

# Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel

Diagnostics guidance

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This guidance is the basis of QS114.

## 1 Recommendations

- 1.1 Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
- cancer is not suspected, having considered the risk factors (for example, age) described in the NICE guideline on [suspected cancer](#) and
  - appropriate quality assurance processes and locally agreed care pathways are in place for the testing.
- 1.2 Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment, if:
- appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

## 2 The technologies

- 2.1 Several technologies that measure the level of calprotectin in stool samples (faecal calprotectin) were evaluated, including fully quantitative laboratory-based tests, fully quantitative rapid tests and semi-quantitative point-of-care tests. Faecal calprotectin is excreted in excess into the intestinal lumen during the inflammatory process and so can act as a marker for inflammatory diseases of the lower gastrointestinal tract. The tests are intended to help distinguish between inflammatory bowel diseases and non-inflammatory bowel diseases. Additional details are provided in [section 4](#).

### 3 Clinical need and practice

#### *The problem addressed*

- 3.1 The aim of this evaluation was to examine the clinical and cost effectiveness of faecal calprotectin tests to help differentiate between non-inflammatory disorders such as irritable bowel syndrome (IBS) and inflammatory disorders such as inflammatory bowel disease (IBD) in people presenting with any of the following lower gastrointestinal symptoms for at least 6 weeks: abdominal pain or discomfort, bloating, or change in bowel habit. Patients with IBD need to be referred to specialist care (most likely, gastroenterology) for further investigation.
- 3.2 The External Assessment Group suggested that, in adults, the distinction between IBD and IBS is likely to be most clinically useful. It was also suggested that children presenting with these symptoms can have a different range of conditions than adults, and the most clinically useful distinction in children was thought to be between IBD and non-IBD.

#### *The conditions*

#### **Background, epidemiology and incidence**

- 3.3 Chronic abdominal pain or discomfort, with diarrhoea or constipation, are common. The symptoms can be caused by several different conditions, including IBD, of which ulcerative colitis and Crohn's disease are the most common, and IBS.
- 3.4 Lower bowel symptoms are very common in general practice. They are most often associated with IBS. However, the symptoms can be caused by IBD, which can lead to serious complications. For example, over 50% of people with Crohn's disease need surgery within 10 years of diagnosis. It is important to distinguish IBD from non-IBD, such as IBS, so that the conditions can be appropriately managed and monitored. IBD is characterised by inflammation of the bowel, which is not seen in most patients with IBS.

### ***Irritable bowel syndrome***

- 3.5 IBS is a functional bowel disorder characterised by frequent bouts of bowel disturbance, abdominal pain and discomfort, and bloating. There is no clear cause, no distinctive pathology and treatment is symptomatic. Exacerbations may be triggered by diet or stress. Physiological studies often show an increase in bowel sensitivity, and the condition may be associated with abnormal muscle activity in the wall of the bowel. It is troublesome and can interfere with activities of daily life, although it does not usually cause serious morbidity.
- 3.6 [NICE clinical guideline 61](#) on irritable bowel syndrome in adults suggests a prevalence of between 10% and 20% in the general population. Prevalence figures can vary depending on the diagnostic criteria used, which may account for the range of reported values. The true prevalence of IBS may be higher than estimated because many people with IBS symptoms do not seek medical advice; the NICE guideline cites NHS Direct online data that suggest 75% of people using this service rely on self-care. 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 shows that there is also a significant prevalence of IBS in older people. In terms of non-IBD conditions, the percentage of people with IBS is greater in adults than children.

### ***Inflammatory bowel disease***

- 3.7 IBD is the term normally given to a group of conditions that involves inflammation of the gastrointestinal tract, such as Crohn's disease and ulcerative colitis. These conditions can sometimes have serious complications, including a high risk of surgery and an increased risk of colorectal cancer. In both ulcerative colitis and Crohn's disease, some people have active disease but no symptoms.
- 3.8 Ulcerative colitis and Crohn's disease are the 2 most common forms of IBD. The incidence of ulcerative colitis is approximately 10–20 per 100,000 per year, with a reported prevalence of 100–200 per 100,000 people. 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 people. There is little gender difference in the prevalence of IBD, but it is more common in white people than in African-Caribbean people or those of Asian origin. The condition is most prevalent in 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, while the ratio in children is much higher (2.3:1).

- 3.9 **Ulcerative colitis:** is a relapsing and remitting disease characterised by inflammation of the colon, sometimes intense, with bloody diarrhoea, but more often milder. The cause is not known, but some people seem to be 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 natural bacteria that live in the gut. Sometimes, ulcerative colitis occurs after an episode of gastroenteritis caused by organisms such as *Salmonella*, *Shigella* and *Campylobacter*. However, in this case, the condition is more commonly triggered by resulting changes in the natural gut flora than by the direct effects of these organisms.
- 3.10 **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 can be a much more extensive disease and can affect any part of the gastrointestinal tract. The cause is unknown, but there is a genetic susceptibility. Like ulcerative colitis, it can occur after infectious gastroenteritis and is associated with disturbances in the natural gut flora. The highest incidence of Crohn's disease is in the 15–30 year age range, but 20–30% of people with the condition are younger than 20 years and onset occurs in people younger than 17 years about 25% of the time. The incidence of Crohn's disease in the general population has been increasing both within the UK and internationally.
- 3.11 The pattern of symptoms in children is different from that in adults. The largest prospective survey in the UK and Ireland was carried out by the British Paediatric Surveillance Unit, the British Society of Gastroenterology Research Unit and the Paediatric Register of IBD. The commonest presenting symptoms of Crohn's disease are abdominal pain, weight loss and diarrhoea, but 44% of children in the survey did not report diarrhoea, and only 25% reported all 3 together. Other symptoms at presentation included lethargy and anorexia. Paediatric IBD is often more extensive at diagnosis than in adults.



## Prognosis

### *Irritable bowel syndrome*

- 3.12 IBS is not associated with the development of serious comorbidities, and there is no indication that it is linked with a worse prognosis compared with the general population.
- 3.13 However, IBS can be painful, disrupt normal activities and reduce quality of life. For example, Spiegel et al. (2009) reported that quality of life in people with IBS is reduced by 26% on average and by 30% if the condition is severe when compared with a person 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.

### *Inflammatory bowel disease*

- 3.14 IBD can be painful, disrupt normal activities and reduce quality of life, particularly during periods of active disease. For example, Stark et al. (2010) reported that quality of life is reduced by an average of 16% (by 9% for those in remission and by 29% for those with active disease) in people with ulcerative colitis, and reduced by an average of 23% (by 11% for those in remission and by 39% for those with active disease) in people with Crohn's disease when compared with a person at full health.
- 3.15 **Ulcerative colitis:** at first presentation, most patients have mild disease and only 10% have severe disease. About 50% will continue to have mild disease or be in remission but, in about 20% of patients, ulcerative colitis will be chronic and continuous, and be more likely to become extensive throughout the colon. Ordas et al. (2012) noted that, 10 years after onset, 20–30% of patients will have needed removal of the colon (colectomy). Ford and Talley (2013) estimated a lower colectomy rate of around 10%. The risk of mortality does not seem to be raised in people with ulcerative colitis compared with the general population.
- 3.16 **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% need hospital admission each year, and 50% will need surgery within 10 years of diagnosis. Life

expectancy is slightly decreased in people with Crohn's disease compared with the general population (Baumgart and Sandborn 2012).

- 3.17 There are 3 main serious intestinal complications in Crohn's disease. One is stricture (narrowing) of the bowel, which can lead to intestinal obstruction, so Crohn's disease can present as an 'acute abdomen' needing surgery, sometimes mimicking appendicitis. Another is fistulas, which are abnormal connections between sections of the bowel, or between the bowel and bladder. The third is colorectal cancer, and surveillance for this is needed.

## *The diagnostic and care pathways*

### **Diagnosis of IBS and IBD**

#### ***Primary care***

- 3.18 The symptoms of lower gastrointestinal disorders (including IBD and IBS) can be sufficiently similar to sometimes make diagnosis difficult. Tests are often carried out to exclude conditions rather than to diagnose them, leading to repeat visits and investigations.
- 3.19 In most cases the diagnosis of IBS can be made on the basis of clinical history alone. [NICE clinical guideline 61](#) on irritable bowel syndrome in adults recommends that people presenting with abdominal pain or discomfort, bloating or a change in bowel habit for at least 6 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 (faecal calprotectin is not specifically mentioned) and late onset (older 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 or test results indicative of IBD are referred to secondary care for specialist investigation (most likely to a gastroenterology clinic).
- 3.20 If there are no red flag indicators to cause concern, [NICE clinical guideline 61](#) states 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 antibody).

3.21 Of these, the 2 main tests for inflammation are erythrocyte sedimentation rate and C-reactive protein. However, these tests can be influenced by non-intestinal diseases and can lack diagnostic accuracy. Therefore, while both tests can identify inflammation, they cannot localise it to the bowel. As a result, many patients are referred for further investigation involving endoscopy, which may not be needed. [NICE clinical guideline 61](#) on irritable bowel syndrome in adults states that an endoscopy (and a range of other tests) is not needed to confirm the diagnosis of IBS.

