



***National Institute for
Health and Clinical Excellence***

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE**

Diagnostics Assessment Programme

**Faecal calprotectin diagnostic tests for inflammatory diseases
of the bowel**

Final scope

September 2012

1 Introduction

The Medical Technologies Advisory Committee identified the EK-CAL calprotectin ELISA test (manufacturer: Buhlmann Laboratories AG), the LF-CAL25 Quantum Blue calprotectin test (manufacturer: Buhlmann Laboratories AG) and the KST11005 CalDetect Calprotectin Rapid test (alternative name: PreventID Caldetect, manufacturer: Immundiagnostik), as potentially suitable for evaluation by the Diagnostics Assessment Programme (DAP) on the basis of two briefing notes. These technologies are designed to detect intestinal inflammation by measuring levels of faecal calprotectin (FC). FC is a protein found in the cytosol of neutrophil granulocytes (inflammatory cells) that correlates well with neutrophilic infiltration of the intestinal mucosa. FC is excreted in excess into the intestinal lumen during the inflammatory process and, therefore, can act as a surrogate marker for inflammatory disease of the lower gastrointestinal tract. The tests are intended to aid in discriminating diseases characterised by inflammation of the bowel from non-inflammatory diseases of the bowel. An important application of FC is to help discriminate inflammatory bowel disease (IBD) from non-inflammatory diseases of the bowel (many of whom are likely to be individuals with irritable bowel syndrome or IBS), with the ultimate aim of minimising the unnecessary use of endoscopy. FC has also been shown to correlate well with IBD disease activity and, consequently, may have a role in patient monitoring (by monitoring levels of lower gastrointestinal inflammation). However, clinical experts suggest that this is a relatively new development with an emerging evidence base. Therefore, given the low levels of evidence, the role of FC tests in patient monitoring is not included in the scope. The scope has been

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

The scope has been compiled using a variety of sources, including the briefing note, a request for information from manufacturers, a scoping literature review, the opinions of experts and attendees at the scoping workshop held on 03 September 2012 and input from assessment subgroup members. NICE has not carried out an independent evaluation of this information. Assumptions made in the scope will be verified in the assessment.

2 Target conditions/indications

2.1 Diseases characterised by inflammation of the bowel

Bowel inflammation can be triggered by a range of causes, including: adverse effects of drugs (for example, non-steroidal anti-inflammatory drugs), infections (for example, in diverticulitis), poor blood supply to the bowel (for example, ischemic colitis) and diseases (for example, IBD). Given the potential severity of disease and its chronic nature, an important role for FC testing is envisaged to aid in the discrimination of IBD from non-inflammatory diseases of the bowel.

IBD is a broad term used to describe conditions characterised by chronic inflammation of the gastrointestinal tract. The two main types of IBD are Ulcerative Colitis and Crohn's Disease.

Inflammatory bowel disease

Ulcerative colitis or Crohn's disease, are the two most common forms of IBD that involve chronic inflammation of the gastrointestinal tract. Together these long-term conditions are estimated to affect about 240,000 people in the UK. The incidence of ulcerative colitis is approximately 10–20 per 100,000 per year with a reported prevalence of 100–200 per 100,000. The incidence of Crohn's disease is around 5–10 per 100 000 per year (and thought to be increasing) with a prevalence of 50–100 per 100,000. There is no significant gender difference in the prevalence of inflammatory bowel diseases. IBD is more common in Caucasian people than in Afro-Caribbean people or those of Asian origin. The condition is most prevalent among Jewish people of European origin. Adults with IBD have a higher risk of developing colorectal cancer than the general population.

2.2 Symptoms and the impact of lower gastrointestinal disorders

Patients with lower gastrointestinal disorders can have similar symptoms (such as abdominal pain/discomfort, bloating, change in bowel habit, weight loss and fatigue), which can make diagnosis difficult. One in 20 general practitioner consultations are related to lower gastrointestinal disorders. Education, employment, personal relationships, social and family life can all be disrupted by the unpredictable nature of lower gastrointestinal disorders. The need for the toilet, loss of sleep, symptoms of pain, and fatigue can affect self-esteem and social functioning, particularly among the young and newly-diagnosed. A proportion of patients may follow a limited pattern of life either due to inadequate control of symptoms from poor medical management or because of the loss of self-esteem and anxiety about losing bowel control.

