlap, in others they do. For example: in El-Badry et al. (2010), the value of FC in people with IBD ranged between 98 and 637µg/g which does not overlap with the value of FC in people with IBS (14 to 65µg/g). In all other studies, the range of FC in patients with IBD overlapped with the range of FC in patients with IBS. In some studies, such as Li et al. (2006) and Schroder et al. (2007), the range of FC levels in people with IBD was wide with the lowest value being 15µg/g and the highest being 2574µg/g.

The range of results in studies comparing IBD and non-IBD in children was similar to that found in studies comparing IBD and IBS in adults. In some studies (Canini et al. [2006]; Diamanti et al. [2010]; Sidler and Leach [2008]), the ranges of FC levels overlapped in children and FC levels were high, considerably more than the manufacturer's cut-off levels.

Choice of test

The External Assessment Group summarises a number of studies that evaluate the comparative performance of FC tests in particular situations. For example, some studies assess the performance of the tests for distinguishing IBS from IBD and others assess the tests in distinguishing organic from non-organic disease.

Overall, the External Assessment Group concludes that studies comparing the performance of POCTs with ELISA tests do not suggest any significant differences between them. However, studies comparing different ELISA tests show that different tests can lead to different diagnostic accuracies. For

example, an abstract by Loitsch et al. (2010) showed that in IBS vs. IBD the Immunodiagnostik ELISA and Buhlmann EK-CAL ELISA test led to different sensitivity (94% vs. 97%, respectively) and specificity (79% vs. 63%, respectively) figures. It is also worth noting that from the earlier review of diagnostic accuracy of FC tests in IBS vs. IBD, 4 different studies of the PhiCal (Calpro [ALP]) ELISA test at the 50µg/g cut-off, led to different sensitivities (83% - 96%) and specificities (87% - 100%).

These points are particularly important because not all of the tests included in the assessment have estimates of clinical and/or cost effectiveness and, therefore, whether the evidence can be extrapolated to apply to such tests may need to be considered carefully.

4.1.5. Clinical outcomes

Modelling was used to estimate clinical outcomes and quality-adjusted life years (QALYs). Please refer to the section on cost effectiveness below.

4.2. Economic analysis

4.2.1. Review of existing economic analyses

Seven references were identified by the systematic review of economic analyses. Although previous economic analyses have typically concluded that FC testing is cost saving compared with diagnostic pathway costs without it, several issues were highlighted in the critique of the literature, which need further consideration. These included the use of a small sample size to inform the analysis (Hornung and Anwar [2011]), assumptions about test accuracy and no consideration of false negatives (Mindemark and Larsson [2012]), analyses considered colonoscopy but did not consider FC testing (Goldfarb et al. [2004] and Dubinsky et al. [2002] – also, this analysis was conducted in the US context), studies were conducted in England but in primary care only (YHEC economic report for the CEP [2010]) and some studies were available in abstract/poster format which did not allow for a full critique of the analysis (Mascialino et al. [2012 & 2013]).

The External Assessment Group constructed a de novo economic model to address the decision problem for this evaluation.

4.2.2. Review of quality of life data

The External Assessment Group summarise studies identified following a review of quality of life data that may be suitable for inclusion in a cost effectiveness analysis of FC testing where quality-adjusted life years are to be estimated (also known as a cost utility model). Health related quality of life

data and considerations for three conditions are presented: IBS, Crohn's disease and ulcerative colitis. In essence, the data show the reduction in quality of life experienced by people with these conditions and, in some cases, how this varies depending on the severity of the disease. For example, Spiegel et al. (2009) reported quality of life in people with IBS to be reduced by 26% on average and 30% if severe when compared with an individual at full health. Stark et al. (2010) reported quality of life to be reduced by an average of 16% (9% for those in remission and 29% for those with active disease) in people with ulcerative colitis and reduced by an average of 23% (11% for those in remission and 39% for those with active disease) in people with Crohn's disease when compared with an individual at full health. Given the centrality of colonoscopy in the assessment, a brief review of the adverse events associated with colonoscopy (for example, bleeding, perforation and perforation associated mortality) is then presented.

Together, these data provide the basis for selecting appropriate quality of life and adverse event parameters/inputs to the model. Further details are provided in the section on cost effectiveness.

4.2.3. Cost effectiveness model constructed by the External Assessment Group

The External Assessment Group approached the modelling exercise in a step-wise fashion. Initially, a limited model was constructed to allow for consideration of the quality of life experienced (for a duration of 12 weeks assumed in the base case) by those people who receive a false negative diagnosis against the costs of initial diagnostic testing. This analysis does not account for the costs and benefits of induction therapy (defined here as a therapy or set of therapies that aim to induce disease remission) and maintenance in IBD. The External Assessment Group suggests that the outputs of this limited analysis may provide a useful sense check to the results of a full cost effectiveness model (results of the limited analysis are not reported in the Diagnostics Assessment Report). The External Assessment Group went on to construct a full cost effectiveness model; the details of this model are presented in the remainder of this section.

The cost effectiveness model built for this assessment is informed by the model used in NICE Clinical Guideline 152: Crohn's disease: Management in adults, children and young people, the modelling for the draft NICE clinical guideline for ulcerative colitis and the YHEC model (informed by the modelling for NICE Clinical Guideline 61: Diagnosis and management of irritable bowel syndrome in primary care). In particular, these models are used to inform induction therapy and remission patterns in people with IBD and IBS.

Key model characteristics/inputs and results for both primary and secondary analyses are described below (a full set of model inputs can be found in appendix 7 of the Diagnostics Assessment Report).

Model aim

In essence, the main aim of the model is to assess the impact of FC testing when added to current clinical practice compared with current practice alone for distinguishing between IBD and IBS in primary care. The External Assessment Group has previously highlighted, in the clinical effectiveness review, that this is the most important application of FC testing for adults. This model was then adjusted to reflect the differing test performance and costs in the paediatric population to provide an approximation of the cost effectiveness of FC testing in IBD vs non-IBD (previously highlighted as the most important application of FC testing in the paediatric population by the External Assessment Group). However, the External Assessment Group highlight the limitation of this approach because the main model structure does not fully account for the non-IBD case mix in the paediatric population (prevalence of IBS in the non-IBD group is lower than that seen in adults)..

Model structure

The model uses a linked evidence approach to combine the outcomes of diagnostic strategies with the management (induction therapy and remission patterns) of patients, to allow the estimation of clinical outcomes and QALYs. The modelling allows for multiple test sequences to be considered (for example, an initial POCT followed by a colonoscopy and ELISA testing followed by colonoscopy). The main outcomes considered from the modelling of diagnostic strategies are patients classified as true positive for Crohn's disease, true positive for ulcerative colitis, false negative (patient has IBD but is diagnosed as IBS), true negative (IBS) and death following colonoscopy. False positives (incorrectly diagnosed with IBD) will eventually be correctly diagnosed with IBS given that all false positives will be referred to secondary care and will undergo a colonoscopy (assumed 100% specificity). The costs of additional diagnostic testing and adverse events associated with colonoscopy have been accounted for in the model. The outcomes from the diagnostic pathway are then linked to the care pathway following diagnosis. True positives for Crohn's disease and ulcerative colitis are considered separately because patients in these groups follow different and complicated induction and remission pathways post diagnosis. Both true and false negatives follow the care pathway for IBS, with non-responders to dietary advice and subsequent medical treatment for IBS being retested for IBD. It is assumed that 45% of people with IBS and classified as true negatives respond to

dietary advice, and of the remaining 55% that 50% will respond to medication. This results in 5% of true negatives not responding to IBS treatment, so being retested for IBD after 3 months with an FC test, despite being correctly treated for IBS. It is assumed that 100% of false negatives are non-responders to dietary advice and subsequent medical treatment for IBS, so are retested for IBD after 3 months with an FC test, and have received treatment for IBS and not IBD during this time. The model employs a weekly cycle and adopts a 10 year time horizon.

Scenarios modelled

Although the scope allows for the assessment of FC testing for both adults and children in both primary and secondary care, the External Assessment Group has modelled two specific scenarios: 1) an adult population in primary care, with FC test accuracies for IBD versus IBS and, 2) a paediatric population in secondary care, with FC test accuracies for IBD versus non-IBD.

Tests assessed in the modelling

The use of ELISA FC testing has been evaluated in the base case for both of the primary and secondary care scenarios. However, not all of the ELISA tests included in the assessment have informed the estimates of diagnostic accuracy. The POCT Prevent ID CalDetect has been evaluated in the base case primary care scenario. Rapid quantitative tests (for example, the Quantum Blue test) have not been evaluated in the base case analysis for either scenario. However, the cost effectiveness of Quantum Blue LF-CAL25 has been explored in sensitivity analyses to the primary care scenario.