3.22 Most people diagnosed with IBS at this stage are managed in primary care.

### *Secondary care*

3.23 People with lower bowel symptoms are likely to be referred to secondary care when there is uncertainty about the diagnosis, or a high clinical suspicion of IBD that needs further investigation.

3.24 British Society of Gastroenterology guidelines on IBS (2007) suggest that tests conducted in secondary care are largely based on the likely differential diagnosis. Initial laboratory tests in secondary care include full blood count, erythrocyte sedimentation rate, C-reactive protein, endomysial antibodies and tissue transglutaminase antibody. These tests may already have been done at the request of primary care. The next level of investigation involves endoscopy and imaging.

3.25 British Society of Gastroenterology guidelines on IBD (2011) state that '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. 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.

- 3.26 Endoscopy can be colonoscopy, involving inspection of the whole colon; sigmoidoscopy, inspecting only the distal part of the bowel (the sigmoid colon); or gastroscopy, visualising the 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. Options then include capsule camera endoscopy (the 'camera pill'), and imaging methods including ultrasound and MRI.
- 3.27 Therefore, the British Society of Gastroenterology guidelines suggest that patients with symptoms indicative of IBD or IBS presenting in secondary care follow a similar diagnostic pathway of initial investigations before 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.
- 3.28 A UK and Ireland survey found that delays in diagnosis of Crohn's disease in children were common; 18% had had a pre-diagnosis symptom for 1 to 3 years, and 9% had had one for more than 3 years. Only 9% had isolated small bowel disease.

## Differential diagnosis

- 3.29 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 not always possible. Blood tests that show 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, colonoscopy in specialist care has often been needed to distinguish between IBD and IBS. This is an invasive and unpleasant investigation needing sedation, and is usually carried out on a day-case basis. In younger patients, over 60% of colonoscopies are normal.

## Management

### *Irritable bowel syndrome*

3.30 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 need a combination of different interventions to achieve effective relief. These include watchful waiting, diet and lifestyle interventions, patient education and self-help, drugs, behavioural and psychological therapies, and complementary and alternative therapies. Drugs include antispasmodic agents, laxatives, antimotility agents and, as second-line treatment, antidepressants. The treatment of IBS often requires trials of different therapies because some do not improve symptoms. The process of trying different therapies may take several months; the significance of this is that the patient may have IBD and there may be a delay before the correct diagnosis is suspected and the patient is referred for specialist investigation.

### *Inflammatory bowel disease*

3.31 The treatments and the aims of management for IBD have changed in recent years. Schoepfer et al. (2012) comment that the aims 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, which can induce and maintain mucosal healing.

3.32 The aim of treatment in active disease is to secure and maintain remission. Management involves diet and lifestyle interventions, drugs and surgery to induce and maintain remission. Drugs include aminosalicylates, corticosteroids, thiopurines, disease-modifying anti-rheumatic drugs (such as methotrexate), immunosuppressants (such as ciclosporin) and anti-TNF drugs (such as infliximab). There is an increased risk of colorectal cancer, so surveillance is part of patient care.

## 4 The diagnostic tests

### *The interventions*

- 4.1 Several faecal calprotectin tests are available to the NHS in England, including fully quantitative laboratory-based technologies (many of which use an enzyme-linked immunosorbent assay [ELISA] platform), fully quantitative rapid tests and semi-quantitative point-of-care tests (POCTs). Rapid tests have not been characterised as POCTs in this assessment because they need a dedicated reader to process the tests but with appropriate training and quality assurance processes they may be appropriate for use in point-of-care settings. In principle, all technologies can be used to provide a faecal calprotectin testing service to either primary or secondary care.

**Table 1 Technologies included in the assessment**

| Manufacturer | Test                                     | Platform   |
|--------------|--|--|
| Bühlmann     | EK-CAL calprotectin ELISA test           | ELISA – quantitative<br>Range: 10–600 micrograms/g   |
| Bühlmann     | EK-CAL calprotectin ELISA test           | ELISA – quantitative<br>Range: 30–1800 micrograms/g  |
| Bühlmann     | LF-CAL25 Quantum Blue calprotectin test  | Rapid test – Immunoassay designed for the quantitative determination of faecal calprotectin in combination with the BÜHLMANN Quantum Blue reader<br>Range: 30–300 micrograms/g   |
| Bühlmann     | LF-CHR 25 Quantum Blue calprotectin test | Rapid test – Immunoassay designed for the quantitative determination of faecal calprotectin in combination with the BÜHLMANN Quantum Blue reader<br>Range: 100–1800 micrograms/g |

|   |   |  |
|---|---|--|
| Calpro  | CALPRO<br>CALPROTECTIN<br>ELISA TEST (ALP) –<br>formerly known as<br>the Phical test<br>CAL0100 | ELISA – quantitative<br>Range: up to 1250 mg/kg  |
| Calpro  | CALPROLAB<br>CALPROTECTIN<br>ELISA (ALP) –<br>formerly known as<br>the Phical test<br>CALP0170  | ELISA – quantitative<br>Range: up to 2500 mg/kg  |
| Eurospital  | Calprest  | ELISA – quantitative   |
| Eurospital  | CalFast   | Rapid test – Quantitative determination of faecal calprotectin in combination with a dedicated reader  |
| Immundiagnostik   | ELISA (K6927)   | ELISA – quantitative   |
| Phadia AB, part of Thermo Fisher Scientific                                       | EliA Calprotectin   | EliA – quantitative<br>Quantitative fluorescence enzyme immunoassay (FEIA) test<br>Range 15–3000 mg/kg   |
| Preventis (sister company to Immundiagnostik)                                     | KST11005 CalDetect Calprotectin Rapid test (version 1 – Caldetect)                              | POCT – immunochromatographic rapid test<br>A semi-quantitative test with 3 lines corresponding to: Calprotectin 'negative', Calprotectin ≤ 15 micrograms/g, Calprotectin 16–60 micrograms/g and Calprotectin > 60 micrograms/g stool |
| Preventis (sister company to Immundiagnostik)                                     | CalDetect Calprotectin Rapid test (version 3 – CalScreen)                                       | POCT – immunochromatographic rapid test<br>A yes/no test with only 1 test-line corresponding to the cut-off value of 50 micrograms/g stool (no inflammation = < 50 micrograms/g and inflammation present = ≥ 50 micrograms/g)        |
| Abbreviations: ELISA, enzyme-linked immunosorbent assay; POCT, point-of-care test |   |  |

- 4.2 Immundiagnostik tests K6967 and K6937 were included in the scope but were not included in the assessment conducted by the External Assessment Group because one is a variant (K6967) and the other (K6937) was superseded by the Immundiagnostik test K6927, which was included in the assessment.
- 4.3 In total, 12 tests were included in the assessment conducted by the External Assessment Group. The reference standard was histology after endoscopy.
- 4.4 Because faecal calprotectin correlates with the level of bowel inflammation, test results need to be interpreted in the context of a cut-off value, below which the test is deemed negative and above which is deemed positive. In the context of distinguishing between irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), this would mean a negative result would support a diagnosis of IBS (a disease not characterised by inflammation) and a positive result would support a diagnosis of IBD (a disease characterised by inflammation). For a quantitative test, the output is often a single number representing micrograms of calprotectin per gram of stool sample (for example, 15 micrograms/g). If the cut-off value is selected as 50 micrograms/g for distinguishing between IBS and IBD, then a person with a faecal calprotectin level of 15 micrograms/g would be classified as negative (indicating the person is likely to have IBS). The cut-off value selected influences the diagnostic accuracy of the tests under consideration and different cut-off values can be selected for different purposes. Cut-off values can include a middle range in which results are considered indeterminate, below which are deemed negative and above which are deemed positive. Although a cut-off value needs to be selected for interpreting results of a quantitative test, the cut-offs for a POCT might be pre-specified in the design of the test. For example, CalDetect reports 1 of 4 results when the test runs correctly: negative – faecal calprotectin is not detectable; negative – faecal calprotectin level is equal to or less than 15 micrograms/g; positive – faecal calprotectin level is 16–60 micrograms/g; and positive – faecal calprotectin level is more than 60 micrograms/g. Users might apply local cut-offs for interpreting the results of POCTs; for example, a cut-off of 60 micrograms/g might be applied, test results below which are deemed negative and above which are deemed positive. The most common cut-off recommended by manufacturers is 50 micrograms/g. It should be noted that, in some cases, people with IBS can have raised levels of faecal calprotectin above the selected cut-off value and the opposite is true for people with IBD (faecal calprotectin levels can be below the selected cut-off).



### *The comparator*

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

## 5 Outcomes

The Diagnostics Advisory Committee ([section 11](#)) considered evidence from a number of sources ([section 12](#)).