3 Current management and care pathway(s)

As there are a variety of possible causes of bowel inflammation, sections 3.2 and 3.3 focus on IBD (likely to be one of the most important and prevalent conditions characterised by inflammation of the bowel) and irritable bowel syndrome or IBS (likely to be one of the most important and prevalent non-inflammatory conditions of the bowel). These conditions will be used to highlight potential differences and similarities in the diagnosis and management of typical inflammatory and non-inflammatory diseases of the bowel.

3.1 Diagnostic and care pathway information

The diagnostic and care pathway information can be ascertained from existing guidelines, these include but are not limited to:

- NICE Clinical Guideline (draft) – ‘Crohn’s disease – Management in adults and children’. Anticipated publication date: Oct 2012
- NICE Clinical Guideline (CG) 61 – ‘Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care’
- British Society of Gastroenterology (BSG) guideline – ‘Guidelines on the Irritable Bowel Syndrome: Mechanisms and Practical Management’
- British Society of Gastroenterology (BSG) guideline – ‘Guidelines for the Management of Inflammatory Bowel Disease’.
- European Crohn’s and Colitis Organisation (ECCO): The second European evidence-based consensus on the diagnosis and management of Crohn’s disease: Definitions and diagnosis.

Guidelines may be supplemented with clinical expert input as appropriate in the analysis.

3.2 Diagnosis of IBS and IBD

3.2.1 Primary care

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

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

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

- Full blood count (FBC)
- Erythrocyte sedimentation rate (ESR) or plasma viscosity
- C-reactive protein (CRP)
- Antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

Of these, the two main tests for inflammation are ESR and CRP. However, these tests are not a direct indication of bowel inflammation, as they can be influenced by non-intestinal diseases, and can lack diagnostic accuracy. As a result, many patients are referred for further investigation involving endoscopy, which may not be required. CG61 states that an endoscopy (and a range of other tests) is not needed to confirm the diagnosis of IBS.

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

3.2.2 Secondary care

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

BSG guidelines on IBS suggest that tests conducted in secondary care are largely based on the likely differential diagnosis. Following initial laboratory tests (FBC, ESR, CRP, EMA and TTG – as in primary care), which may be repeated in secondary care, the next level of investigation involves endoscopy and imaging.

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

Therefore, clinical guidelines (and expert opinion concurs) suggest that patients with symptoms indicative of IBD/IBS presenting in secondary care follow a similar diagnostic pathway of initial investigations prior to receiving endoscopy (second level of testing). As in primary care, ESR and CRP are the main markers used to measure intestinal inflammation.

3.3 Management

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

The management of IBD involves diet and lifestyle interventions, pharmacological intervention and surgery. Pharmacological intervention

includes aminosalicylates, corticosteroids, thiopurines, disease-modifying anti-rheumatic drugs (methotrexate), immunosuppressants (for example, cyclosporine) and anti-TNF monoclonal antibodies (infliximab).

4 Summary and objectives of the evaluation

4.1 Summary

FC tests are designed to aid in the identification of those individuals who are at an increased risk of diseases characterised by inflammation of the bowel. Individuals with increased levels of FC, indicative of inflammation in the lower gastrointestinal tract, are referred for further investigation. Such investigation can include invasive/expensive diagnostic tests including endoscopy and imaging tests. The literature suggests that FC tests seem to perform better in adults than children and have been shown to have better diagnostic accuracy when compared to currently used markers for inflammation (ESR and CRP).

In terms of diagnosis, the main goal of testing in primary care is likely to be ruling out disease characterised by inflammation of the bowel as the prevalence of such diseases in this environment is relatively low. The main goal of testing in secondary care is likely to be ruling in disease characterised by inflammation of the bowel to justify further invasive/expensive investigation. FC testing is seen as one of a variety of tools that may be used to achieve these goals.

The management of individuals with inflammatory diseases of the bowel (for example, IBD) is significantly different to those with non-inflammatory diseases of the bowel (for example, IBS). Individuals with IBS are at low risk of incorrect diagnosis of and treatment for IBD, based on FC testing alone, because they would not receive that treatment without further investigation (however, the correct diagnosis would be delayed). There may be significant consequences for individuals with IBD who are incorrectly diagnosed with IBS and may not receive appropriate timely treatment.