Health-related quality of life (HRQoL)

The base case applies the quality of life decrements from remission to active disease of 0.280 for Crohn's disease and 0.200 for ulcerative colitis from Stark et al. (2010). But sensitivity analyses applying the quality of life decrements from mild to moderate disease of 0.075 for Crohn's disease as drawn from Gregor et al. (1997) and of 0.165 as drawn from Poole et al. (2010) are also explored. The utility decrements for IBS are less important for current modelling purposes, given the 100% specificity assumed for colonoscopy meaning that there are no false positives by the end of the test sequence. For the base case, the 0.071 increment for response to treatment estimated within NICE CG61 will be applied. The 0.662 baseline HRQoL that this increment is applied to is taken from Brazier et al. (2004). A sensitivity analysis using the EQ-5D values of Spiegel et al. (2009) are also considered; 0.780 for response to treatment and 0.730 for no response to treatment, but the algorithm used to construct the EQ-5D utilities is not clear. It is noteworthy that the baseline

HRQoL value for IBS will have an impact due to the small mortality rate associated with colonoscopy, with this impact enduring for the 10 year time horizon of the model.

Adverse events associated with colonoscopy

Due to data constraints, the cost impacts have been limited to modelling the cost impacts of the relatively rare (less than 0.5%) serious adverse events of bleeds and perforations. The quality of life impacts are limited to the mortality associated with perforations. While perforations are rare, so resulting in a very low mortality rate, the QALY impact of this persists for the duration of the model.

There is evidence from the literature that colonoscopies result in minor adverse events among a reasonable proportion of patients; e.g. de Jonge et al. (2012) suggest that around 40% of those investigated with colonoscopy have some effects persisting 30 days subsequent to the colonoscopy. In common with the NICE CG118 guideline on screening for colorectal cancer with colonoscopy, these minor adverse events have not been taken into account in the modelling principally due to a lack of quality of life data. The External Assessment Group suggest that the effects of minor and transient colonoscopy side effects seem unlikely to affect the conclusions for the comparisons of no FC testing with FC testing, but they may take on a greater significance in the context of comparing different FC tests or different cut-offs. Depending upon the prevalence of IBD in the presenting population, inclusion of these minor adverse events would increase the importance of tests' sensitivities.

Costs

The costs included in the model are the costs of the different tests, treatment costs (including induction therapy and maintenance therapy costs for those in remission), NHS resource costs (for example, staff time) and costs of adverse events associated with colonoscopy.

The per person costs of an ELISA test and POCT Prevent ID CalDetect are estimated to be £22.79 (based on an assumption of 40 patient samples per 96 well plate, costed at the list price + an average 11-12 minutes of staff time at grade 6/7) and £24.03 (test list price + cost of 15 minutes of GP practice nurse time), respectively.

Colonoscopy was estimated to cost £741.68 per person. This estimate is based on a weighted average of NHS reference cost outpatient and day case (procedures payment by results code FZ51Z/FZ54Z) without biopsy, or

(procedures payment by results code FZ52Z/FZ55Z) with biopsy for colonoscopy or, where used, sigmoidoscopy. Cost includes an outpatient gastroenterology appointment (£164) and costs of adverse events (an average of £12 per colonoscopy).

4.2.3.1. Primary care analysis (IBS vs IBD in adults) – key model characteristics and results

The base case considers the cost effectiveness of GP testing with and without FC in the adult population for distinguishing IBS from IBD.

Patient characteristics

For the primary care adult population, the model adopts a baseline age of 25 years for those presenting with symptoms as drawn from the Crohn's disease CG152 modelling, though the External Assessment Group suggests this may be quite low for IBS patients. In line with the Crohn's disease CG152 modelling, the female proportion is taken to be 50% for both Crohn's disease and ulcerative colitis. IBS appears to have a higher proportion of women presenting, the Brazier et al. (2004) sample being 86% female though the External Assessment Group suggests this estimate may be towards the upper end. The base case adopts a 75% female proportion for IBS. Note that these estimates only affect the all population mortality risks. Since these are low during mid-adulthood for both women and men, the average age and proportion of women model inputs have minimal impact upon the results.

The base case 6.3% (7/111) prevalence of IBD is drawn from the Durham data while the 60% (539/904) prevalence of ulcerative colitis among IBD patients is drawn from Shivananda et al. (1996).

Strategies assessed

The strategies assessed are; 1) GP current practice (clinical assessment with no FC testing), 2) current practice plus the POCT Prevent ID CalDetect using a cut-off of 15µg/g and, 3) current practice plus ELISA testing using a cut-off of 50µg/g. The External Assessment Group has opted to use the lower 15µg/g cut-off of Otten et al. (2008) as the data for the 60µg/g cut-off suggests only a slight gain in terms of a better specificity, 97.8% compared with 94.5%, but significant loss in terms of a worse sensitivity, 60.9% compared with 100.0%. However, it should be noted that the Prevent ID CalDetect test reports 1 of 4 results when the test has run correctly. These are 1) negative – FC not detectable, 2) negative - FC ≤ 15µg/g, 3) positive - FC 15 – 60µg/g and, 4) positive - FC > 60µg/g. Therefore, assessing the test at one cut-off as

described above does not represent a natural interpretation of the test. Test accuracy data used in the model are summarised in table 6.

The delay between referral and colonoscopy is assumed to be 4 weeks and the time to retesting among those testing negative but not responding to IBS therapy is assumed to be 12 weeks, both estimates being based upon expert opinion. This may be optimistic because a sequence of unsuccessful treatments may be pursued for IBS, and so is explored in sensitivity analyses.

The current modelling assumes that all people who test positive or have an indeterminate result (indeterminate results are treated as if the results are determinate) are referred to secondary care and all of these people receive a colonoscopy. Due to a lack of data, the External Assessment Group was not able to incorporate the impact of a gastroenterologist's assessment on the number of people who will go on to receive a colonoscopy (which may also include the use of FC testing). Since FC testing has largely been used, to date, in a secondary care environment the sensitivity and specificity of an ELISA/POC test could be seen as the closest available proxy for this. In addition, the lack of data also means that the External Assessment Group was unable to explore the rates of people with indeterminate test results having a follow up test prior to any referral to colonoscopy.

Table 6 Primary care analysis - base case test accuracy data*

Test	GP current practice	CalDetect	ELISA	Colonoscopy
Cut-off	..	15µg/g	50µg/g	..
Sensitivity	100.0%	100.0% (95% CI: 85 – 100%)	93.0% (95% CI: 85 – 98%)	95.0%
Specificity	79%	94.5% (95% CI: 88 – 98%)	94.0% (95% CI: 76 – 100%)	100.0%
Test accuracy data source	Primary care data from the NTAC pilot	Secondary care data from Otten et al. 2008 (figure 2)	External Assessment Group meta-analysis of secondary care data (figure 3)	Expert opinion

*Confidence intervals, where reported, used in the probabilistic sensitivity analysis are given in brackets

To characterise the uncertainty in the estimates of diagnostic test accuracy of the ELISA test from the meta-analysis (figure 3), the sensitivity and specificity, or rather, the tests' deviation from 100% accuracy, is simulated using the gamma distribution. Over 1,000 iterations resulted in a reasonable approximation of the data, means and 95% confidence intervals, observed in the meta-analysis. It should be borne in mind that these simulations assume

independence between each receiver-operating characteristic (ROC) curve's sensitivity and the specificity.

Base case cost effectiveness results

The results relate to people being tested initially by a GP using current practice, the POCT Prevent ID CalDetect or ELISA testing and then all people with positive (true and false positives) and indeterminate results from each of these initial tests being referred to secondary care and all being assumed to receive colonoscopy.

Without FC testing, GP current practice is highly sensitive in referring people with IBD, and is as good as, if not better than FC testing. Of the 6.3% of people with IBD in the total population, all were identified by GP current practice and when the POCT Prevent ID CalDetect was used. Colonoscopy would correctly identify 6.0% of the 6.3% referred as true positives (due to its 95% sensitivity), resulting in a total of 0.3% false negatives. ELISA testing is slightly worse, identifying 5.9% of the 6.3% (due to its lower sensitivity when compared with current practice and the POCT) with 0.4% being wrongly classified as false negatives. Of the 5.9% referred to colonoscopy, 5.6% are identified as true positive with 0.4% being wrongly classified as false negatives, resulting in a total of 0.7% false negatives. Therefore, a slightly larger number of people will have IBD but will be incorrectly diagnosed as having IBS when using an ELISA testing strategy when compared with current practice strategy and a POCT Prevent ID CalDetect strategy (0.7% vs 0.4%).