### *How outcomes were assessed*

- 5.1 The assessment consisted of a systematic review of the evidence on test performance and clinical-effectiveness data for faecal calprotectin testing. The outcome measures included in the assessment were:
- referral rates
  - numbers of colonoscopies with or without faecal calprotectin testing
  - proportion of colonoscopies with no abnormal findings
  - duration from onset of symptoms to definite diagnosis of inflammatory bowel disease (IBD) – late diagnosis of Crohn's disease
  - costs
  - adverse events such as complications of colonoscopy
  - quality of life and hence quality-adjusted life years (QALYs).
- 5.2 The External Assessment Group did a systematic review of the evidence on cost effectiveness for faecal calprotectin testing and constructed a de novo economic model. The outcomes of interest for the economic evaluation were the morbidity and mortality associated with inflammatory and non-inflammatory diseases of the bowel and their treatment, and particularly of people with IBD incorrectly diagnosed as irritable bowel syndrome (IBS). Given the chronic nature of the conditions and their potential impact on a person's quality of life, the main outcome of interest was health-related quality of life, including the impact of adverse effects associated with colonoscopy. The de novo economic model followed a linked evidence approach in which intermediate outcomes (results of faecal calprotectin testing) were linked to treatment outcomes and hence QALY gains. Costs and QALYs were assigned to each of the strategies assessed in the model.

5.3 Although the scope allowed for the assessment of faecal calprotectin testing for both adults and children in both primary and secondary care, the External Assessment Group modelled 2 specific scenarios: faecal calprotectin testing for distinguishing between IBD and IBS in an adult population in primary care; and faecal calprotectin testing for distinguishing between IBD and non-IBD in a paediatric population in secondary care. The External Assessment Group believed these scenarios reflect the most likely use of faecal calprotectin testing in clinical practice.

## *Clinical effectiveness*

### **Previous systematic reviews**

5.4 Five previously conducted systematic reviews of faecal calprotectin testing were quality assessed and summarised by the External Assessment Group.

5.5 In summary, reviews conducted recently (published in 2010 or later) and judged to be medium or high quality by the External Assessment Group concluded that faecal calprotectin testing is a useful tool. For example, the Centre for Evidence-based Purchasing (2010) review focusing on faecal calprotectin for distinguishing between IBS and IBD concluded that faecal calprotectin performs well in distinguishing organic bowel disease from functional bowel disease (organic disease includes IBD and functional disease includes IBS). Sensitivity and specificity were over 80% in most of these studies (at a 50 micrograms/g cut-off) and, when calculated, most positive and negative predictive values were 70–90%.

### **Diagnostic accuracy of faecal calprotectin – the comparisons**

5.6 The External Assessment Group summarised the ability of faecal calprotectin testing in 4 sets of comparisons:

- organic compared with non-organic
- IBS compared with IBD (most appropriate comparison for adults)
- organic compared with IBS
- IBD compared with non-IBD (most appropriate comparison for paediatrics).

- 5.7 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).
- 5.8 The External Assessment Group suggested that comparisons 2 and 4 represent the most likely use of faecal calprotectin testing in clinical practice and therefore that the economic analysis should focus on the cost effectiveness of faecal calprotectin testing within these applications of the test. Diagnostic accuracy data for comparisons 2 and 4 are summarised below. Faecal calprotectin testing is used in symptomatic patients to distinguish between 2 different types of disease. Diagnostic sensitivity refers to the proportion of patients whose test is positive in the presence of an inflammatory disease of the bowel (such as IBD); diagnostic specificity refers to the proportion of patients whose test is negative in the absence of inflammatory disease of the bowel. Patients whose test is negative may be found to have IBS.
- 5.9 Nearly all of the evidence came from studies in secondary care, with few data from primary care. Data from a pilot project supported by the NHS Technology Adoption Centre were available to the External Assessment Group and were used in the economic analysis. These data are also summarised below.

### ***IBS compared with IBD***

- 5.10 Seven studies gave results that compared IBS and IBD, at 8 cut-off levels ranging from 8–150 micrograms/g, all in adults in secondary care. All studies assessed enzyme-linked immunosorbent assay (ELISA) tests, and one also assessed the performance of the point-of-care test (POCT) CalDetect. As expected, low cut-offs gave high sensitivity for IBD but poor specificity. Sensitivity was consistently high (usually 100% at levels under 50 micrograms/g; ranging from 83–100% at a cut-off of 50 micrograms/g), but specificity was more varied (51–100%).
- 5.11 Many of the studies had a small sample size. The largest study was by Li et al. (2006), which employed a sample of 240 people. Studies were of mixed quality. Schroder et al. (2007) and Schoepfer et al. (2008) were assessed as having the least risk of bias.

- 5.12 Five studies reported data for faecal calprotectin testing with ELISA with a cut-off of 50 micrograms/g. This allowed for the meta-analysis of the studies to provide an overall combined estimate of sensitivity and specificity. The combined estimates for ELISA tests, at a 50 micrograms/g cut-off, were a sensitivity of 93% and a specificity of 94%. The meta-analysis estimates were informed by a pool of 596 people, of which 40% were from the Li et al. (2006) study. The mean age of people in these studies, when reported, ranged from 40–52 years in people with IBS and 34–45 years in people with IBD. However, the age of people in the Schoepfer et al. (2008) study went as high as 78 years.
- 5.13 The only study using a POCT was Otten et al. (2008), which assessed the CalDetect test in a sample of 114 people. Otten et al. showed that the test performed well at a cut-off of 15 micrograms/g, with a sensitivity of 100% and a specificity of 95%. At a cut-off of 60 micrograms/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 was 52 years in people with IBS and 45 years in people with IBD.
- 5.14 The cost effectiveness of faecal calprotectin testing for distinguishing between IBD and IBS in an adult population in primary care was assessed in the economic evaluation conducted by the External Assessment Group.

### ***IBD compared with non-IBD***

- 5.15 Eleven studies reported IBD compared with non-IBD, at 8 cut-off levels. 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 (not identified in the scope for the assessment).
- 5.16 The studies showed consistently high sensitivity at lower cut-offs, nearly all over 90%, with most at the 50 micrograms/g cut-off having sensitivities of 100%. Specificity was more varied, ranging from 44–93% at a 50 micrograms/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 were of mixed quality with Canini et al. (2006), Diamanti et al. (2010), Fagerberg et al. (2005), Henderson et al. (2012) and van

de Vijver et al. (2012) assessed as having the least risk of bias compared with the other studies.

- 5.17 Six separate estimates of sensitivity and specificity were available at a cut-off of 50 micrograms/g and another 6 estimates at 100 micrograms/g, which allowed the individual estimates to be meta-analysed into combined overall estimates of sensitivity and specificity for ELISA tests. The overall pooled results for IBD compared with non-IBD showed very high sensitivity of 99% but moderate specificity of 74% at a cut-off of 50 micrograms/g. These estimates were informed by a pool of 531 people with most of these studies including people up to the age of 18 years. At a cut-off of 100 micrograms/g, sensitivity was found to fall to 94% but specificity to improve to 82%. These estimates were informed by a pool of 656 people; however, the upper age limit varied in these studies. Two studies recruited people up to the age of approximately 15 years, 2 studies up to the age of 18 years and 1 study up to an age of 20 years. The age limit was not reported in the sixth study.
- 5.18 The cost effectiveness of faecal calprotectin testing for distinguishing between IBD and non-IBD in a paediatric population in secondary care was assessed in the economic evaluation conducted by the External Assessment Group.

### Primary care pilot data on faecal calprotectin testing

- 5.19 Implementation projects for faecal calprotectin testing in 2 North East Clinical Commissioning Groups in Northumberland and Durham Dales during 2011/12 were undertaken by the NHS Technology Adoption Centre. The Durham Dales data were available to the External Assessment Group and were used to inform the economic analysis, which also allowed exploration of what might happen if faecal calprotectin testing is introduced in primary care.
- 5.20 The Durham Dales project provided data on GP referrals following the introduction of faecal calprotectin testing in primary care. GPs made diagnostic decisions based on clinical assessment and knowledge of the faecal calprotectin test result. They referred patients who they thought might have IBD, and managed those who they thought had IBS in primary care.
- 5.21 A final consultant diagnosis was made, based on faecal calprotectin test results and clinical data including colonoscopy. The clinical data came from GP and

outpatient data, when patients were referred, or just from GP data, when patients were not referred. Patients diagnosed as having IBS and not referred for specialist investigation did not have colonoscopy, so it was not possible to completely exclude patients with false negative results (partial verification bias). The Durham Dales data could not be used to inform the estimates of test accuracy for the CalDetect test (used in the implementation project) in the main economic analysis in primary care because of the partial verification bias.

- 5.22 Using the Durham Dales data of 111 patients who were followed up, the External Assessment Group used a prevalence of IBD of 6.3% in primary care and, in the absence of faecal calprotectin testing, a sensitivity of GP current practice of 100%, and 79% specificity in the model. The data also showed that GPs referred about 25% (29/111) of patients who presented with symptoms. The External Assessment Group created a scenario analysis that arbitrarily assumed that, if faecal calprotectin testing becomes available, GPs will test twice as many patients (50%) than they would have referred in the absence of faecal calprotectin testing.
- 5.23 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, and of Crohn's disease 8.7, based on 365 cases) would be expected in this adult population.