4.2 Objectives of the evaluation

The objective of the evaluation is to assess the clinical and cost-effectiveness of faecal calprotectin diagnostic tests to distinguish inflammatory from non-inflammatory diseases of the bowel in primary care and secondary care. Scoping workshop feedback suggests that the following questions may be helpful in guiding this evaluation:

- Is an FC test result a reliable way of discriminating diseases characterised by inflammation of the bowel?

- How do the different cut-off values used to interpret the results of fully quantitative laboratory-based FC tests affect their cost-effectiveness? What are the optimal cut-offs for use in primary and secondary care?
- What is the cost-effectiveness of the rapid point-of-care tests included in this evaluation in primary and secondary care? How does this compare to the fully quantitative FC tests?
- How will the performance of FC tests be affected when used in primary care, given the paucity of data on the use of these tests in this environment, and what is the likely impact on cost-effectiveness?

The results of the evaluation will contribute to identifying the optimal diagnostic strategies/service delivery frameworks for FC testing in primary and secondary care. Depending on the evidence base, the guidance may make recommendations on individual tests, or groups of tests such as semi- and fully quantitative tests, or on the overall technique of FC testing in primary care and secondary care.

These objectives are discussed further in sections 5 and 6.

5 Scope of the evaluation

5.1 Population

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

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

The secondary care population will include the following sub-groups:

- Individuals previously assessed using traditional inflammatory markers (ESR and CRP)
- Individuals previously assessed using FC (for example, those who have an indeterminate FC result)
- Individuals who were not previously assessed with inflammatory markers (for example, clinical history alone)

The external assessment group (EAG) may introduce a lower age limit for the populations considered (primary and secondary care) based on the evidence base in the paediatric population.

There is uncertainty surrounding which patients should be referred from primary care and the exact role of FC testing in secondary care. This will be explored in the analysis.

5.2 Interventions

Several FC tests designed for use as fully quantitative laboratory-based technologies (the majority of which use an enzyme-linked immunosorbent assay [ELISA] platform) or as rapid point of care tests are available to the NHS in England. In principle, all technologies may be used to provide an FC testing service in either primary or secondary care. Technologies identified during scoping are summarised in Table 1. The details of these tests will be validated in the assessment conducted by the EAG.

Table 1 – Interventions identified during scoping

| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|--|--------------------------------|--|--|---------------------------------|-----------------------------------|
| Fully quantitative laboratory-based tests | | | | | |
| Buhlmann | EK-CAL calprotectin ELISA test | ELISA – quantitative Range: 10-600µg/g | Yes – CE mark | Yes – secondary care (hospital) | Yes |
| Buhlmann | EK-CAL calprotectin ELISA test | ELISA – quantitative Range: 30-1800µg/g | Yes – CE mark | Yes – secondary care (hospital) | Yes |

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| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|---------------------|---|---|--|--|---|
| Buhlmann | LF-CAL25 Quantum Blue calprotectin test | Rapid test - Immunoassay designed for the quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. For laboratory use only. Range: 30-300µg/g | Yes – CE mark | Yes – secondary care (hospital) Primary care pilot project currently in progress (Northumberland) Higher levels of evidence when compared to LF-CHR25. | Main analysis: to be assessed when used in a laboratory. The EAG may assess the use of the test as a POCT. |

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| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|--------------|--|---|---------------------------------|---|---|
| Buhlmann | LF-CHR 25 Quantum Blue calprotectin test | Rapid test - Immunoassay designed for the quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. For laboratory use only. Range: 100 - 1800µg/g | Yes – CE mark | Yes – secondary care (hospital) Lower levels of data when compared to the LF-CAL25 | Main analysis: to be assessed when used in a laboratory. The EAG may assess the use of the test as a POCT. |
| Calpro | CALPRO CALPROTECTIN ELISA TEST (ALP) – formerly known as the Phical test CAL0100 | ELISA – quantitative Range: up to 1250 mg/kg | Yes – CE mark | Yes – secondary care (hospital) | Yes |

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| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|---------------------|--|---|--|------------------------------------|-----------------------------------|
| Calpro | CALPROLAB CALPROTECTIN ELISA (ALP) – formerly known as the Phical test CALP0170 | ELISA – quantitative Range: up to 2500 mg/kg | Yes - CE mark | Yes – secondary care (hospital) | Yes |
| Eurospital | Calprest | ELISA – quantitative | Yes - CE mark | Yes – secondary care | Yes |