Within the total patient population, GP current practice incorrectly identified 19.8% as false positives (people thought to have IBD but actually have IBS) requiring referral to colonoscopy. The rates of false positives incorrectly referred to colonoscopy for the POCT Prevent ID CalDetect and ELISA are much lower, 5.1% and 5.6%, respectively. Therefore, without FC testing, many of the false positives would go on to colonoscopy, which has a low risk of serious complications such as perforation. Such events are too rare to significantly affect costs, but they do have some QALY impact, as might the much more common minor adverse effects of colonoscopy (the latter not explicitly considered in the model due to lack of data).

Given the diagnostic performance of the different testing strategies summarised above, total costs and QALYs are provided in table 7.

Table 7 Primary Care - base case results

Comparators	QALYs	Test costs	Other costs	Total costs
GP current practice (no FC testing)				
Crohn's disease	0.1832	£22	£493	£515
Ulcerative colitis	0.2771	£32	£144	£176
IBS	5.7682	£202	£2,404	£2,606
Total	**6.2285**	£257	£3,041	**£3,297**
POCT Prevent ID CalDetect (15µg/g cut-off)				
Crohn's disease	0.1832	£23	£493	£516
Ulcerative colitis	0.2771	£33	£144	£177
IBS	5.7691	£114	£2,408	£2,522
Total	**6.2293**	£170	£3,044	**£3,214**
ELISA (50µg/g cut-off)				
Crohn's disease	0.1831	£23	£492	£515
Ulcerative colitis	0.2770	£34	£143	£177
IBS	5.7690	£116	£2,407	£2,524
Total	**6.2291**	£173	£3,042	**£3,215**

The different FC tests are estimated to result in similar average cost savings compared with GP current practice: £83 for the POCT Prevent ID CalDetect and £82 for ELISA per patient. This is due mainly to the lower number of referrals and colonoscopies for the false positives. Average QALY gains of around 0.0007 QALYs also accrue, though these are limited since the low prevalence of IBD and the similar high sensitivities of the tests result in relatively few false negatives. Some of the QALY differences accrue from the very slightly lower mortality associated with the lower number of colonoscopies. The POCT Prevent ID CalDetect and ELISA are estimated to

be broadly equivalent with only minor differences between them. Probabilistic modelling results in similar estimates

Sensitivity analyses

A range of sensitivity analyses were conducted to explore the impact of varying the main model parameters. These included varying the prevalence of IBD between 5% - 25% (6.3% used in the base case), changing the source of utility values, adjusting the costs of colonoscopy (no outpatient appointment cost) and removing any associated mortality, varying the number of non-responders to IBS medication and varying the time it takes for false negatives to represent to the clinician (8, 16 and 24 weeks – 12 weeks used in the base case). Scenario analyses were also undertaken using different sources of test accuracy and alternative assumptions surrounding the uptake of FC testing in primary care. Results are presented below.

Varying the prevalence of IBD: suggests that FC testing results in QALY gains and remains cost saving compared with GP current practice up to an IBD prevalence of 25% (6.3% used in base case). At this point, due to ELISA having a less than perfect sensitivity ELISA starts to result in very slight QALY losses compared with the GP current practice, though retains cost savings of around £63 per patient on average. The resulting estimate for the incremental cost effectiveness ratio (ICER) of GP current practice compared with ELISA is £378,000 per QALY gained at IBD prevalence of 25%. Due to its perfect sensitivity, POCT prevent ID CalDetect remains both more effective and cheaper than the GP current practice up to and including an IBD prevalence of 25%.

Primary care uptake of FC: the primary care patient group in whom FC testing is used may be wider than the data set used for the estimation of the sensitivity and specificity of the GP current practice. The base case assumes that FC testing would occur in the 25% of patients that would be referred to secondary care by GPs. Doubling the size of this patient group (to 50%) and allowing for some additional people with IBD within the wider patient group results in a lower IBD prevalence of only 3.3%, and also sensitivity and specificity estimates for GP current practice in this wider patient group of 94% and 90%, respectively (100% and 79% used in the base case, respectively). Despite this improvement in specificity, GP current practice is still estimated to result in higher costs and lower QALYs than both the POCT Prevent ID CalDetect and ELISA testing, though the margin between current practice and FC testing narrows quite significantly.

Different sources of test accuracy: the External Assessment Group explored the use of different estimates of test accuracy from Otten et al. (2008), Basumani et al. (2012) and Hessells et al. (2012).

Otten et al. (2008) - diagnostic accuracy estimates for the POCT Prevent ID CalDetect 60µg/g cut-off (estimates from this study at the 15µg/g cut-off were used in the base case) were modelled by the External Assessment Group.

Table 8 Sensitivity analysis: Primary Care: Otten et al (2008) POCT Prevent ID CalDetect cut-offs

	Test accuracy	**QALYs**	**Costs**	**ICER**
CalDetect 60µg/g	Sensitivity: 60.9% Specificity: 97.8%	6.2281	£3,187	
CalDetect 15µg/g	Sensitivity: 100% Specificity: 94.5%	6.2293	£3,214	£22,500 (CalDetect 15µg/g vs. CalDetect 60µg/g)

The slightly better specificity of the 60µg/g cut-off results in slight cost savings of £27 compared with the 15µg/g cut-off, but gains of 0.0012 QALYs are anticipated from the 15µg/g cut-off. This suggests an incremental cost effectiveness ratio of £22,500 per QALY gained for the 15µg/g cut-off (GP current practice and ELISA testing are dominated). It should be noted that the External Assessment Group suggests it is doubtful that the low sensitivity of the 60µg/g cut-off (61%) would be acceptable in practice. Note also the ICER is almost exactly inversely proportionate to the prevalence of IBD in the presenting population; that is, if the prevalence of IBD doubles, the ICER halves.

Basumani et al. (2012) –

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	

[redacted]

Hessels et al. (2012) – the External Assessment Group produced alternative estimates of cost effectiveness for the POCT Prevent ID CalDetect and estimates of cost effectiveness for a rapid quantitative test not assessed in the base case, Quantum Blue LF-CAL25, using diagnostic accuracy data from this study. However, this study did not meet the inclusion criteria for the systematic review as the study sample comprised a mixture of patients with suspected or relapse of IBD. Therefore, these analyses are not considered further here.

Univariate sensitivity analyses: suggest that the primary care base case results are reasonably robust. The main sensitivity of the results of the POCT Prevent ID CalDetect compared with ELISA arises from changing the source of utilities and shortening the time spent as false negatives. These both tend to reduce the importance of false negatives and so reduce the importance of tests' relative sensitivities. This reduces the estimated net QALY gain from the POCT Prevent ID CalDetect over ELISA, but it should be stressed that the QALY differences between the FC tests are very small.

4.2.3.2. Secondary care (IBD vs. non-IBD in children) – key model characteristics and results

The base case considers the cost effectiveness of FC testing prior to colonoscopy compared with direct referral for colonoscopy in the secondary care paediatric population for distinguishing IBD from non-IBD.

Patient characteristics

For the secondary care paediatric population, female proportions of 38% (35/91) for IBD patients and 44% (44/99) for non-IBD patients are drawn from Henderson et al. (2012). An average age of 16 years is assumed, as for the adult modelling this has minimal impact upon results.

The base case 48% (91/190) prevalence of IBD and the 75% (62/83) prevalence of Crohn's disease among IBD patients are drawn from Henderson et al (2012).

Strategies assessed

The strategies assessed are 1) direct referral to colonoscopy, 2) ELISA testing when used at the 50µg/g cut-off followed by colonoscopy and, 3) ELISA testing when used at the 100µg/g cut-off followed by colonoscopy. Test accuracy data used in the model are summarised in table 10.

Table 10 Secondary care scenario - base case test accuracy data *

Test	**ELISA**	**ELISA**	**Colonoscopy**
Cut-off	50µg/g	100µg/g	..
Sensitivity	99.0% (95% CI: 95 – 100%)	94.0% (95% CI: 87 – 99%)	95.0%
Specificity	74.0% (95% CI: 59 – 85%)	82.0% (95% CI: 68 – 92%)	100.0%
Test accuracy data source	External Assessment Group meta-analysis of secondary care data	External Assessment Group meta-analysis of secondary care data	Expert opinion

	(figure 6)	(figure 7)	

*Confidence intervals, where reported, used in the probabilistic sensitivity analysis are given in brackets

To characterise the uncertainty in the estimates of diagnostic test accuracy from the meta-analyses, the sensitivity and specificity, or rather their deviation from 100% accuracy, is simulated using the gamma distribution. Over 1,000 iterations resulted in a reasonable approximation of the data, means and 95% confidence intervals, observed in the meta-analyses (figures 6 and 7). It should be borne in mind that these simulations assume independence between each ROC curve's sensitivity and specificity.