## Ranges of faecal calprotectin values and choice of test

### *Ranges*

- 5.24 The distribution of faecal calprotectin values is highly skewed and a wide range can be observed. Low levels may be seen in people with IBD and raised levels may be seen in people with IBS/non-IBD (for example, people with infectious gastroenteritis or food poisoning).
- 5.25 In some studies, the ranges did not overlap, but in others they did. For example, in El-Badry et al. (2010), the value of faecal calprotectin in people with IBD ranged from 98–637 micrograms/g, which did not overlap with the value of faecal calprotectin in people with IBS (14–65 micrograms/g). In all other studies, the range of faecal calprotectin in patients with IBD overlapped with the range of faecal calprotectin in patients with IBS. In some studies, such as Li et al. (2006) and Schroder et al. (2007), the range of faecal calprotectin levels in

people with IBD was wide, with the lowest value being 15 micrograms/g and the highest being 2574 micrograms/g.

- 5.26 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 faecal calprotectin levels overlapped in children and faecal calprotectin levels were high.
- 5.27 The External Assessment Group noted that faecal calprotectin levels were often raised in conditions other than IBD, such as larger colorectal adenomas and some colorectal cancers. The accuracy of faecal calprotectin testing is lower in these other conditions when compared with IBD.

### *Choice of test*

- 5.28 The External Assessment Group summarised several studies that evaluated the comparative performance of faecal calprotectin tests in particular situations. For example, some studies assessed the performance of the tests for distinguishing IBS from IBD and others assessed the tests in distinguishing organic from non-organic disease.
- 5.29 Overall, the External Assessment Group concluded that there are limited data comparing the performance of different faecal calprotectin tests. Of the studies conducted, they concluded that none suggested any considerable differences between the various faecal calprotectin tests.

### *Clinical outcomes*

- 5.30 Modelling was used to estimate clinical outcomes and QALYs. Please refer to the economic analysis below.

### *Economic analysis*

#### **Review of existing economic analyses**

- 5.31 Seven references were identified in the systematic review of economic analyses. Although previous economic analyses have typically concluded that faecal calprotectin 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 negative results (Mindemark and Larsson 2012); the analysis considering colonoscopy but not faecal calprotectin testing (Goldfarb et al. 2004 and Dubinsky et al. 2002 – also, this analysis was conducted in the US context); studies that were conducted in England but in primary care only (York Health Economics Consortium [YHEC] economic report for the Centre for Evidence-based Purchasing review, 2010); and some studies that were available only in abstract/poster format, which did not allow for a full critique of the analysis (Mascialino et al. 2012 and 2013).

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

### **Cost-effectiveness model constructed by the External Assessment Group**

- 5.33 The External Assessment Group constructed a full cost-effectiveness model. The External Assessment Group model was informed by the model used in [NICE clinical guideline 152](#) on Crohn's disease, the modelling for [NICE clinical guideline 166](#) on ulcerative colitis, the modelling for [NICE clinical guideline 61](#) on irritable bowel syndrome in adults and the YHEC model. In particular, these models were used to inform induction therapy and remission patterns in people with IBD and IBS.

### ***Model structure***

- 5.34 The model uses a linked-evidence approach to combine the outcomes of diagnostic strategies with the management (induction therapy and remission patterns) of patients' conditions, to allow the estimation of clinical outcomes and QALYs. The model assesses multiple diagnostic strategies and allows for multiple test sequences to be considered (for example, an initial ELISA test followed by colonoscopy). The outcomes from the diagnostic pathway are linked to the care pathway following diagnosis. Patients with true positive results for Crohn's disease and ulcerative colitis are considered separately from one another because patients in these groups follow different and complicated induction and remission pathways post diagnosis. Both patients with true negative and with false negative results follow the care pathway for IBS, with those patients whose disease does not respond to dietary changes after advice

and subsequent medical treatment for IBS being retested for IBD. Patients with false positive results (incorrectly diagnosed as having IBD) are eventually correctly diagnosed as having IBS, given that it is assumed all patients with false positive results are referred for specialist investigation and undergo a colonoscopy (assumed 100% specificity). The model employs a weekly cycle and adopts a 10-year time horizon.

### ***Model aim***

- 5.35 Although the scope allowed for the assessment of faecal calprotectin testing for both adults and children in both primary and secondary care, the External Assessment Group modelled 2 specific populations: an adult population in primary care, with faecal calprotectin test accuracies for IBD compared with IBS, and a paediatric population in secondary care, with faecal calprotectin test accuracies for IBD compared with non-IBD. The External Assessment Group believed these populations reflect the most likely use of faecal calprotectin testing in clinical practice.
- 5.36 The main aim of the model was to assess the impact of faecal calprotectin testing when added to current clinical practice compared with current practice alone on the differentiation of IBD and IBS in primary care. This model was then adjusted to reflect the differing test performances and costs in the paediatric population to provide an approximation of the cost effectiveness of faecal calprotectin testing for distinguishing between IBD and non-IBD. However, the External Assessment Group highlighted 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).

### ***Tests assessed in the modelling***

- 5.37 The use of an ELISA faecal calprotectin testing service was evaluated in the base case for both of the primary and secondary care scenarios. The POCT CalDetect was evaluated in the base case primary care scenario.

### ***Health-related quality of life (HRQoL)***

- 5.38 The base case applied 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 for ulcerative colitis, as drawn from Poole et al. (2010), were also explored. The utility decrements for IBS were less important for modelling purposes, given that the 100% specificity assumed for colonoscopy meant that there were no patients with false positive results by the end of the test sequence. For the base case, the 0.071 increment for response to treatment estimated within [NICE clinical guideline 61](#) was applied. The 0.662 baseline HRQoL that this increment was applied to was taken from Brazier et al. (2004). A sensitivity analysis using values from Spiegel et al. (2009) was 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 was not clear. The baseline HRQoL value for IBS has an impact because of the small mortality rate associated with colonoscopy, with this impact enduring for the 10-year time horizon of the model.

### *Adverse effects associated with colonoscopy*

- 5.39 Because of data constraints, the cost impacts were limited to modelling the relatively rare (less than 0.5%) serious adverse events of bleeds and perforations. The quality-of-life impacts were limited to the mortality associated with perforations. While perforations are rare, resulting in a very low mortality rate, the QALY impact of this persisted for the duration of the model.
- 5.40 There is evidence from the literature that colonoscopies result in minor adverse events among a reasonable proportion of patients; for example, de Jonge et al. (2012) suggested that around 40% of those investigated with colonoscopy have some effects persisting for 30 days after the colonoscopy. In common with [NICE clinical guideline 118](#) on colonoscopic surveillance for the prevention of colorectal cancer, these minor adverse events were not taken into account in the modelling principally because of a lack of quality-of-life data.

### **Costs**

- 5.41 The costs included in the model were the costs of the different tests, treatment costs (including induction therapy and maintenance therapy costs for people in remission), NHS resource costs (for example, staff time) and costs of adverse effects associated with colonoscopy.

- 5.42 The per person costs of an ELISA test and POCT CalDetect were estimated to be £22.79 (based on an assumption of 40 patient samples per 96 well-plate, costed at the list price, plus an average 11–12 minutes of staff time at grade 6/7) and £24.03 (test list price plus cost of 15 minutes of GP practice-nurse time) respectively.
- 5.43 Colonoscopy was estimated to cost £741.68 per person. This estimate was based on a weighted average of the NHS reference cost for outpatient and day cases without biopsy (procedures payment by results code FZ51Z/FZ54Z), or with biopsy (procedures payment by results code FZ52Z/FZ55Z) for colonoscopy or, when used, sigmoidoscopy. The cost included an outpatient gastroenterology appointment (£164) and costs of adverse effects (an average of £12 per colonoscopy).

## Primary care analysis (IBS compared with IBD in adults) – key model characteristics and results

- 5.44 The base case considered the cost effectiveness of GP testing compared with GP testing plus faecal calprotectin testing in the adult population for distinguishing IBS from IBD.

### *Patient characteristics*

- 5.45 For the primary care adult population, the model adopted a baseline age of 25 years for those presenting with symptoms, as used in [NICE clinical guideline 152](#) on Crohn's disease. Consistent with the modelling in this guideline, the proportion of females was taken to be 50% for both Crohn's disease and ulcerative colitis. It appears that a higher proportion of people with IBS are female; in the Brazier et al. (2004) sample, 86% were female, although the External Assessment Group suggested this estimate may be towards the upper end. For IBS, the base case adopted a proportion of females of 75%. These estimates only affect the all-population mortality risks. Because these risks are low during mid-adulthood, for both women and men, the average age and proportion of model inputs for women will have had a minimal impact on the results.
- 5.46 The base-case prevalence of IBD (6.3%) was drawn from the Durham Dales data, while the prevalence of ulcerative colitis among patients with IBD (a ratio

of ulcerative colitis to Crohn's disease of 3:2) was drawn from Shivananda et al. (1996).

### *Strategies assessed*

5.47 The strategies assessed were:

- GP current practice (clinical assessment with no faecal calprotectin testing)
- GP current practice plus the POCT CalDetect using a cut-off of 15 micrograms/g
- GP current practice plus ELISA testing using a cut-off of 50 micrograms/g.

The External Assessment Group opted to use the lower 15 micrograms/g cut-off from Otten et al. (2008) because the data for the 60 micrograms/g cut-off suggested only a slight gain in terms of a better specificity, 97.8% compared with 94.5%, but considerable loss in terms of a worse sensitivity, 60.9% compared with 100.0%. Test accuracy data used in the model are summarised in table 2 below.

