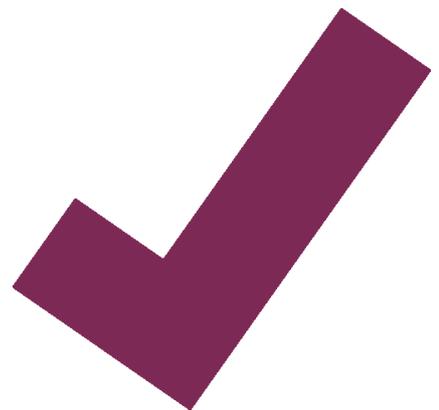


# **Faecal Calprotectin in Primary Care as a Decision Diagnostic for Inflammatory Bowel Disease and Irritable Bowel Syndrome**



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## 2 Foreword

Obtaining a prompt, precise and accurate diagnosis is the cornerstone of ensuring equitable and high quality care for patients and is essential to improving outcomes for all. The provision of high quality diagnostic services is therefore important to ensure the effectiveness and long-term sustainability of the NHS.

NHS England is delighted to endorse this consensus paper to support implementation of the National Institute for Health and Care Excellence (NICE) recommendation for the use of faecal calprotectin in distinguishing between Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS). I have been proud to lead this project as part of NHS England's mandate to drive forward the commissioning of high quality, innovative, patient-centred, diagnostic and scientific services to support the delivery of new models of care.

This document supports healthcare professionals by providing clarity about how faecal calprotectin testing should be delivered to simply and accurately distinguish between patients with IBD and IBS. This removes diagnostic uncertainty for individuals and the potential for unnecessary and invasive testing.

By providing clarity on the appropriate testing regime, this document should drive the uptake of new care pathways leading to improved outcomes and improved patient experience. As a consequence it should also reduce the pressure on endoscopy services nationally.

I would like to pay tribute to the clinical experts and academics who came together to form the Chief Scientific Officer's (CSO) Faecal Calprotectin Working Group and, in particular, thank Consultant Clinical Scientist Dr Martin Myers for leading the work of the group. Together they have analysed the evidence base and the diagnostic operations around faecal calprotectin to develop an approach that has clear and broad support across the clinical community.

I know this document will have a great impact on the many patients who suffer from these distressing conditions, providing better and clearer answers for them much sooner in their journey. It will also help to improve the efficiency and value for money for the services that support them.

Professor Sue Hill OBE PhD DSc CBIol FRSB FRCP (Hon) FRCPATH (Hon) FHCS (Hon)  
Chief Scientific Officer for England

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I welcome and endorse this initiative to promote the use of Calprotectin in helping frontline clinicians manage patients with abdominal and digestive symptoms. By supporting GPs in making a positive diagnosis of IBS, patients can be more readily and confidently reassured allowing them to move forward and manage their symptoms as recommended by NICE and other groups, such as the [www.IBSNetwork.org.uk](http://www.IBSNetwork.org.uk). For others, the faecal calprotectin test will facilitate more rapid access, and appropriate use of, tests such as colonoscopy. The technology behind the faecal calprotectin test heralds a new era for other innovative faecal tests which will have an even wider and greater impact for patients, doctors and the wider NHS.

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NCA for Endoscopy, NHS England

### 3 Background

The difficulty in distinguishing between Inflammatory Bowel Diseases (IBD) and Irritable Bowel Syndrome (IBS) can have a significant impact on individual wellbeing and health outcomes. The similarity in symptoms does not only cause delay in an accurate diagnosis for those suffering with IBD, but can subject those with IBS to unnecessary investigations and treatment.

By using the simple faecal calprotectin test when a patient first presents in primary care a GP then has a clear indication if the patient needs to be referred to secondary care for further testing or to treat IBD if the test is negative.

There is a lack of consensus on how to use faecal calprotectin as a biomarker and this has resulted in either non-adoption of the test or the use of multiple and different algorithms across the NHS. Since the publication of NICE guidance in 2013 (NICE, 2013), uptake of the test in the UK has been slow and as a consequence many patients are not benefitting from more appropriate referral.

Using the approaches defined in the NHS Five Year Forward View and under the direction of the NHS England Chief Scientific Officer (CSO) Professor Sue Hill a national working group was established to look at the opportunities to increase use, spread and adoption of the diagnostic test for faecal calprotectin.