Base case cost effectiveness results

The results relate to children who have been referred to secondary care and either undergo colonoscopy or receive an FC test prior to colonoscopy.

The base case prevalence of IBD of 47.9% increases the importance of test sensitivities compared with the primary care setting, and so the effect of false negatives on the modelling outputs. Within the total patient population, ELISA with the 50µg/g cut-off refers 47.4% as true positives for colonoscopy, while ELISA with the 100µg/g cut-off refers 45.0% as true positives for colonoscopy. Colonoscopy is assumed to have a sensitivity of 95%, so the end diagnosis if all (47.9%) are referred immediately to colonoscopy is 45.5% being diagnosed with IBD. For those referred to colonoscopy by ELISA with the 50µg/g cut-off 45.0% are diagnosed as having IBD, while for those referred to colonoscopy by ELISA with the 100µg/g cut-off 42.8% are diagnosed as having IBD; a net difference between the cut-offs of 2.2%.

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

Given the diagnostic performance of the different testing strategies summarised above, total costs and QALYs are provided in table 11.

Table 11 Secondary Care: Base case results

Comparators	**QALYs**	**Tests**	**Other**	**Total**
Direct referral to colonoscopy				
Crohn's disease	2.5773	£244	£6,938	£7,183
Ulcerative colitis	0.8942	£83	£463	£546
Non-IBD	3.2094	£338	£629	£967
Total	**6.6809**	£665	£8,031	**£8,696**
ELISA 50µg/g prior to colonoscopy				
Crohn's disease	2.5767	£254	£6,934	£7,188
Ulcerative colitis	0.8941	£86	£463	£549
Non-IBD	3.2117	£120	£634	£754
Total	**6.6824**	£460	£8,031	**£8,491**
ELISA 100µg/g prior to colonoscopy				
Crohn's disease	2.5757	£256	£6,921	£7,177
Ulcerative colitis	0.8938	£87	£462	£549
Non-IBD	3.2119	£95	£634	£729
Total	**6.6814**	£438	£8,018	**£8,456**

Prior testing with ELISA testing is estimated to be cost saving when compared with the strategy of sending all patients directly for a colonoscopy. The additional ELISA test costs are more than offset by the savings from reduced colonoscopies. Compared to referring all directly to colonoscopy, ELISA used at the 50µg/g cut-off is estimated to save £205 per patient, while ELISA used at the 100µg/g cut-off is estimated to save £240 per patient. QALY gains of around 0.001 QALYs are estimated for ELISA compared with direct referral to colonoscopy, these being slightly larger for ELISA with the 50µg/g cut-off due to its better sensitivity. But given the additional average £35 cost, the ICER for ELISA with the 50µg/g cut-off compared with ELISA with the 100µg/g cut-off is £35,000 per QALY gained. Probabilistic modelling results in similar estimates.

Sensitivity analyses

A range of sensitivity analyses were conducted to explore the impact of varying the main model parameters. These included varying the prevalence of IBD to 40% and 60% (48%% used in the base case), changing the source of utility values, removing any associated mortality of colonoscopy, varying the time it takes for false negatives to represent to the clinician (8, 16 and 24 weeks; 12 weeks used in the base case) and the annualised net cost of false negatives to £376 (£188 used in the base case). Results are presented below (table12).

Table 12 Secondary care: Univariate sensitivity analyses

	QALYs					Costs				
	Colon. S1	50µg S2	100µg S3	net S2 - S1	net S2 - S3	Colon. S1	50µg S2	100µg S3	net S2 - S1	net S2 - S3
Base case	6.6809	6.6824	6.6814	0.0015	0.0010	£8,696	£8,491	£8,456	-£205	£35.21
40% IBD prev.	6.5950	6.5970	6.5962	0.0020	0.0008	£7,569	£7,330	£7,292	-£239	£37.11
60% IBD prev.	6.8127	6.8135	6.8121	0.0008	0.0014	£10,425	£10,271	£10,239	-£154	£32.28
8 week represent	6.6828	6.6845	6.6839	0.0017	0.0006	£8,707	£8,493	£8,463	-£214	£30.34
16 week represent	6.6789	6.6805	6.6789	0.0015	0.0016	£8,689	£8,479	£8,442	-£209	£37.18
Utilities non-Stark	7.2055	7.2069	7.2066	0.0014	0.0003	£8,696	£8,491	£8,456	-£205	£35.21
No colon. mort.	6.6815	6.6829	6.6818	0.0013	0.0011	£8,697	£8,492	£8,456	-£205	£35.21

As for primary care, most of the changes appear to broadly affect the three comparators in a like manner. The main difference arises from varying the prevalence of IBD, which tends to reduce the cost savings from FC testing as the prevalence rises, as would be anticipated. The source of utilities also has an impact upon the anticipated net gain from ELISA with the 50µg/g cut-off compared with ELISA with the 100µg/g cut-off, the ICER for which worsens to £117, 000 per QALY gained. However, the External Assessment Group beleives this may be to overstate the effect given the prevalence of Crohn's disease within the presenting population and the perhaps rather small quality of life decrement sourced from Gregor et al. (1997).

5. Evidence summary and the External Assessment Group's principal findings

5.1. Evidence summary for each test included in the scope (table 13)

Note that to be included in meta-analyses, studies had to provide sufficient data for a 2 x 2 table. Some of the studies listed below did not. In some studies, tests used could have more than one range, but little detail was given of which was used. Levels observed in the studies were sometimes used to deduce the range used.

The cost effectiveness comparison for primary care relies upon the results of Otten (2008) for CalDetect and the meta-analysis of figure 3 for ELISA.

The cost effectiveness comparison for secondary care relies upon the meta-analysis of figures 6 and 7 for ELISA.

The economic analysis also includes additional sensitivity analyses around the cut-offs for:

- CalDetect with these relying upon the results of Otten et al. (2008)
- CalDetect with these relying upon the results of Hessells et al. (2012)
- Quantum Blue with these relying upon the results of Hessells et al. (2012)
- ELISA with these relying upon the data of Basumani et al. (2012)

Table 13 Evidence summary of tests included in the scope

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?	Were studies of the test identified in the systematic review?	Included in the cost effectiveness analysis?
Buhlmann	EK-CAL calprotectin ELISA test *Referred to as the 'EK-CAL' test in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: 10-600µg/g	Yes	**Studies included in meta-analysis:** • Burri 2013; • Kok 2012 • Manz 2012 **Studies comparing FC tests:** • Burri 2013; • Kok 2012 (range 10 to 600µg/g) • Labaere 2013 (meeting abstract only- just says Buhlmann ELISA. This study compared 4 ELISAs, 3 POCTs and an automated immunoassay from Phadia); • Loitsch 2010 (meeting abstract gives little detail. Referred to as Calp-Bu manufactured by Buehlmann Laboratories, Switzerland) • Tomkins 2012 (meeting abstract just says Bulhmann EK-CAL)	No.
Buhlmann	EK-CAL calprotectin ELISA test *Referred to as the 'EK-CAL' test in table 2 of the diagnostics*	ELISA – quantitative Range: 30-1800µg/g	Yes	**Studies included in meta-analysis:** Damms 2008 **Studies comparing FC tests:** • Damms 2008 • Kolho 2012 [paper just says ELISA test; it is presumably EK-CAL as the test kit was provided by Bulhmann. Test range	The economic analysis for secondary care relies upon the data relating to the ELISA 50µg/g and 100 µg/g cut-offs of figures 6 and 7, encompassing Damms 2008

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?	Were studies of the test identified in the systematic review?	Included in the cost effectiveness analysis?
	assessment report			not stated but highest level reported was 1656] • Coorevits 2012	
Buhlmann	LF-CAL25 Quantum Blue calprotectin test *Referred to as the 'Quantum Blue' test in table 2 of the diagnostics assessment report*	Rapid test - Immunoassay designed for the quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. For laboratory use only. Range: 30-300µg/g	Yes	**Studies included in meta-analysis:** • Kok 2012 **Studies comparing FC tests:** • Kok 2012 • Kolho 2012 [paper says the dynamic range of the test is 30-300 µg/g but in the results, the FC ranges up to 1800 µg/g] • Wassell 2012 • Dolci 2012 • Coorevits 2012 (based on the ELISA result, both types of POCT reader i.e. 30-300 and 100-1800 µg/g were used); • Hessels 2012 • Sydora 2012 (from figure 2 it appears the reader used was 30-300 µg/g. Not clear which type of ELISA test was used. Paper says standard calprotectin ELISA – both QB and ELISA provided by Alpco Immunoassays Salem, NH); • Labaere 2013 (just says Quantum Blue)	Sensitivity analyses around the Quantum Blue cut-offs are conducted using the data of Hessells 2012 (study was excluded from the systematic review of clinical effectiveness)
Buhlmann	LF-CHR 25 Quantum Blue calprotectin test	Rapid test - Immunoassay designed for the	Yes	**Studies included in meta-analysis:** • none	No.