5.48 The External Assessment Group assumed, given lack of evidence to the contrary, that the accuracy of ELISA testing is the same as would be obtained from ELISA testing in conjunction with GP current practice.

5.49 The delay between referral and colonoscopy was assumed to be 4 weeks and the time to retesting among those with negative tests but not responding to IBS therapy was assumed to be 12 weeks, both estimates being based on expert opinion. The latter estimate may have been optimistic because a sequence of unsuccessful treatments might be tried for people with IBS. This was explored in sensitivity analyses.

5.50 The modelling assumed that all people who test positive or have an indeterminate result are referred to secondary care and all of these people receive a colonoscopy (indeterminate results are treated as if the results are determinate). Because of 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 faecal calprotectin testing) in the base case; however, this is explored in sensitivity analysis.

Table 2 Primary care analysis – base-case test accuracy data<sup>1</sup>

| Test   | GP current practice   | CalDetect (POCT)                             | ELISA  | Colonoscopy    |
|--|---|--|--|----------------|
| Cut-off  | –   | 15 micrograms/g                              | 50 micrograms/g  | –              |
| Sensitivity  | 100%  | 100.0%<br>(95% CI 85–100%)                   | 93.0%<br>(95% CI 85–98%)                                       | 95.0%          |
| Specificity  | 79%   | 94.5%<br>(95% CI 88–98%)                     | 94.0%<br>(95% CI 76–100%)                                      | 100.0%         |
| Test accuracy data source  | Primary care data from the NHS Technology Adoption Centre project | Secondary care data from Otten et al. (2008) | External Assessment Group meta-analysis of secondary care data | Expert opinion |
| Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; POCT, point-of-care test             |   |  |  |                |
| <sup>1</sup> Confidence intervals used in the probabilistic sensitivity analysis, when reported, are given in brackets |   |  |  |                |

### Base-case cost-effectiveness results – primary care

5.51 Without faecal calprotectin testing, GP current practice is highly sensitive in terms of referring people with IBD and is as good as, if not better, than faecal calprotectin testing. Of the 6.3% of people with IBD in the total population, all were identified by the GP current practice strategy and the POCT CalDetect strategy. Colonoscopy would correctly identify 6.0% of the 6.3% referred as patients with true positive results (because of its 95% sensitivity), resulting in a total of 0.3% of patients with false negative results. ELISA testing is slightly worse, identifying 5.9% of the 6.3% (because of its lower sensitivity when compared with current practice and the POCT), with 0.4% of patients being classified as having false negative results. Of the 5.9% referred for colonoscopy, 5.6% of patients would be identified as having true positive results, with 0.3% being classified as having false negative results, resulting in a total of 0.7% of

patients with false negative results. 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 CalDetect strategy (0.7% compared with 0.3%).

- 5.52 Within the total patient population, GP current practice incorrectly identified 19.8% of patients as having false positive results (people thought to have IBD but who actually have IBS) and requiring referral for colonoscopy. The rates of patients with false positive results incorrectly referred for colonoscopy for POCT CalDetect and ELISA were much lower, at 5.1% and 5.6% respectively. Therefore, without faecal calprotectin testing, many of the patients with false positive results would go on to have a colonoscopy, which has a risk (although low) of serious complications such as perforation. Such events are too rare to significantly affect costs, but they do have some QALY impact. This is also true for the more common minor adverse effects of colonoscopy (which were not explicitly considered in the model because of a lack of data).
- 5.53 Taking the diagnostic performance of the different testing strategies summarised above into account, the resulting total per patient costs and QALYs are provided in table 3.

**Table 3 Primary care – base-case results (per patient)**

| Strategies   | QALYs         | Test costs  | Other costs  | Total costs  |
|--|---------------|-------------|--------------|--------------|
| GP current practice (no faecal calprotectin testing)           |               |             |              |              |
| Crohn's disease  | 0.1832        | £22         | £493         | £515         |
| Ulcerative colitis   | 0.2771        | £32         | £144         | £176         |
| IBS  | 5.7682        | £202        | £2404        | £2606        |
| <b>Total</b>   | <b>6.2285</b> | <b>£257</b> | <b>£3041</b> | <b>£3297</b> |
| Current practice plus POCT CalDetect (15 micrograms/g cut-off) |               |             |              |              |
| Crohn's disease  | 0.1832        | £23         | £493         | £516         |
| Ulcerative colitis   | 0.2771        | £33         | £144         | £177         |
| IBS  | 5.7691        | £114        | £2408        | £2522        |

|  |               |             |              |              |
|--|---------------|-------------|--------------|--------------|
| <b>Total</b>   | <b>6.2293</b> | <b>£170</b> | <b>£3044</b> | <b>£3214</b> |
| Current practice plus ELISA (50 micrograms/g cut-off)  |               |             |              |              |
| Crohn's disease  | 0.1831        | £23         | £492         | £515         |
| Ulcerative colitis   | 0.2770        | £34         | £143         | £177         |
| IBS  | 5.7690        | £116        | £2407        | £2524        |
| <b>Total</b>   | <b>6.2291</b> | <b>£173</b> | <b>£3042</b> | <b>£3215</b> |
| Abbreviations: ELISA, enzyme-linked immunosorbent assay; IBS, irritable bowel syndrome; POCT, point-of-care test; QALYs, quality-adjusted life years |               |             |              |              |

- 5.54 The faecal calprotectin tests were estimated to result in similar average cost savings compared with GP current practice: £83 for the POCT CalDetect and £82 for ELISA per patient. This was mainly because of the lower number of referrals and colonoscopies for false positive results. Average QALY gains of around 0.0007 QALYs were also accrued, although these were limited because the low prevalence of IBD and the similar high sensitivities of the tests resulted in relatively few false negative results. Therefore, the faecal calprotectin testing strategies dominated current practice (provided greater benefit at reduced cost). Some of the QALY differences accrued were from the very slightly lower mortality associated with the lower number of colonoscopies. The POCT CalDetect and ELISA strategies were estimated to be broadly equivalent in terms of costs and QALYs, with only minor differences between them.

### ***Sensitivity analysis***

- 5.55 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 patients whose condition did not respond to IBS medication; varying the time it takes for patients with false negative results to re-present to the clinician (8, 16 and 24 weeks; 12 weeks was used in the base case); and exploring the impact of varying the specificity of the consultant's diagnosis at an outpatient clinic assessment in people referred with a false positive diagnosis. Scenario analyses were also undertaken using different sources of test accuracy for faecal



calprotectin and alternative assumptions surrounding the uptake of faecal calprotectin testing (assuming 50% of patients are tested as opposed to the 25% used in the base case) in primary care.

- 5.56 The sensitivity and scenario analyses appeared to broadly affect the 3 strategies in a similar way and suggested that the results of the base case were reasonably robust. The most notable impact was from assuming 50% of patients are tested in primary care, as opposed to 25%, which reduced the cost savings with faecal calprotectin testing.

## Secondary care (IBD compared with non-IBD in children) – key model characteristics and results

- 5.57 The base case considered the cost effectiveness of faecal calprotectin testing before colonoscopy compared with direct referral for colonoscopy in the secondary care paediatric population for distinguishing IBD from non-IBD.

### *Patient characteristics*

- 5.58 For the secondary care paediatric population, the proportions of females included were 38% (35/91) for patients with IBD and 44% (44/99) for patients without IBD; these were drawn from Henderson et al. (2012). An average age of 16 years was assumed because, for the adult modelling, this had minimal impact on results.
- 5.59 In the base case, a 48% (91/190) prevalence of IBD and a 75% (62/83) prevalence of Crohn's disease among patients with IBD were drawn from Henderson et al. (2012).

### *Strategies assessed*

- 5.60 The strategies assessed were:

- direct referral for colonoscopy
- ELISA testing when used at the 50 micrograms/g cut-off followed by colonoscopy
- ELISA testing when used at the 100 micrograms/g cut-off followed by colonoscopy.

Test accuracy data used in the model are summarised in table 4.

Table 4 Secondary care scenario – base-case test accuracy data<sup>1</sup>

| Test   | ELISA  | ELISA   | Colonoscopy    |
|--|--|---|----------------|
| Cut-off  | 50 micrograms/g  | 100 micrograms/g  |                |
| Sensitivity  | 99.0%<br>(95% CI: 95–100%)                                     | 94.0%<br>(95% CI: 87–99%)                                       | 95.0%          |
| Specificity  | 74.0%<br>(95% CI: 59–85%)                                      | 82.0%<br>(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 |
| Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay                                       |  |   |                |
| <sup>1</sup> Confidence intervals used in the probabilistic sensitivity analysis, when reported, are given in brackets |  |   |                |

### Base-case cost-effectiveness results – secondary care

- 5.61 The base-case prevalence of IBD of 47.9% increased the importance of test sensitivities compared with the primary care setting, and so the effect of false negative results on the modelling outputs. Within the total patient population, ELISA with the 50 micrograms/g cut-off led to 47.4% of patients with true positive results being referred for colonoscopy, while ELISA with the 100 micrograms/g cut-off led to 45.0% of patients with true positive results being referred for colonoscopy. Colonoscopy was assumed to have a sensitivity of 95%. So, if all (47.9%) patients were referred immediately for colonoscopy, 45.5% would be diagnosed with IBD. With ELISA with the 50 micrograms/g cut-off, 45.0% of the 47.4% of patients referred for colonoscopy were diagnosed as having IBD, while 42.8% of the 45.0% of patients referred for colonoscopy after ELISA with the 100 micrograms/g cut-off were diagnosed as having IBD; a net difference between the cut-offs of 2.2%.
- 5.62 Despite the higher IBD prevalence in the secondary care population, the main test differences still lay in the number of unnecessary colonoscopies. Without faecal calprotectin testing, all 52.1% of patients without IBD received a

colonoscopy, compared with 13.5% for ELISA with the 50 micrograms/g cut-off and only 9.4% for ELISA with the 100 micrograms/g cut-off.