The CSO Faecal Calprotectin Working Group brought together key partners to oversee the use, spread and adoption of faecal calprotectin testing as a decision diagnostic test in primary and secondary care settings. The particular focus was to demonstrate that through appropriate use of this diagnostic that the health system has the ability to produce better experience for patients and best value for money by reducing the pressure on endoscopy services nationally.

This group of experts (listed in appendix 1) considered a number of issues including; what opportunities were available to increase adoption, which tests were most appropriate, the health economics of this group of diagnostics. Using data from a 12 month pilot and input from all partners across the health system including early adopters, the working group have developed this consensus document.

## 4 Introduction

IBS affects 20% of the population and it generates 28% of all gastroenterology referrals to secondary care and represents 12% of primary care consultations (Thompson *et al.* 2000).

Patients often see their GP because of lower gastrointestinal symptoms (Canavan *et al.* 2014). Most often these are due to a benign disorder of bowel function in the absence of inflammation, generally referred to as IBS (Ford & Tally, 2012). Whilst IBS can be a challenging condition, the reassurance of a confident diagnosis and simple supportive measures will usually be sufficient to permit effective self-management. When diagnosed with certainty, this can be delivered within primary care. More rarely, with a prevalence of 3-5% in patients with bowel symptoms presenting to primary care, the patient will be suffering from IBD (Crohn's disease or ulcerative colitis) (NICE, 2015a). IBD requires early diagnosis and specialist secondary care management to prevent complications, such as surgery (NICE, 2015a). Unfortunately the challenge for the GP is that the symptoms of IBS and IBD are often similar and existing screening blood tests (such as C-reactive protein) are insensitive and nonspecific. Often there is diagnostic uncertainty. This adds to the anxiety caused by the symptoms (Crohn's and Colitis UK, 2016; Mozdiak *et al.* 2015).

Diagnostic uncertainty currently leads to patients being referred to secondary care for additional investigations. The use of blood testing diagnostics may be influenced by other conditions resulting in a lack of accuracy. The impact to patients of a referral to secondary care cannot be underestimated. Factors include time taken to be seen, an invasive and unpleasant experience and alongside this additional costs to the healthcare system.

Elevated levels of calprotectin in faeces are an indicator of IBD and not IBS. **Measuring calprotectin levels appropriately prior to referral would aid diagnosis, reduce burden on secondary care, improve patient experience and create financial savings.** Calprotectin testing can be carried out in a laboratory, or within a primary care setting using a point of care test (POCT) kit. Although NICE recommends that GPs test faecal calprotectin and diagnostic testing is possible, their use is limited.

In order to improve uptake of the use of faecal calprotectin and for the NHS to take advantage of the benefits that this biomarker can offer, the CSO National Faecal Calprotectin Working Group and the associated stakeholders prepared this consensus document, providing an algorithm to guide the diagnostic management and referral of patients through a faecal calprotectin pathway.

The aim of the algorithm is to assist GPs in the decisions they make in the management of patients with IBS or IBD however it is beyond the remit of the CSO Faecal Calprotectin Working Group to provide therapeutic guidance. Further information on IBS care can be found on the IBS Network website (IBS Network, 2018).

## 5 Faecal calprotectin as a decision diagnostic

IBD and IBS can appear sufficiently similar to make differential diagnosis difficult. While IBS is a functional bowel disorder for which no specific treatment is available, IBD (including Crohn's disease and ulcerative colitis), encompasses serious conditions where early recognition is required (NICE, 2015a). Crohn's disease and ulcerative colitis can also cause symptoms serious enough for major surgery to be needed, so it is important to distinguish between IBD and IBS and prompt and accurate diagnosis of IBD is therefore essential (Ford & Tally, 2012; NICE, 2015a; NICE, 2015b).

Advances in biomarker identification for IBD have resulted in the publication of NICE DG11 (NICE 2013) recommending faecal calprotectin testing as a decision diagnostic to help doctors distinguish between IBD and non-inflammatory bowel diseases, such as IBS. Calprotectin is a protein found in neutrophils and in the presence of active intestinal inflammation, neutrophils migrate to the intestinal mucosa from the circulation. Any disturbance to the mucosal architecture, due to the inflammatory process, results in leakage of neutrophils and hence calprotectin into the lumen, and its subsequent excretion in faeces.