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?	Were studies of the test identified in the systematic review?	Included in the cost effectiveness analysis?
	Referred to as the 'Quantum Blue' test in table 2 of the diagnostics assessment report	quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. For laboratory use only. Range: 100 - 1800µg/g		**Studies comparing FC tests:** • Coorevits 2012 (based on the ELISA result, both types of POCT reader i.e. 30-300 and 100-1800 µg/g were used)	
Calpro	CALPRO CALPROTECTIN ELISA TEST (ALP) – formerly known as the Phical test CAL0100 *Referred to as the 'CALPRO Calprotectin ELISA test (ALP)' in table 2 of the diagnostics assessment report* *Table 2 of the diagnostics assessment*	ELISA – quantitative Range: up to 1250 mg/kg	Yes	**Studies included in meta-analysis:** In the following studies, no details on ranges given so can't say whether the test measures up to 1250 mg/kg or up to 2500 mg/kg • Van de Vijver 2012 (the paper says Phical CALPRO ALP, but not whether CAL0100 or the CALP0170. Other studies used in meta-analysis just reporting Phical: • Ashorn 2009; • Bharathi 2005; • El-Badry 2010; • Otten 2008; • Schoepfer 2008; • Turvill 2012 **Studies comparing FC tests:** • Otten 2008 (Phical);	The economic analysis for primary care relies upon the data relating to the ELISA 50µg/g cut-off of figure 3, encompassing that of El-Badry 2010, Otten 2008 and Schoepfer 2008 The economic analysis for secondary care relies upon the data relating to the ELISA 50µg/g and 100 µg/g cut-offs of figures 6 and 7, encompassing Van de Vijver 2012.

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?	Were studies of the test identified in the systematic review?	Included in the cost effectiveness analysis?
	report also refers to the 'Phical ELISA kit' test which is believed to be the same test as the 'CALPRO Calprotectin ELISA test (ALP)'. Therefore, studies of the 'Phical ELISA kit' test are also summarised here			• Wassell 2012 (not clear whether it is CAL0100 or CALP0170); • Vastegaard 2008 (measure up to 1250 mg/kg); • Labaere 2013 (just says Calpro)	
Calpro	CALPROLAB CALPROTECTIN ELISA (ALP) – formerly known as the Phical test CALP0170 *Referred to as the 'CALPRO Calprotectin ELISA test (ALP)' in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: up to 2500 mg/kg	Yes	**Studies included in meta-analysis:** • Burri 2013; • Henderson 2012 (local assay range is 20 to 2500 mg/g); • Li 2006 (based on the maximum level of FC measured being 2574 mg/kg) • Limburg 2000 (overall FC level ranged from 4 to 6781 mg/g of stool); • Sidler 2008 (in the IBD group, FC ranged from 52 to 12000 mg/kg) **Studies comparing FC tests:** • Burri 2013; • Labaere 2013 (just says Calprolab)	The economic analysis for primary care relies upon the data relating to the ELISA 50µg/g cut-off of figure 3, encompassing Li 2006 The economic analysis for secondary care relies upon the data relating to the ELISA 50µg/g and 100 µg/g cut-offs of figures 6 and 7, encompassing Sidler

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?	Were studies of the test identified in the systematic review?	Included in the cost effectiveness analysis?
					2008, Henderson 2012 and Limburg 2000.
Eurospital	Calprest *Referred to as the 'Calprest' test in table 2 of the diagnostics assessment report*	ELISA – quantitative	Yes	**Studies included in meta-analysis:** • Canani 2006; • Carroccio 2003; • Diamanti 2010; • Fagerberg 2005; • Garcia 2006; • Licata 2012; • Shitrit 2007; • Tomas 2007 **Studies comparing FC tests:** • Dolci 2012; • Labaere 2013 (just says Eurospital)	The economic analysis for secondary care relies upon the data relating to the ELISA 50µg/g and 100 µg/g cut-offs of figures 6 and 7, encompassing Tomas 2007, Fagerberg 2005 and Diamanti 2010
Eurospital	CalFast *This test is not referred to in table 2 of the diagnostics assessment report*	Rapid test - Quantitative determination of FC in combination with a dedicated reader	Yes	**Studies included in meta-analysis:** • No studies **Studies comparing FC tests:** • Labaere 2013 (says Eurospital Calfast)	No.
Immundiagnostik	ELISA (K6927) *Referred to as the 'PhiCal Calprotectin*	ELISA – quantitative	Yes	**Studies included in meta-analysis:** • [redacted]Schroder 2007 (the maximum FC measured was up to 2553 µg/g)	The economic analysis for primary care relies upon the data relating to the ELISA 50µg/g cut-off of figure 3,

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?	Were studies of the test identified in the systematic review?	Included in the cost effectiveness analysis?
	ELISA kit' in table 2 of the diagnostics assessment report			Neither study reports which type of Immundiagnostik ELISA test was used: K6927 or K6937 or K9697 **Studies comparing FC tests:** • Shastri 2009 (poster gives no details) • Loitsch 2010 (meeting abstract says only " manufactured by Immundiagnostics Bensheim, Germany") • Tomkins 2012 (meeting abstract says only FC measured by Immundiagnostik Phical version 1)	encompassing that of [redacted]
Immundiagnostik	ELISA (K6937)	ELISA – quantitative	No – superseded.	Probably not, but see Schroder study above.	
Immundiagnostik	ELISA (K6967)	ELISA – quantitative	No - variant of K6927		
Thermo Fisher Scientific	EliA Calprotectin *Referred to as the 'EliA platform)' in table 2 of the diagnostics assessment report*	EliA – quantitative In contrast to ELISA, EliA measures the presence of target antibodies by fluorescence signal detection.	Yes	**Studies included in meta-analysis:** • No studies **Studies comparing FC tests:** • Labaere 2013 (mentioned as an automated immunoassay from Phadia)	No
Preventis (sister company to Immundiagnostik)	KST11005 CalDetect Calprotectin Rapid test	POCT – immunochromatographic rapid test. A semi-quantitative	Yes, IBD versus non-IBD (Otten 2008)	**Studies included in meta-analysis:** • [redacted] Otten 2008	The economic analysis for primary care relies upon the data relating to the CalDetect 15µg/g cut-

Manufacturer	Test	Platform	Included in the External Assessment Group assessment?	Were studies of the test identified in the systematic review?	Included in the cost effectiveness analysis?
	(version 1 - Caldetect) *Referred to as the 'Prevent ID Caldetect' test in table 2 of the diagnostics assessment report*	test with 3 lines corresponding to: Calprotectin "negative", Calprotectin ≤ 15 µg/g, Calprotectin 15-60 µg/g and Calprotectin > 60 µg/g stool	[redacted]	**Studies comparing FC tests:** • Otten 2008 • Hessels 2012; • Vastegaard 2008; • Shastri 2009	off as drawn from Otten 2008. Additional sensitivity analyses are conducted for CalDetect cut-off based upon the data of Otten 2008 and upon the data of Hessells 2012 (excluded from the systematic review of clinical effectiveness)
Preventis (sister company to Immundiagnostik)	CalDetect Calprotectin Rapid test (version 3 – CalScreen) *This test is not referred to in table 2 of the diagnostics assessment report*	POCT – immunochromatographic rapid test. A yes-no test with only 1 Test-Line corresponding to the cut-off value of 50 µg/g stool (no inflammation = <50 µg/g and inflammation present = ≥50 µg/g)	Yes	**Studies included in meta-analysis:** • No studies **Studies comparing FC tests:** • No studies	No.