- 5.63 Taking the diagnostic performance of the different testing strategies summarised above into account, the resulting total per patient costs and QALYs are provided in table 5.

**Table 5 Secondary care: base-case results (per patient)**

| Strategies   | QALYs         | Tests       | Other        | Total        |
|--|---------------|-------------|--------------|--------------|
| Direct referral for colonoscopy  |               |             |              |              |
| Crohn's disease  | 2.5773        | £244        | £6938        | £7183        |
| Ulcerative colitis   | 0.8942        | £83         | £463         | £546         |
| Non-IBD  | 3.2094        | £338        | £629         | £967         |
| <b>Total</b>   | <b>6.6809</b> | <b>£665</b> | <b>£8031</b> | <b>£8696</b> |
| ELISA 50 micrograms/g before colonoscopy   |               |             |              |              |
| Crohn's disease  | 2.5767        | £254        | £6934        | £7188        |
| Ulcerative colitis   | 0.8941        | £86         | £463         | £549         |
| Non-IBD  | 3.2117        | £120        | £634         | £754         |
| <b>Total</b>   | <b>6.6824</b> | <b>£460</b> | <b>£8031</b> | <b>£8491</b> |
| ELISA 100 micrograms/g before colonoscopy  |               |             |              |              |
| Crohn's disease  | 2.5757        | £256        | £6921        | £7177        |
| Ulcerative colitis   | 0.8938        | £87         | £462         | £549         |
| Non-IBD  | 3.2119        | £95         | £634         | £729         |
| <b>Total</b>   | <b>6.6814</b> | <b>£438</b> | <b>£8018</b> | <b>£8456</b> |
| Abbreviations: ELISA, enzyme-linked immunosorbent assay; IBD, inflammatory bowel disease; QALYs, quality-adjusted life years |               |             |              |              |

- 5.64 Prior testing using ELISA was estimated to dominate (provided greater benefit at reduced cost) the strategy of sending all patients directly for colonoscopy. Compared with referring all patients directly for colonoscopy, ELISA used at the

50 micrograms/g cut-off was estimated to save £205 per patient, while ELISA used at the 100 micrograms/g cut-off was estimated to save £240 per patient. QALY gains of around 0.001 QALYs were estimated for ELISA compared with direct referral for colonoscopy, these being slightly larger for ELISA with the 50 micrograms/g cut-off because of its better sensitivity. The additional average cost of £35 and additional average QALYs of 0.0001 for ELISA with the 50 micrograms/g cut-off compared with ELISA with the 100 micrograms/g cut-off resulted in an incremental cost-effectiveness ratio (ICER) of £35,000 per QALY gained.

### ***Sensitivity analysis***

- 5.65 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 patients with false negative results to re-present to the clinician (8, 16 and 24 weeks; 12 weeks was used in the base case); and changing the annualised net cost of false negative results to £376 (£188 was used in the base case).
- 5.66 As for primary care, most of the changes appeared to broadly affect the 3 strategies in a similar manner. The main difference arose from varying the prevalence of IBD, which tended to reduce the cost savings from faecal calprotectin testing because of the rise in prevalence, as would be anticipated. The source of utilities also had an impact on the anticipated net gain from ELISA with the 50 micrograms/g cut-off compared with ELISA with the 100 micrograms/g cut-off, the ICER for which increased to £117,000 per QALY gained. However, the External Assessment Group thought that this may have overstated 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).

## 6 Considerations

- 6.1 The Diagnostics Advisory Committee discussed the focus of the evaluation and the evidence available for faecal calprotectin testing. It noted that evidence existed on faecal calprotectin testing in differing populations with differing conditions. For example, some study populations included large numbers of adults with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) (for example, Li et al. 2006), while others included children with a much wider range of organic and non-organic conditions (for example, Tomas et al. 2007). It also noted that, while the evaluation was concerned with the role of faecal calprotectin testing for distinguishing between inflammatory and non-inflammatory conditions of the bowel, the External Assessment Group suggested that the role of faecal calprotectin in 2 specific scenarios is likely to be the most important in clinical practice. These are IBD and IBS in the adult population presenting in primary care and IBD and non-IBD in children who are referred for specialist investigation. Furthermore, the Committee noted that, although the use of faecal calprotectin testing is most relevant for helping to distinguish between inflammatory and non-inflammatory conditions of the bowel, the number of conditions involved placed a prohibitively large burden on the data requirements for a cost-effectiveness analysis. Therefore, the scenarios above represent a reasonable proxy for the likely clinical use of faecal calprotectin testing, balanced against the demands of the economic analysis. The Committee agreed with the External Assessment Group that it was appropriate for the evaluation to focus on the clinical and cost effectiveness of faecal calprotectin testing in these 2 scenarios. Faecal calprotectin testing is used in symptomatic patients to distinguish between 2 different types of disease. Diagnostic sensitivity refers to the proportion of patients whose test is positive in the presence of an inflammatory disease of the bowel (such as IBD); diagnostic specificity refers to the proportion of patients whose test is negative in the absence of inflammatory disease of the bowel. Patients whose test is negative may be found to have IBS. The Committee also noted that, although there is a growing focus on faecal calprotectin testing in primary care, there were limited data on faecal calprotectin testing in this environment.
- 6.2 The Committee understood that several different types of faecal calprotectin tests are available to the NHS in England and that such tests are continually improving. The Committee noted that there were limited data on the comparative effectiveness of different faecal calprotectin tests and agreed with

the External Assessment Group that sufficiently robust data suggesting considerable differences in clinical reliability and performance between the tests were not available. The Committee recommended research on the comparative performance of different faecal calprotectin tests.

- 6.3 The Committee discussed pre-analytical factors that may affect the results of faecal calprotectin testing. The Committee heard from specialists that several factors can affect the result of faecal calprotectin testing, including: sample storage, stool consistency, stool sampling, extraction and extract dilution. The Committee also heard that a UK National External Quality Assessment Service scheme (UK NEQAS scheme) has been set up for faecal calprotectin testing. The Committee encouraged participation in the UK NEQAS scheme and, when possible, standardisation of sample preparation methodology.
- 6.4 The Committee discussed the evidence on the clinical effectiveness of faecal calprotectin testing in IBD and IBS in adults. It noted that multiple studies of diagnostic accuracy were identified, which assessed faecal calprotectin testing when interpreted using different thresholds. The Committee noted that the evidence mainly concerned the use of quantitative ELISA tests in a secondary care adult population. The most commonly used threshold value in these studies was 50 micrograms/g, which allowed the results of 5 studies to be meta-analysed. The Committee noted that the results of the meta-analysis showed that faecal calprotectin testing performed well, with a sensitivity of 93% and a specificity of 94%. The Committee was aware that a study was also published on the performance of a point-of-care test (POCT), CalDetect, when used in secondary care (Otten et al. 2008), which showed that the test performed well, with a sensitivity of 100% and a specificity of 95%. However, the Committee noted that the Otten et al. study included relatively few patients. The Committee concluded that, on the whole, faecal calprotectin was a reliable marker for distinguishing between IBD and IBS in a secondary care adult population, but that further data are needed on point-of-care testing, to verify the results seen in the Otten et al. study. The Committee recommended further research on the use and clinical utility of faecal calprotectin testing for the diagnosis and long-term management of these conditions in the community. The Committee also recommended that support pathways be developed for faecal calprotectin testing to support consistent and appropriate use.