There are many reasons why faecal calprotectin improves patient care:

- Many people with IBS have unnecessary invasive hospital investigations before their condition is diagnosed. Faecal calprotectin testing offers the potential to improve the management of most people with IBS without the need for these investigations (Vaughn *et al.* 2013).
- There are significant delays in diagnosis of IBD, sometimes as a result of having received an initial diagnosis of IBS (IBD Standards Group, 2013), leading to a higher incidence of surgery and reduced response to medication (Mozdiak *et al.* 2015).
- Faecal calprotectin testing can also improve the diagnostic pathway for patients with IBD, ensuring appropriate referral and earlier diagnosis. If used appropriately in primary care it can effectively triage which patients with lower gastrointestinal symptoms need referral to a gastroenterologist for further investigations, such as colonoscopy, and which patients are unlikely to have IBD and do not necessarily require referral.
- Those with a raised faecal calprotectin are likely to have IBD and so urgent initial investigation may be directed. In secondary care (and self-monitoring) faecal calprotectin can be used to assess disease activity, assess response to treatment, to predict disease relapse and to monitor for recurrence in patients with IBD (Walsham & Sherwood, 2016).

## 6 Commissioning impact of the faecal calprotectin pathway

NICE suggested that the use of faecal calprotectin should reduce the number of referrals and number of endoscopies and further work should be performed to identify the economic advantage of introducing this test. The NHS Business Services Authority Pacific Programme analysed the data from a 12 month pilot consisting of 41 GP practices across two CCGs (NHS BSA, 2017). The pilot identified that POCT for faecal calprotectin reduced referrals to secondary care by 56-88% and has considerably reduced waiting times.

Further, a pilot roll out of the new pathway across 7 CCGs and 198 GP practices in the North of England, supported by Yorkshire and Humber Academic Health Science Network (AHSN, 2017) has resulted in:

- a 40-57% reduction in new hospital outpatients' appointments and
- a 21-50% reduction in colonoscopies

Based on these results the patient's pathway, and thus their experience, will be improved with reducing their inconvenience and removing the need for unnecessary and uncomfortable procedures.

## 7 Development of a national algorithm

The CSO Faecal Calprotectin Working Group compared the NICE faecal calprotectin recommendations with how early adopters in the NHS (Appendix 2) are using this biomarker. It was not the intention of the working group to carry out a systemic review of the literature. These resources were then translated into this consensus document that could be used to assist the uptake of this test throughout the NHS. The consensus pathway was significantly influenced by the York Faecal Calprotectin Care Pathway as this pathway has been used effectively in the Yorkshire and the Humber region and its impact has been evaluated (Turvill *et al.*, 2016a).

NICE faecal calprotectin recommendations have been incorporated with implementation experience from 14 early adopter sites across England (Appendix 2) to produce a national algorithm for faecal calprotectin. The group supported the recommendation by NICE that further research is needed on the impact of faecal calprotectin testing on clinical decision-making. However it is important that this biomarker is used more widely in the NHS so that information such as clinical effectiveness and appropriate cut-offs can be identified (NICE, 2013).

NICE (2013) did not recommend any specific cut-off levels, but recorded that the level of 50 microgram/g is often quoted by the manufacturers. NICE issued a report on the experiences of the early adopters of faecal calprotectin (NICE 2015c). The report highlighted how different cut-offs were being used, but also emphasised that local adoption of the faecal calprotectin test improved the diagnostic yield in endoscopies.

It was found that multiple algorithms were being used throughout England using cut-offs at 50, 100, 150, 250 microgram/g and it is clear that more evidence is required to determine the most appropriate level. A cut-off of 50 microgram/g improves the sensitivity but lowers specificity resulting in unnecessary invasive investigations. However a cut-off of 250 microgram/g may improve specificity, yet miss or delay diagnosis of IBD in a number of patients (NICE, 2005; Mowat *et al.* 2015; Turvill *et al.* 2016b; Widlak *et al.* 2016; Turvill, 2012; Turvill 2014; Williams *et al.* 2014; Robin *et al.* 2017 and Menees *et al.* 2015). Different analysers may produce different results (accuracy) and different variability (imprecision) but within the range of 50-150 microgram/g the variation is not so wide. External assessment schemes are now being developed which will provide the local laboratory and clinician's information on the performance of the local test and it is essential that local review of the test chosen is performed when adopting local cut-offs.