Table 2 of the diagnostics assessment report also refers to the 'Prevista' POCT. Data was noted on the Prevista test but this test was not identified for inclusion in the scope for the assessment and, subsequently to compiling the assessment report, the External Assessment Group believes this test is not available to the NHS in England and may be out of production. Therefore, the Prevista POCT will not be the subject of NICE guidance.

5.2. External Assessment Group's key findings

- In adults, FC is a good indicator of inflammation in the bowel and can be used to distinguish between IBS and IBD in cases where the differential diagnosis is in doubt.

- FC could be very useful for GPs as a way of confirming a diagnosis based on clinical assessment of IBS, though it will not be required in all people with IBS, because in some, other features such as a long history, co-morbidities, relationship to stress and an absence of weight loss, may tilt the balance of probability to IBS.

- It is not a perfect test because some patients with IBS have raised FC levels, but false negative IBD is unusual if the cut-off of 50µg/g (for ELISA tests) and 15µg/g (for the POCT Prevent ID CalDetect) recommended by the manufacturers is used.

- In children, FC is useful for distinguishing between IBD and non-inflammatory conditions.

- The balance of risk between sensitivity (not missing any cases of IBD) and specificity (avoiding false positives - people with IBS thought to have IBD) may best be towards sensitivity because missed IBD can lead to much more serious consequences than an unnecessary colonoscopy.

- There are a few people who have slightly raised FC levels (50µg/g to 150µg/g, or perhaps to 200µg/g in children) who may only need monitoring. In many cases, FC level will fall and no further investigation will be necessary. In those who have low-grade IBD, FC will usually rise.

- There are few head to head comparisons of different FC tests, but such data as there are, do not suggest significant differences in clinical reliability between tests.

- There are no published studies in patients drawn only from primary care.

- If FC testing is made available in primary care, GPs will be able to be much more selective in whom they refer to specialist care. Referrals are likely to fall considerably.

- In secondary care, both paediatric and adult, the availability of FC testing is likely to lead to a reduction in the number of colonoscopies performed.

- It is likely that delays in diagnosing IBD will be reduced since a raised FC level will alert clinicians to patients needing to be put on the IBD management pathway. This may be particularly useful in children where the onset of IBD can be insidious, as it can also be in some adults.

- FC testing appears to lead to cost savings, mainly in secondary care from a reduction in colonoscopies.

5.3. Questions included in the scope with External Assessment Group responses

- *Is FC testing a reliable way of differentiating inflammatory disease of the bowel from non-inflammatory ones?*

  Yes. FC testing identifies patients with inflammation of the bowel, who need referral to specialist care. 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 FC test means that IBD is very unlikely. They can then 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 – 50µg/g. This is based on ensuring high sensitivity, and not missing people with IBD. Some people assessed as positive by this cut-off will have borderline levels of 50 to 200µg/g, and may initially be monitored with repeat FC testing, but some of this group will progress to definite IBD.

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

  There are few studies directly comparing tests, and on clinical effectiveness grounds, there is insufficient evidence to recommend one test over the others. The point of care tests can provide faster results. Costs vary amongst tests. None of the test kits are expensive but labour costs vary. The evidence base varies amongst tests. There are currently no grounds on either diagnostic reliability or cost-effectiveness considerations for preferring one test over another.

- *How will FC testing perform in primary care?*

  Sensitivity and specificity will be as good in primary care, but the lower prevalence will increase the negative predictive value. The main benefit in primary care will be to confirm the clinical diagnosis by GPs of IBS. Making FC testing available to general practitioners will greatly reduce the number of younger adults referred to specialist care, and the need for invasive investigations such as colonoscopy.

- *Impact in secondary care*

  In secondary care, the main benefit will be a marked reduction in colonoscopies that find no abnormalities. FC testing will considerably reduce the number of colonoscopies required. In various studies, over 60% of colonoscopies in this group of adult patients have been normal

  FC testing will lead to considerable savings to the NHS, as well as the avoidance of an unpleasant invasive procedure in people whose symptoms are due to IBS.

  FC 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.

6. Issues for consideration

The following section summarises some of the key questions (in bold) and associated notes (taken from the information in previous sections) for the Committee's consideration.

1. Is the evidence from the systematic review of clinical effectiveness applicable to the decision problem identified in the scope?

Decision-problem
The decision-problem for this evaluation concerns the use of FC testing to help distinguish between inflammatory and non-inflammatory conditions of the bowel. The External Assessment Group has presented evidence on the ability of FC tests to distinguish between two conditions in four sets of comparisons:

1. Organic vs. non-organic disease

2. IBS vs. IBD (most appropriate comparison for adults)

3. Organic vs. IBS

4. IBD vs. non-IBD (most appropriate comparison for paediatrics)

Comparison 1, organic vs. non-organic is the closest comparison to the decision-problem set out in the scope. However, the External Assessment Group asserts that in practice the most important distinction is between IBS vs. IBD (comparison 2) in the adult population and IBD vs non-IBD (comparison 4 – as IBS is much less common than in the adult population) in the paediatric population. Comparison 3, organic vs. IBS, is another way of distinguishing between conditions as in adult medicine there are organic causes other than IBD that can cause symptoms. The modelling exercise also focuses on the cost-effectiveness of FC testing in comparisons 2 and 4. It is possible that although the use of FC testing is most relevant for helping to distinguish between inflammatory and non-inflammatory conditions of the bowel, the number of conditions involved may place a prohibitively large burden on the data requirements for a cost effectiveness analysis. Therefore, comparisons 2 and 4 may represent a reasonable proxy for the likely clinical use of FC testing, balanced against the demands of the economic analysis.

Spectrum of data
Most of the evidence for FC testing comes from secondary care. In the primary care economic analysis: limited data from the NTAC pilot project of FC testing in 111 people in primary care informed the estimates of diagnostic accuracy for GP current practice. However, diagnostic accuracy estimates for both FC tests (Prevent ID CalDetect and ELISA) are taken from secondary care data. Given the likely differences in the case-mix between the two environments, the data are at risk of spectrum bias such that the diagnostic accuracy estimates for FC testing are likely to be different in primary care.

It is not clear if there are studies that compare the performance of FC tests when used in secondary care vs. primary care in section 2.10 of the diagnostics assessment report (given the limited data in primary care the likelihood of such a comparison is low or, if available, may be based on relatively small sample sizes). Some limited primary care data were identified in the review of FC testing for distinguishing between organic and non-organic disease. In the secondary care adult data, sensitivities ranged from 43% - 89% and specificities ranged from 79% - 98% using a 50µg/g cut-off. A study of a ELISA test and a rapid quantitative test in a primary care adult population reported a sensitivity of 74% and 64%, and a specificity of 47% and 53% at a cut-off of 50µg/g, respectively. The role of FC testing for distinguishing organic from non-organic disease was not assessed in the economic analysis. The estimates above suggest that secondary care data may overestimate the performance of an FC test when used in primary care.

2. What are the general limitations of the economic analysis performed by the External Assessment Group?

Limitations in the data have meant that the model does not account for or explore the way in which people with indeterminate results would be followed up before receiving a colonoscopy. The base case assumes all people with test positive and indeterminate FC results are referred to secondary care and undergo colonoscopy. In reality, it is likely that those people with indeterminate test results will likely be retested with an FC test before undergoing an endoscopy.

It is assumed that all patients referred to secondary care will receive a colonoscopy such that a gastroenterologist's current practice is not accounted for; this is likely to reduce the number of patients that receive colonoscopy under current practice. This limitation also impacts the FC testing strategies as it is assumed that all patients will receive an FC test and the test result will determine which patients go on to receive colonoscopy. However, decisions will not be made purely on FC results but on a range of information. Therefore, this limitation may lead to an overestimate of the benefit of FC testing in reducing the number of colonoscopies if a clinician's current practice impacts FC testing strategies differentially to current practice assumed in the model.

Although the External Assessment Group suggests that FC testing has been assessed in addition to current practice (consistent with its anticipated use) in the primary care analysis, the model utilises the diagnostic accuracy estimates from studies in a secondary care population of FC. Such studies are likely to evaluate the performance of FC testing alone for differentiating IBS from IBD and, therefore, it is not clear if the primary care analysis is actually of FC testing when added to current practice. In addition, the Durham Dale implementation project demonstrated that 9 of the 43 people referred to secondary care had been referred even though they had a low FC test result. This is consistent with the understanding that GP decision-making will incorporate both FC test results and current practice such that some people with low levels of FC may still be referred for specialist investigation. It is not clear if and how this has been accounted for in the External Assessment Group analysis.

It should be noted that despite the limitations in the economic model the results of the External Assessment Group's economic analysis yields similar results to previously conducted economic analyses identified in the systematic review (section 4.2.1).