- 6.5 The Committee discussed the de novo model constructed by the External Assessment Group. The Committee understood that limitations in the available data and/or variability in clinical practice meant that the model did not account for: (1) the way in which people with indeterminate results would be followed up before receiving a colonoscopy (all are assumed to be determinate and, therefore, receive a colonoscopy) and (2) the costs associated with the more common but relatively minor adverse events associated with colonoscopy (the costs of relatively rare but serious adverse effects are accounted for in the model). The Committee noted that, despite these limitations, the outcomes of the External Assessment Group's model were similar to those observed in previously conducted economic analyses. The Committee thought that, although the analysis may have benefitted from further sensitivity analysis, the results of the model are likely to be reasonably robust. The Committee concluded that the model was acceptable for decision-making.
- 6.6 The Committee went on to discuss the economic analysis that assessed the cost effectiveness of faecal calprotectin for distinguishing between IBD and IBS in a primary care adult population. It noted that data from the Durham Dales implementation project were used to inform the sensitivity and specificity estimates of GP current practice (see [section 5.47](#)). The Committee noted from the data that GPs were currently very good at identifying those patients with IBD who needed to be referred for specialist investigation (near-perfect sensitivity); however, a lower specificity of GP assessment meant that a significant proportion of people with IBS are being referred for specialist investigation, which may be avoided. The cost-effectiveness analysis compared GP current practice plus quantitative ELISA testing, GP current practice plus point-of-care testing with CalDetect and GP current practice without faecal calprotectin testing as separate diagnostic strategies in adults presenting in primary care with lower gastrointestinal symptoms of abdominal pain or discomfort, bloating or change in bowel habit for at least 6 weeks. The Committee noted that the main goal of faecal calprotectin testing in primary care is to help reduce the number of unnecessary referrals of people with IBS (given the relatively high prevalence compared with IBD) and so reduce the number of unnecessary colonoscopies. The Committee noted that the model demonstrated that the differing diagnostic accuracies of the different strategies resulted in 19.8% (GP current practice), 5.6% (ELISA strategy) and 5.1% (CalDetect strategy) of the total modelled population being classified as having a false positive result and referred for colonoscopy. Furthermore, the

Committee noted that the lower number of referrals after faecal calprotectin testing meant that both ELISA and CalDetect strategies dominated current practice (produced greater health benefits at reduced cost); however, the Committee agreed that the greatest benefit of faecal calprotectin testing is in reduced costs. Both ELISA and CalDetect strategies led to cost savings of £82 and £83 per patient respectively. The Committee concluded that faecal calprotectin testing is a cost-effective use of NHS resources for distinguishing between IBD and IBS in adults in primary care and that sensitivity analysis showed these results to be robust.

- 6.7 The Committee discussed the use of faecal calprotectin testing of adults in secondary care. The Committee heard from clinical specialists that most of the faecal calprotectin testing in adults is expected to take place in primary care rather than secondary care. The Committee also recognised that there is a trend towards reducing the number of referrals to secondary care. It noted, however, that testing may also be appropriate for adults who have been referred for specialist assessment if testing has not already been done in primary care, in order to inform the decision on whether to do further investigations such as colonoscopy. Furthermore, the Committee concluded that cost savings from reduced numbers of colonoscopies are likely in this situation. Therefore, the Committee recommended faecal calprotectin testing as an option to aid differential diagnosis in adults with recent onset of lower gastrointestinal symptoms for distinguishing between IBD and IBS.
- 6.8 The Committee discussed the use of faecal calprotectin testing for clinical decision-making. It agreed with the clinical specialists that faecal calprotectin should be used with other clinical information to support a physician's assessment and that physicians should be aware that inflammatory and non-inflammatory diseases other than IBD and IBS respectively may affect levels of faecal calprotectin. The Committee emphasised that faecal calprotectin testing has the potential to falsely reassure GPs when used in people suspected of having bowel cancer, and so these people should be excluded from the recommendations. The Committee strongly emphasised that, when uncertainty remains in primary care around whether to refer a patient for specialist assessment based on faecal calprotectin testing, the clinician will benefit from further specialist input (clinical or laboratory) before making a decision. The Committee also considered that a repeat testing strategy may be considered as part of patient follow-up (see section 6.14). The Committee was aware that



there are limited data on the use of faecal calprotectin testing in primary care. However, the Committee concluded that the assessment had demonstrated the benefit of using faecal calprotectin testing in adults who meet the specific criteria set out in [section 1.1](#) and the benefits were, on balance, generalisable to testing in primary care.

- 6.9 The Committee discussed the evidence on the clinical effectiveness of faecal calprotectin testing for distinguishing between IBD and non-IBD in children. It noted that multiple studies of diagnostic accuracy were identified that assessed faecal calprotectin testing using different thresholds. The Committee noted that the evidence mainly concerned the use of quantitative ELISA tests in a secondary care paediatric population. The most commonly used threshold values in these studies were 50 micrograms/g and 100 micrograms/g, which allowed the results of 6 studies for each threshold to be meta-analysed. The Committee noted that the results of the meta-analysis showed that faecal calprotectin testing performed reasonably well at both thresholds (50 micrograms/g with a sensitivity of 99% and a specificity of 74%, and 100 micrograms/g with a sensitivity of 94% and a specificity of 82%). The Committee concluded that, on the whole, faecal calprotectin was a reliable marker for distinguishing between IBD and non-IBD in a secondary care paediatric population.
- 6.10 The Committee went on to discuss the economic analysis that assessed the cost effectiveness of faecal calprotectin for distinguishing between IBD and non-IBD in a secondary care paediatric population. It noted that this model was an adaptation of the primary care model for IBD and IBS in a primary care adult population. The Committee agreed with the External Assessment Group that the secondary care paediatric model was limited because it did not fully account for the non-IBD case mix in the paediatric population (the prevalence of IBS in the non-IBD group is lower than that seen in adults). The Committee concluded that, despite this and other limitations in the model (see section 6.5), this analysis would provide a reasonable proxy for the expected costs and benefits of faecal calprotectin testing in a secondary care paediatric population. The cost-effectiveness analysis compared quantitative ELISA testing interpreted using a threshold of 50 micrograms/g followed by colonoscopy; quantitative ELISA testing interpreted using a threshold of 100 micrograms/g followed by colonoscopy; and direct referral for colonoscopy as separate diagnostic strategies in children with lower gastrointestinal symptoms of abdominal pain

or discomfort, bloating or change in bowel habit, for at least 6 weeks, who had been referred for specialist investigation. The Committee noted that the main goal of faecal calprotectin testing in people who have been referred for specialist investigation is to help identify those who are likely to have IBD and will need further diagnostic tests (because the prevalence of IBD in this population is much greater than that seen in primary care), for example, colonoscopy. The Committee noted that the model demonstrated the different strategies resulted in 100% (direct referral for colonoscopy), 61.5% (ELISA with a 50 micrograms/g threshold) and 54.4% (ELISA with a 100 micrograms/g threshold) of the total modelled population receiving a colonoscopy. These estimates include 13.5% of people with false positive results being referred to colonoscopy with the 50 micrograms/g cut-off strategy, and 9.4% of people with false positive results being referred to colonoscopy with the 100 micrograms/g cut-off strategy. Furthermore, the Committee noted that the lower number of people expected to receive colonoscopies with the faecal calprotectin strategies meant that ELISA testing at both thresholds dominated current practice (produced greater health benefits at reduced cost); however, the Committee agreed that the greatest benefit of faecal calprotectin testing is in reduced per-patient costs. Both ELISA interpreted at a threshold of 50 micrograms/g and ELISA interpreted at a threshold of 100 micrograms/g led to cost savings, of £205 and £240 per patient respectively. The Committee concluded that faecal calprotectin testing is a cost-effective use of NHS resources for distinguishing between IBD and non-IBD in a secondary care paediatric population and that sensitivity analysis showed these results to be robust. Therefore, the Committee recommended faecal calprotectin testing as an option in children with suspected IBD who have been referred for specialist assessment.

- 6.11 The Committee discussed the clinical interpretation of test results in children. The Committee heard from, and agreed with, the clinical specialists that faecal calprotectin should be used with other clinical information to support a specialist's assessment and that the specialist should be aware that inflammatory and non-inflammatory diseases, other than IBD and IBS respectively, may affect levels of faecal calprotectin.
- 6.12 The Committee was aware that most of the data on faecal calprotectin identified for this assessment came from studies of ELISA testing in a secondary care population. Therefore, in the absence of robust primary care data (in particular, robust primary care data for POCTs), the Committee recommended

that faecal calprotectin testing is performed in accordance with appropriate quality assurance processes and locally agreed care pathways to ensure results are reliable and replicable, and to increase the likelihood that the benefits and cost savings estimated by the model are delivered in the NHS. In addition, the Committee recommended that additional expertise should be sought when the faecal calprotectin tests are used in general practice, as outlined in section 6.8.

6.13 Given the lack of robust evidence comparing different tests, the Committee thought it appropriate that preferred faecal calprotectin tests might be selected locally in the NHS but that people should be aware that differences between tests may exist. The Committee noted that POCTs currently have a smaller evidence base and are not yet widely used in routine practice. The Committee therefore concluded that robust evidence is needed on the comparative performance of different faecal calprotectin tests, including the performance of POCTs compared with laboratory-based tests.

6.14 The Committee discussed the different thresholds for interpreting faecal calprotectin results. The Committee heard from clinical specialists that, while faecal calprotectin has been studied when interpreted using different thresholds (and investigated in the economic analysis), further research is needed on the impact of testing on clinical decision-making when added to current practice before a recommendation on a particular cut-off can be made. The Committee was aware of emerging evidence from a study of faecal calprotectin in primary care by Pavlidis et al. (publication in press, provided to the Committee as academic in confidence). However, the Committee concluded that it was too early to make judgements on these data. The Committee was aware that the assessment did not account for people with minimally elevated (intermediate) levels of faecal calprotectin who, as suggested by clinical specialists, may have low-grade IBD and might be better off following a repeat testing strategy with faecal calprotectin to monitor levels of bowel inflammation through time as opposed to being subjected to invasive colonoscopies. The Committee heard from clinical specialists that faecal calprotectin levels can vary markedly between the time a person is tested in primary care and then subsequently retested (likely to be after several weeks) either by their GP or a specialist. The Committee noted that differences in tests may exist in the intermediate range of faecal calprotectin levels but may not have been measured in studies to date because of selective sampling of study populations. Therefore, the Committee recommended further research on the

impact of faecal calprotectin testing on clinical decision-making when added to current practice in both primary and secondary care. The Committee also recommended research into optimal cut-off values for tests and the investigation of repeat testing strategies in people with intermediate levels of faecal calprotectin. Development of a consistent definition for the 'intermediate range' is encouraged by the Committee. The Committee further recommended that test result cut-offs should be discussed and agreed locally as part of the implementation process for this testing pathway.