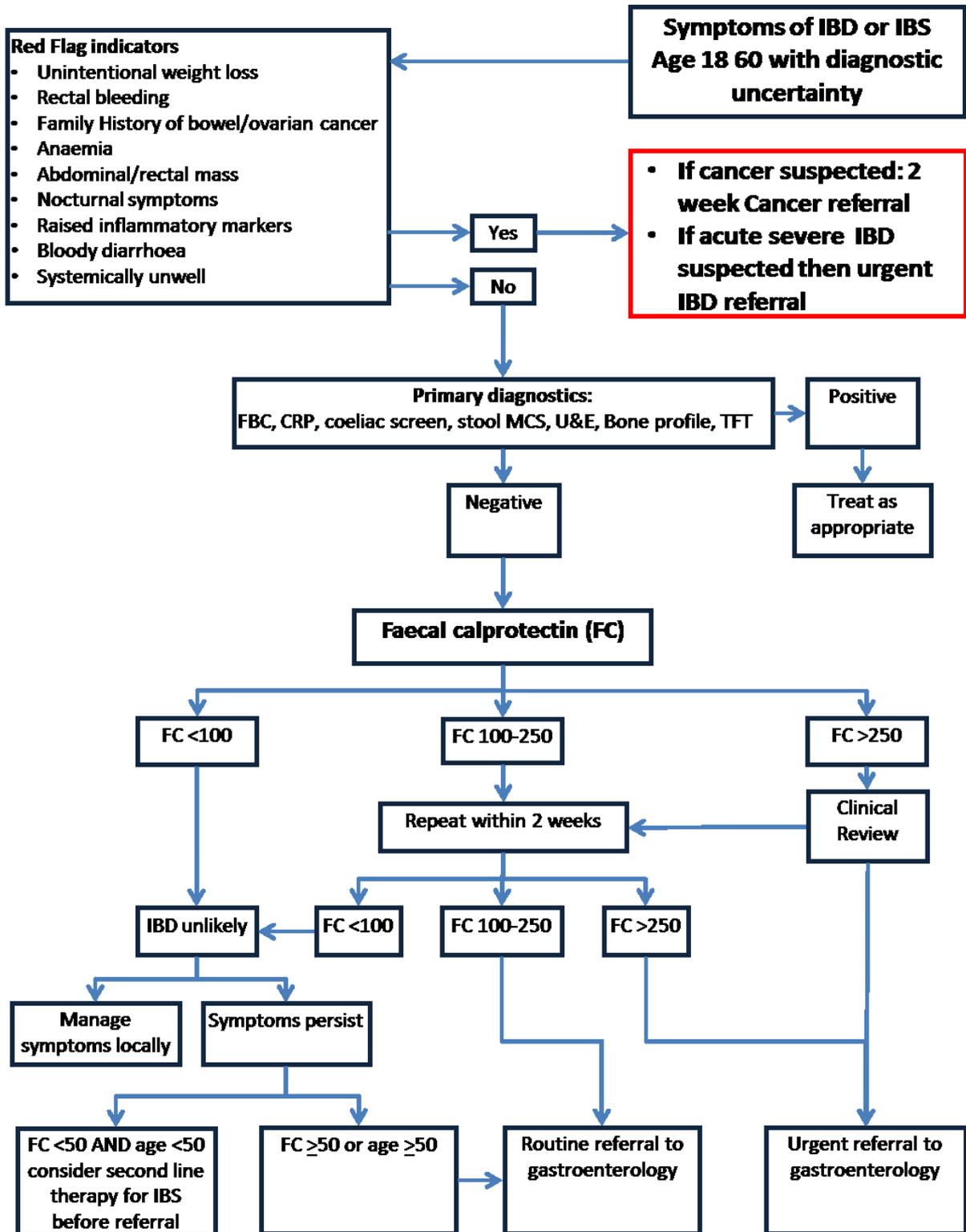
Cut-offs can only be used as a guide, and irrespective of what cut-off is used a balance between sensitivity and specificity is required; false positives and false negatives can occur (Walsham and Sherwood, 2016). If strong clinical suspicion of IBD remains following negative faecal calprotectin then referral to gastroenterology should be considered. NICE (2013) recommended that test result cut-offs should be discussed and agreed locally as part of the implementation process for this testing pathway. **The group endorse this recommendation that whilst a single cut-off may be easier to use, a balance between sensitivity, specificity and delayed treatment needs to be taken into account at a local level.**