3. Is FC testing able to cost effectively distinguish between inflammatory and non-inflammatory conditions of the bowel in primary care?

The population of interest is individuals aged up to 60 years presenting to their GP with any of the following lower gastrointestinal symptoms for at least 6 weeks - abdominal pain or discomfort, bloating or change in bowel habit.

The External Assessment Group's cost effectiveness model is primarily designed to address the role of FC testing in symptomatic adult patients (as defined above) in primary care for distinguishing between IBD and IBS. The base case analysis evaluates ELISA testing using a 50µg/g cut-off, a POCT Prevent ID CalDetect at a 15µg/g cut-off and GP current practice. Both FC tests are assessed when added to current practice. Both were found to be cost saving when compared with GP current practice and generated similar per patient QALYs and costs. Cost savings are driven by the reduction in secondary care referrals and, therefore, colonoscopies.

- Five studies (four on the Phical test (Calpro [ALP]) and one on the Immunodiagnostik test) reported data for FC testing in **secondary care** with ELISA when a cut-off of 50µg/g was applied. These studies were meta-analysed and the results used to inform the base case (sensitivity 93% and specificity 94%). The meta-analysis estimates are informed by a pool of 596 people of which 40% are from the Li et al. (2006) study.

- The only study using a POCT was Otten et al. (2008) study which assessed the Prevent ID CalDetect test in **secondary care** in a sample of 114 people. This study was used to inform the base case analysis (sensitivity 100% and specificity 94.5%).

- GP current practice was informed by the NTAC pilot project in **primary care**. Implementation projects for FC testing in two North East Clinical Commissioning Groups within Northumberland and Durham Dales during 2011/12 were undertaken by NTAC. Data from the Durham Dales project of 111 people was used to inform GP current practice in the base case analysis (sensitivity 100% and specificity 79%). The diagnosis and management pathway used in Durham Dales suggests that erythrocyte sedimentation rate and C-reactive protein blood tests, suggested initial laboratory tests in the BSG guidelines for IBS and IBD, may or may not be used be used for distinguishing IBS from IBD depending on individual physician preferences. Erythrocyte sedimentation rate and C-reactive protein may be used to exclude

other diagnoses. Therefore, GP current practice may be based on clinical assessment without testing for these inflammatory markers. However, it is noteworthy that the economic analysis conducted by YHEC for the Centre for Evidence-based Purchasing report (2010) showed that the use of FC compared with erythrocyte sedimentation rate plus C-reactive protein resulted in an additional 63 correctly diagnosed IBS cases and an additional 55 correctly diagnosed IBD cases, at a cost saving of £13.50 per patient.

- Expert input suggests that the Durham Dale data is likely to represent the best-case scenario of GP current practice and, therefore, FC testing may have an even greater benefit in primary care than suggested by the results of the analysis.

Sensitivity and scenario analyses suggest that the primary care base case results are reasonably robust. At a relatively high prevalence of IBD in the population (25% - 6.3% used in the base case as taken from the NTAC project) ELISA testing results in an incremental cost effectiveness ratio of £378,000 per QALY gained when compared with GP current practice.

Expert input suggests that, contrary to the results of the analysis, other pilot projects of FC testing in primary care in England have led to increased numbers of referrals to secondary care. Therefore, the crafting and implementation of any potential recommendations requires consideration.

3a. Which cut-off value is most consistent with the aim of FC/diagnostic testing in primary care and is this a cost effective use of NHS resources?

Generally, the most common cut-off for defining normality was 50µg/g, as recommended by manufacturers, and as used in the 2010 YHEC report. Some adults with IBS have raised FC levels and would be false positives, who might be referred for colonoscopy as people with IBD. However there is some evidence that organic pathology is rare with FC levels under 100µg/g, and clinical consensus is that if there are people with IBD but FC levels under 200µg/g, they are likely to have low grade IBD and would come to no harm if simply monitored by repeated FC tests, with referral into secondary care if the level rose.

Expert input indicates that the main application of FC testing in primary care, given the analysis performed by the External Assessment Group, is to confirm a diagnosis of IBS. Therefore, the focus of FC testing/the diagnostic pathway in primary care is to maximise specificity (or negative predictive value) in patients presenting with lower abdominal symptoms. Scenario analyses using

estimates of FC testing performance at different cut-offs or alternative sources of these estimates are summarised below.

POCT – Prevent ID CalDetect

The Prevent ID CalDetect test reports 1 of 4 results when the test has run correctly. These are 1) negative – FC not detectable, 2) negative - FC ≤ 15µg/g, 3) positive - FC 15 – 60µg/g and, 4) positive - FC > 60µg/g. Therefore, assessing the test at one cut-off does not represent a natural interpretation of the test. Scenario analysis was used to assess the cost effectiveness of the Prevent ID CalDetect at the 60 µg/g cut-off using data from Otten et al. (2008). Test accuracy estimates at a 15 µg/g cut off from Otten et al. (2008) were used in the base case.

- The slightly better specificity of the 60µg/g cut-off results in slight cost savings of £27 compared with the 15µg/g cut-off, but gains of 0.0012 QALYs are anticipated from the 15µg/g cut-off. This suggests an ICER of £22,500 per QALY gained for the 15µg/g cut-off. It should be noted that the External Assessment Group suggests it is doubtful that the low sensitivity estimates of the 60µg/g cut-off (61%) would be acceptable in practice. Note also the ICER is almost exactly inversely proportionate to the prevalence of IBD in the presenting population; that is, if the prevalence of IBD doubles, the ICER halves.

ELISA testing

Basumani et al. (2012),

[redacted]

Hessels et al. (2012)

The External Assessment Group produced alternative estimates of cost effectiveness for the POCT Prevent ID CalDetect and a rapid quantitative test not assessed in the base case, Quantum Blue, using diagnostic accuracy data from this study. However, this study did not meet the inclusion criteria for the systematic review as the study sample comprised a mixture of patients with suspected or relapse of IBD. Therefore, these analyses are not considered in the overview.

3b. If FC testing, at an appropriate cut-off value, is a cost effective use of NHS resources in primary care, to which population should any potential recommendations apply?

The population of interest is individuals aged up to 60 years presenting to their GP with any of the following lower gastrointestinal symptoms for at least 6 weeks - abdominal pain or discomfort, bloating or change in bowel habit. The External Assessment Group's cost effectiveness model addresses the role of FC testing in symptomatic adult patients in primary care for distinguishing between IBD and IBS.

Expert input suggests that FC testing may be inappropriate for people at the upper end of the adult age limit as there is a risk that GPs may start to make a diagnosis of IBS in patients over 50 with persistent diarrhoea or other symptoms suggestive of bowel cancer, because they are falsely re-assured by the negative FC test result. Such patients should be referred for specialist investigation.

Patient age

The results of five studies were meta-analysed into overall estimates of specificity and sensitivity for ELISA tests when used at a 50µg/g cut-off and used in the base case. The mean age of patients in these studies, where reported, ranged from 40 – 52 in IBS patients and 34 – 45 in IBD patients. Although, the age of patients in the Schoepfer et al. (2008) study went as high as 78 years.

The average age of people in the Otten et al. (2008) study, used to inform the diagnostic accuracy estimates for the POCT Caldetect, is 52 in IBS patients and 45 in IBD patients.

The mean age of people in the Basumani et al. (2012) study, [redacted]

3c. How specific/broad should any potential recommendations for primary care be?

The External Assessment Group suggests the clinical effectiveness evidence indicates that FC testing in general can be used to distinguish between IBS and IBD and is likely to be cost saving.

In total, 12 tests were included in the assessment conducted by the External Assessment Group. Accounting for multiple entries of different versions of the same test, there are 4 manufacturers of different ELISA tests, 2 manufacturers of rapid tests, 1 manufacturer of the EliA test and 1 manufacturer of the POCTs. However, not all of the tests informed the diagnostic accuracy estimates used in the primary care economic analysis.

The 5 studies that informed the meta-analysis of diagnostic accuracy of ELISA testing in the base case analysis assessed the performance of the Phical test ((Calpro [ALP]) - 4 studies) and the Immunodiagnostik test (1 study). One study on the POCT Prevent ID CalDetect, when used at 2 different cut-offs, informed the base case and sensitivity analysis.

The External Assessment Group, manufacturers and clinicians (during scoping) suggest that FC tests are likely to perform similarly such that clinical outcomes are not significantly affected. However, there are limited data that suggest ELISA tests may lead to different diagnostic accuracies (section 2.10 of the diagnostics assessment report). Careful consideration is required as to how far the results of the economic analysis, informed by accuracy data from specific ELISA and POC tests, can be extrapolated to other tests. For example, are the results of the economic analysis applicable to the POCT Calscreen for which no studies were identified in the systematic review of clinical effectiveness, but, the test operates at a pre-defined cut-off of 50µg/g?