- 6.15 The Committee noted some general points: (1) the clinical-effectiveness estimates for faecal calprotectin testing summarised in this evaluation have been corroborated by faecal calprotectin databases around the country (for example, the Edinburgh Faecal Calprotectin Registry and the database maintained by King's Health Partners); (2) the Durham Dales project data may represent a best-case scenario for GP current practice and, if this is the case, faecal calprotectin may have an even greater benefit in primary care (this additional benefit may be offset by losses in benefit if more than 50% of people with lower gastrointestinal symptoms are tested); (3) a significant proportion of people with IBD (particularly children with Crohn's disease), largely because of the similarity in symptoms to those in people with non-IBD conditions, face delays in their diagnosis of up to several years, and the introduction of faecal calprotectin may help to reduce such delays.
- 6.16 The Committee was encouraged by the results of the assessment because it is likely that the use of faecal calprotectin testing will result in significant capacity being generated in colonoscopy departments to allow them to focus on people with greater need for a colonoscopy (for example, those suspected of having bowel cancer). Furthermore, the Committee noted that the good diagnostic performance of faecal calprotectin has the ability to provide reassurance to both physicians and patients alike given the heterogeneous and overlapping symptoms in lower gastrointestinal disease.
- 6.17 The Committee considered the impact of this guidance on groups of people with characteristics protected by UK equality legislation. During scoping, it was noted that IBS is most common in people in the 20–40 years age range, and is twice as common in women as men. Additionally, IBD is more common in white people than in African-Caribbean people or those of Asian origin. The condition is most prevalent among Jewish people of European origin. The Committee

considered that the guidance did not present any restrictions in access to diagnosis or treatment in the above groups.

## 7 Recommendations for further research

- 7.1 Further research is needed on the use and clinical utility of faecal calprotectin testing, and support pathways for the long-term management of these conditions in the community should be developed.
- 7.2 Further research is needed on the impact of faecal calprotectin testing on clinical decision-making when added to current practice. This includes research into optimal cut-off values for tests and the investigation of repeat testing strategies in people with intermediate levels of faecal calprotectin. Development of a consistent definition for the 'intermediate range' is encouraged.
- 7.3 Robust evidence is needed on the comparative performance of different faecal calprotectin tests, including the performance of POCTs compared with laboratory-based tests.

## 8 Implementation

- 8.1 NICE has developed [tools](#), in association with relevant stakeholders, to help organisations put this guidance into practice.
- [Adoption support resource](#)
- 8.2 NICE will support this guidance with a range of activities to promote the recommendations for further research. This will include incorporating the research recommendations in [section 7](#) into the NICE guidance research recommendations database (available on the [NICE website](#)) and highlighting these recommendations to public research bodies. The research proposed will also be put forward to NICE's Medical Technologies Evaluation Programme research facilitation team for consideration of the development of specific research protocols.

## 9 Related NICE guidance

- [Ulcerative colitis: management in adults, children and young people](#). NICE clinical guideline 166 (2013).
- [Crohn's disease: management in adults, children and young people](#). NICE clinical guideline 152 (2012).
- [Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas](#). NICE clinical guideline 118 (2011).
- [Infliximab \(review\) and adalimumab for the treatment of Crohn's disease](#). NICE technology appraisal 187 (2010).
- [Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care](#). NICE clinical guideline 61 (2008).
- [Infliximab for acute exacerbations of ulcerative colitis](#). NICE technology appraisal 163 (2008).
- [Infliximab for subacute manifestations of ulcerative colitis](#). NICE technology appraisal 140 (2008).



## 10 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technologies. NICE may review and update diagnostics guidance at any time if significant new evidence becomes available.

Andrew Dillon  
Chief Executive  
October 2013

## 11 Diagnostics Advisory Committee members and NICE project team

### *Diagnostics Advisory Committee*

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

#### **Standing Committee members**

**Professor Ron Akehurst**

Professor in Health Economics, School of Health & Related Research, University of Sheffield

**Dr Trevor Cole**

Consultant Clinical and Cancer Geneticist, Birmingham Women's Hospital

**Professor Paul Collinson**

Consultant Chemical Pathologist & Professor of Cardiovascular Biomarkers, St George's Hospital

**Dr Sue Crawford**

General Practitioner (GP) Principal, Chillington Health Centre

**Professor Ian A Cree**

Senior Clinical Advisor, NIHR Evaluation Trials and Studies Coordinating Centre, University of Southampton

**Professor Erika Denton**

National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

**Dr Simon Fleming**

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

**Professor Chris Hyde**

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

**Professor Noor Kalsheker**

Professor of Clinical Chemistry, University of Nottingham

**Dr Mark Kroese**

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

**Professor Adrian Newland**

Chair, Diagnostics Advisory Committee

**Dr Richard Nicholas**

Consultant Neurologist, Honorary Senior Lecturer, Heatherwood and Wexham Park Hospitals

**Mr Stuart Saw**

Director of Finance, North East London and the City PCTs

**Professor Mark Sculpher**

Professor of Health Economics at the Centre for Health Economics, University of York

**Dr Steve Thomas**

Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals Foundation Trust

**Mr Paul Weinberger**

CEO, Diasolve Ltd, London

**Mr Christopher Wiltsher**

Lay member

**Mr David Evans**

Lay member

**Dr Gail Norbury**

Consultant Clinical Scientist, Guy's & St Thomas' NHS Foundation Trust

**Dr Peter Naylor**

Chair/General Practitioner, Wirral Health Commissioning Consortium

**Dr Steve Edwards**

Head of Health Technology Assessment, BMJ Evidence Centre

**Specialist Committee members**

**Dr Anjan Dhar**

Senior Lecturer in Gastroenterology, Consultant Gastroenterologist, Darlington Memorial & Bishop Auckland Hospitals

**Dr John O'Malley**

Organisational Medical Director/GP, Mastercall Healthcare

**Mr Nick Read**

Lay member

**Dr Raian Sheikh**

General Practitioner, Orchard Medical Practice

**Dr Simon Whitehead**

Trainee Clinical Scientist, New Cross Hospital

**Dr Robert Logan**

Consultant Physician & Gastroenterologist, King's College Hospital NHS Foundation Trust

***NICE project team***

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

**Gurleen Jhuti**

Topic Lead

**Hanan Bell and Pall Jonsson**

Technical Advisers

**Jackson Lynn and Robert Fernley**

Project Managers

## 12 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Warwick Evidence.

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

### *Registered stakeholders*

The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document.

### **Manufacturers/sponsors:**

#### *The technologies under consideration*

- Bühlmann – EK-CAL calprotectin ELISA test
- Bühlmann – LF-CAL25 Quantum Blue calprotectin test
- Bühlmann – LF-CHR 25 Quantum Blue calprotectin test
- Calpro – CALPRO CALPROTECTIN ELISA TEST (ALP) CAL0100
- Calpro – CALPROLAB CALPROTECTIN ELISA (ALP) CALP0170
- Eurospital – Calprest
- Eurospital – CalFast
- Immundiagnostik – ELISA (K6927)
- Immundiagnostik – ELISA (K6937)
- Immundiagnostik – ELISA (K6967)
- Phadia AB, part of Thermo Fisher Scientific – EliA Calprotectin
- Preventis – KST11005 CalDetect Calprotectin Rapid test (version 1 – Caldetect)
- Preventis – CalDetect Calprotectin Rapid test (version 3 – CalScreen)

### **Professional groups:**

- The British Society of Gastroenterology
- The Royal College of Nursing
- The Royal College of Pathologists
- The Royal College of Physicians

### **Patient/carer groups:**

- Lay IBS Network

### **Others:**

- Department of Health
- Healthcare Improvement Scotland
- Leeds General Infirmary
- Birmingham Quality (UK NEQAS)
- Royal Wolverhampton NHS Trust
- Epsom & St Helier NHS Trust
- St George's Hospital and Medical School
- Sherwood Forest Hospitals NHS Foundation Trust
- St George's Medical Centre, New Brighton
- Brighton and Sussex University Hospitals
- St Mark's Hospital, Harrow

## About this guidance

NICE diagnostics technologies guidance is designed to help the NHS adopt efficient and cost-effective medical diagnostic technologies more rapidly and consistently.

The programme concentrates on pathological tests, imaging, endoscopy and physiological measurement, since these represent most of the investigations performed on patients. The types of products that might be included are medical diagnostic technologies that give greater independence to patients, and diagnostic devices or tests used to detect or monitor medical conditions. Diagnostic technologies may be used for various purposes: diagnosis, clinical monitoring, screening, treatment triage, assessing stages of disease progression, and risk stratification.

This guidance was developed using the NICE [diagnostic technologies guidance](#) process.

We have produced a [summary for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

### Your responsibility

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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## Accreditation