In addition, NICE (2013) recommended research into optimal cut-off values for tests and the investigation of repeat testing strategies in people with intermediate levels of faecal calprotectin. **The group endorse this recommendation and it is hoped that this document will increase the use of faecal calprotectin which in turn will generate evidence of optimal cut-offs.**

## **8 The faecal calprotectin algorithm**

The following consensus algorithm is proposed which can be used as a template for discussion between primary care, secondary care and pathology laboratories in localities throughout the NHS:

**Faecal Calprotectin Algorithm**



This algorithm should be considered in patients aged 18-60 years presenting with lower gastrointestinal symptoms where IBS or IBD is suspected but there is

diagnostic uncertainty. It should not be used if colorectal cancer or acute severe IBD are suspected (NICE, 2015a; NICE, 2015c). GPs should refer to the NICE NG12 referral criteria for suspected colorectal cancer. Faecal calprotectin should not be used in place of NICE DG30 directed faecal immunochemical testing of haemoglobin (FIT). However faecal calprotectin may be considered in a FIT negative patient where colorectal cancer is not suspected. Since the prevalence of colorectal cancer increases with age there has been debate regarding the age group for which faecal calprotectin can be used. We judge that faecal calprotectin testing would not normally be considered in patients older than 50 years, however if colorectal cancer is not suspected then it is reasonable for GPs to apply the algorithm up to 60 years, after which the specificity and sensitivity fall (van Rheenen *et al.* 2010; Jellema *et al.* 2011 and Dhaliwal *et al.* 2015). If symptoms of ovarian cancer are suspected, especially in women of 50 years or older with symptoms of IBS then CA125 should be measured (NICE, 2011). If acute severe IBD is suspected (with symptoms such as bloody diarrhoea, systemically unwell and markedly raised inflammatory markers) then urgent referral to the IBD clinic or hospital admission should be considered (29).

If no 'red flag' indicators are present and cancer, or acute severe IBD, is considered unlikely, then primary diagnostic tests should be undertaken (such as coeliac screen, stool culture, full blood count, U&E, bone profile, TFT and CRP).

If primary diagnostics are uninformative and there is diagnostic uncertainty, it is suggested that a faecal calprotectin is requested before referral. The turnaround time of this test should be 2-3 days and the methodology is discussed below.

**Initial faecal calprotectin <100 microgram/g:** IBD is unlikely in this group of patients and should be treated as IBS with a 6 week review. If at review the patient is still symptomatic then patients over 50 years, **or** if the initial faecal calprotectin was greater than 50 microgram/g, should be referred routinely to gastroenterology. Patients under the age of 50 years where the faecal calprotectin is less than 50 microgram/L should be monitored and referred routinely to gastroenterology if the second line IBS treatment is unsuccessful. A FC<100 may also prompt the clinician to consider non-gastrointestinal, such as uro-gynaecological, disease in the differential.

**Initial faecal calprotectin 100-250 microgram/g:** Experience has shown that initial elevations at this level can be normal on repeat, and it is recommended that in this intermediate group a repeat faecal calprotectin is undertaken within 4 weeks. NSAIDs can cause false elevations of faecal calprotectin and whilst repeating faecal calprotectin after withdrawal of NSAIDs would be ideal it was thought that this would add time to the patient pathway and a pragmatic view would be to repeat whilst patient is on NSAIDs.

**Repeat faecal calprotectin:**

- FC > 250: Urgent referral to gastroenterology
- FC 100-250: Routine referral to gastroenterology
- <100: IBD unlikely, plan care as if initial FC was less than 100 microgram/g

**Initial faecal calprotectin >250 microgram/g:** Experience has shown that elevated faecal calprotectin can be lower on repeat. In undiagnosed patients, with no red flag indicators or increased signs for suspicion of acute severe IBD, with an initial faecal calprotectin >250 microgram/g patients should be clinically reviewed in primary care. If symptoms are significant or worsening then the GP should refer to gastroenterology urgently, otherwise repeat the faecal calprotectin.