If the evidence is found to be satisfactory by the Committee then a recommendation for FC testing in general, as oppose to particular tests, could be considered.

4. **Is FC testing able to cost effectively distinguish between inflammatory and non-inflammatory conditions of the bowel in secondary care?**

The population of interest is individuals aged up to 60 years presenting with any of the following lower gastrointestinal symptoms - abdominal pain or discomfort, bloating or change in bowel habit that have been referred for assessment.

The model used for the primary care analysis has been adjusted to assess the cost effectiveness of FC testing in paediatric patients in secondary care for distinguishing between IBD and non-IBD. However, the External Assessment

Group highlight the limitation of this approach as the main model structure does not fully account for the non-IBD case mix in the paediatric population (prevalence of IBS in the non-IBD group is lower than that seen in adults). Strategies assessed; 1) direct referral to colonoscopy, 2) ELISA testing for FC at the 50µg/g cut-off followed by colonoscopy and, 3) ELISA testing for FC at the 100µg/g cut-off followed by colonoscopy. A gastroenterologist's current practice is not accounted for in these strategies; this is likely to reduce the number of patients that undergo colonoscopy under current practice (and, therefore, may overestimate the benefit of FC testing in reducing the number of colonoscopies if a clinicians current practice differentially impacts the FC testing strategies when compared with current practice assumed in the model).

Prior testing with ELISA testing is estimated to be cost saving when compared with the strategy of sending all patients directly for a colonoscopy. The additional ELISA test costs are more than offset by the savings from reduced colonoscopies. Compared to referring all directly to colonoscopy, ELISA used at the 50µg/g cut-off is estimated to save £205 per patient, while ELISA used at the 100µg/g cut-off is estimated to save £240 per patient. Small QALY gains of around 0.001 QALYs are estimated for ELISA compared with direct referral to colonoscopy, these being slightly larger for ELISA with the 50µg/g cut-off due to its better sensitivity. But given the additional average £35 cost, the cost effectiveness estimate for ELISA with the 50µg/g cut-off compared with ELISA with the 100µg/g cut-off is £35,000 per QALY gained. Probabilistic modelling results in similar estimates.

- Six separate estimates of sensitivity and specificity are available at a cut-off of 50µg/g (2 from Calprest, 3 from Phical (Calpro [ALP]), 1 from the EK-CAL) and another six estimates at 100µg/g (2 from Calprest and 4 from Phical (Calpro [ALP])) which allows the individual estimates to be meta-analysed into combined overall estimates of sensitivity and specificity for ELISA tests. These estimates were used in the base case analysis and are informed by a pool of 531 patients at a cut-off of 50 µg/g and 656 patients at a cut-off of 100µg/g.

Sensitivity analyses show, as for primary care, that most of the changes appear to broadly affect the three comparators in a like manner. The main difference arises from varying the prevalence of IBD, which tends to reduce the cost savings from FC testing as the prevalence rises, as would be anticipated. The source of utilities also has an impact upon the anticipated net gain from ELISA with the 50µg/g cut-off compared with ELISA with the

100µg/g cut-off, the ICER for which worsens to £117,000 per QALY gained. But this may be to overstate the effect given the prevalence of Crohn's disease within the presenting population and the perhaps rather small quality of life decrement sourced from Gregor et al. (1997).

4a. Which cut-off value is most consistent with the aim of FC/diagnostic testing in secondary care and is this a cost effective use of NHS resources?

Generally, the most common cut-off for defining normality was 50µg/g, as recommended by manufacturers, and as used in the 2010 YHEC report. Some adults with IBS have raised FC levels and would be false positives, who might be referred for colonoscopy as people with IBD. However there is some evidence that organic pathology is rare with FC levels under 100µg/g, and some experts suggest that if there are people with IBD but FC under 200µg/g, they are likely to have low grade IBD and would come to no harm if simply monitored by repeated FC tests, with referral into secondary care if the level rose.

Expert input indicates that the main application of FC testing in secondary care, given the analysis performed by the External Assessment Group, is to help identify patients who are likely to have IBD and will require further diagnostic tests, for example colonoscopy. Therefore, the focus of FC testing/the diagnostic pathway in secondary care is to maximise sensitivity (or positive predictive value) in patients presenting with lower abdominal symptoms who have been referred for assessment.

Please refer to the notes for question 4. The cost effectiveness of ELISA testing is assessed when used at the 50µg/g and 100µg/g cut-offs followed by colonoscopy.

4b. If FC testing, at an appropriate cut-off value, is a cost effective use of NHS resources in secondary care, to which population should any potential recommendations apply?

The population of interest is individuals aged up to 60 years presenting with any of the following lower gastrointestinal symptoms - abdominal pain or discomfort, bloating or change in bowel habit that have been referred for assessment. The External Assessment Group's model used for the primary care analysis has been adjusted to assess the cost effectiveness of FC testing in the paediatric population in secondary care for distinguishing between IBD and non-IBD.

Patient age

The results of six separate estimates of sensitivity and specificity at a cut-off of 50µg/g were meta-analysed and used to inform the base case. The majority of these studies included patients up to the age of 18.

The results of six separate estimates of sensitivity and specificity at a cut-off of 100µg/g were meta-analysed and used to inform the base case. In terms of the upper limit, the age of patients varied in these studies; two studies recruited patient up to the age of approximately 15, two studies up to the age of 18 and one study of to an age of 20. The age was limit was not reported in the sixth study.

4c. How specific/broad should any potential recommendations for secondary care be?

The External Assessment Group suggests the clinical effectiveness evidence indicates that FC testing in general can be used to distinguish between IBD and non-IBD and is likely to be cost saving.

In total, 12 tests were included in the assessment conducted by the External Assessment Group. Accounting for multiple entries of different versions of the same test, there are 4 manufacturers of different ELISA tests, 2 manufacturers of rapid tests, 1 manufacturer of the EliA test and 1 manufacturer of the POCTs. However, not all of the tests informed the diagnostic accuracy estimates used in the secondary care economic analysis.

The six studies that informed the meta-analysis of diagnostic accuracy of ELISA testing at the 50µg/g used in the base case analysis assessed the performance of several tests. Two studies of Calprest, 3 studies of Phical (Calpro [ALP]), 1 study of EK-CAL. The 6 studies that informed the meta-analysis of diagnostic accuracy of ELISA testing at the 100µg/g used in the base case analysis assessed the performance of two tests. Two studies of Calprest and 4 studies of Phical (Calpro [ALP]).

The External Assessment Group, manufacturers and clinicians (during scoping) suggest that FC tests are likely to perform similarly such that clinical outcomes are not significantly affected. However, there are limited data that suggest ELISA tests may lead to different diagnostic accuracies (section 2.10 of the diagnostics assessment report). Careful consideration is required as to how far the results of the economic analysis, informed by accuracy data from specific ELISA tests, can be extrapolated to other tests.

If the evidence is found to be satisfactory by the Committee then a recommendation for FC testing in general, as oppose to particular tests, could be considered.

7. Equality considerations

People with chronic diarrhoea are likely to be classified as having a disability and therefore be protected under the Equality Act 2010.

IBD is most prevalent among Jewish people of European origin, and is more common in Caucasian people than in Afro-Caribbean people or those of Asian origin.

IBS is most common between 20 and 40 years and is twice as common in women as in men. Recent trends indicate that there is also a significant prevalence of IBS in older people.

The populations included in the scope were limited to 60 years of age as those individuals experiencing symptoms for over 6 weeks and are over 60 years of age (a ‘red flag’ indicator) will likely follow a different diagnostic and care pathway. Therefore, individuals over 60 years of age were not included in the scope.

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this evaluation was prepared by Warwick Evidence.

Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: a systematic review and economic evaluation. Waugh et al. (April, 2013).

B Additional references used:

Guidelines on Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. NICE clinical guideline CG61 (2008). Available from: http://guidance.nice.org.uk/CG61

Guidelines on the Irritable Bowel Syndrome: Mechanisms and Practical Management. British Society of Gastroenterology (BSG) guideline (2007). Available from: http://www.bsg.org.uk/pdf_word_docs/ibs.pdf

Guidelines for the Management of Inflammatory Bowel Disease. British Society of Gastroenterology (BSG) guideline (2011). Available from: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/ibd/ibd_2011.pdf