**Repeat faecal calprotectin:**

- FC > 250: Urgent referral to gastroenterology
- FC 100-250: Routine referral to gastroenterology
- FC <100: IBD unlikely, plan care as if initial FC was less than 100 microgram/and treat as likely IBS if <100 on repeat

## 9 Different types of faecal calprotectin tests

Several faecal calprotectin tests are available to the NHS in England, including fully quantitative laboratory-based technologies, fully quantitative rapid tests and semi-quantitative POCTs. NICE concluded that in principle, all technologies can be used to provide a faecal calprotectin testing service to either primary or secondary care (9).

The cut-off values selected influence the diagnostic accuracy of the tests (as discussed previously). In addition some kits use cut-off values with a middle range in which results are considered indeterminate, below which are deemed negative and above which are deemed positive. Given the lack of robust evidence comparing different tests, NICE 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 (NICE, 2013). Whether the test is performed in the pathology department or by POCT, a governance infrastructure needs to be in place; United Kingdom Accreditation Service's (UKAS) accreditation should be used and Medicines and Healthcare products Regulatory Agency (MHRA) guidance should be applied for POCT (MHRA, 2013).

### 9.1 Laboratory testing

NHS pathology laboratories providing a faecal calprotectin service should be UKAS accredited (ISO 15189) for the test, providing a turnaround time of no more than three days. Although cut-off values have been proposed in this document primary and secondary care should work with the pathology laboratory to ensure that the method used produces results that would work with the proposed cut off levels. This information will be available from the laboratory verification data and External Quality Assessment (EQA) performance.

## 9.2 Point of care

NICE noted that the use of POCTs has a smaller evidence base and they are not yet widely used in routine practice. NICE 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. POCTs vary and some have pre-specified cut-offs in the design of the test or have “intermediate” levels. If a POCT device is chosen locally, users might apply local cut-offs for interpreting the results of POCT using the algorithm as a guide. However the MHRA governance structure (MHRA, 2013) should be followed, UKAS accreditation for POCT (ISO 22870, linked to ISO 15189) should be introduced, and a mechanism should be in place to ensure that the results are captured in the patient record. Apps to record symptoms in real time that are also integrated with faecal calprotectin testing at home are being developed. The potential for closer to home monitoring, prior to gastroenterology referral, is worth exploring to reduce the impact of unnecessary specialist referral and invasive investigation and this could represent a new patient care pathway. In addition, POCTs may have a role in monitoring patients diagnosed with IBD.

## 10 Further research

Whilst the increased use of faecal calprotectin will increase the knowledge base for the use of the test, the working group were cognisant of the developing use of the FIT for occult blood in colorectal cancer and its potential overlap in the diagnostic work up for patients with IBD and IBS (Jellema *et al.* 2011; Dhaliwal *et al.* 2015). Further research is encouraged on how these 2 markers could be used to assist in the diagnostic work up of bowel disorders.

## 11 Conclusion

NICE DG11 faecal calprotectin diagnostic tests for inflammatory diseases of the bowel proposed that faecal calprotectin should be used as part of the assessment of IBD and IBS (NICE, 2013). This consensus document has been developed by experts in the field to assist local health economies to introduce the NICE guidance locally with a view to improve the patient journey and reduce unnecessary referrals to endoscopy services. Increased uptake of the test should produce increased knowledge and evidence, which can be used to enhance NICE DG11.

The development of this algorithm offers significant benefits to the patient’s experience along with savings across the health economy. Its adoption by clinical colleagues is welcomed.

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## Appendix 1

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#### With special thanks to:

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NCA for Endoscopy, NHS-England

## Appendix 2

Algorithms from the following 14 early adopter sites were used in the construction of this consensus document:

- Colchester Hospital University NHS Foundation Trust
- Croydon CCG
- Durham and Dales Primary Care
- Heart of England NHS Foundation Trust
- King's College Hospital NHS Foundation Trust
- Lancashire Teaching Hospitals NHS Foundation Trust
- Northumberland Primary Care
- St George's University Hospitals NHS Foundation Trust
- Somerset NHS England
- Southampton City CCG
- South East London Area Prescribing Committee
- Telford and Wrekin CCG
- Translational Gastroenterology Unit, Oxford University Hospitals NHS Foundation Trust
- York Teaching Hospital NHS Foundation Trust