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| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|-----------------|---------------|--|---------------------------------|---------------------------------|--|
| Eurospital | CalFast | Rapid test - Quantitative determination of FC in combination with a dedicated reader | Yes – CE mark | Yes - secondary care (hospital) | <p>Main analysis: to be assessed when used in a laboratory.</p> <p>The EAG may assess the use of the test as a POCT.</p> |
| Immundiagnostik | ELISA (K6927) | ELISA – quantitative | Yes – CE mark | Yes – secondary care (hospital) | Yes |
| Immundiagnostik | ELISA (K6937) | ELISA – quantitative | Yes – CE mark | Yes – secondary care (hospital) | Yes |

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| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|--------------------------|-------------------|--|--|---------------------------------|-----------------------------------|
| Immundiagnostik | ELISA (K6967) | ELISA – quantitative | Yes – CE mark | Yes – secondary care (hospital) | Yes |
| Thermo Fisher Scientific | EliA Calprotectin | EliA – quantitative In contrast to ELISA, EliA measures the presence of target antibodies by fluorescence signal detection. | Yes – CE mark | Yes – secondary care (hospital) | Yes |

| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|---|--|---|--|--|-----------------------------------|
| Rapid POCTs | | | | | |
| Preventis (sister company to Immundiagnostik) | KST11005 CalDetect Calprotectin Rapid test (version 1 - Caldetect) | <p>POCT – immunochromatographic rapid test.</p> <p>A semi-quantitative test with 3 lines corresponding to: Calprotectin “negative”, Calprotectin ≤ 15 µg/g, Calprotectin 15-60 µg/g and Calprotectin > 60 µg/g stool</p> | Yes – CE mark | <p>Yes – secondary care (hospital)</p> <p>Primary care pilot project currently in progress (Durham Dale)</p> | Yes |

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| Manufacturer | Test | Platform | Available to the NHS in England | Diagnostic Accuracy Data | Included in the evaluation |
|---|---|--|--|---------------------------------|-----------------------------------|
| Preventis (sister company to Immundiagnostik) | CalDetect Calprotectin Rapid test (version 3 – CalScreen) | POCT – immunochromatographic rapid test. A yes-no test with only 1 Test-Line corresponding to the cut-off value of 50 µg/g stool (no inflammation = <50 µg/g and inflammation present = ≥50 µg/g) | Yes – CE mark | Yes – secondary care (hospital) | Yes |

Fully quantitative laboratory-based FC tests – it has been suggested that although these tests may produce slightly different results (for example, due to the different extraction buffers used during sample processing), it may be possible to group certain technologies as the clinical outcomes are highly unlikely to be significantly affected. For example, tests measuring the same antibody are likely to lead to similar sensitivity and specificity estimates and may be combined when assessing the clinical effectiveness of these technologies in the analysis. The EAG can group technologies where appropriate. Any differential costs of the individual technologies should be accounted for in the analysis (for example, the cost of the readers required for the rapid tests that are to be assessed for use in the laboratory only). Differences in the individual technologies (for example, such as type of extraction buffer used and the stool collection device) should be captured in a narrative description.

It is assumed that the capital equipment required to process the majority of these ELISA and ELiA-based tests is readily available in the majority of NHS laboratories. If needed, the manufacturer supplies the equipment required to process ELiA kits free of charge.

Multiple cut-offs – a range of cut-offs can be applied when interpreting the results of the fully quantitative FC tests as these tests provide the user with a single point estimate from a continuous scale. Generally, these cut-offs are chosen to maximise a clinical outcome, for example, high sensitivity to confidently rule-in disease for further investigation or high specificity to confidently rule-out disease or an optimal combination of the two. As such, the cut-off(s) used to interpret the results impact the diagnostic performance of the test. This principle is equally applicable and evident in the Preventis rapid POCTs. However, these tests are designed to be interpreted using pre-determined cut-offs.

Cut-offs may be a single point, such as 50 µg/g, so that values below indicate no inflammation and values equal to and above indicate inflammation is present. Multiple cut-offs may be used, such as ≤ 15 µg/g, 15-60 µg/g and > 60 µg/g, so that results indicate no inflammation, indeterminate result (likely resulting in the individual being re-tested at a later date) and inflammation present, respectively. Anecdotal evidence suggests that as many as 85 – 90% of individuals investigated using an FC test in a gastroenterology clinic will have an FC level of less than 50 µg/g (no inflammation). Of the remaining 10 – 15%, 50% of these individuals will have an indeterminate result (defined as 50 – 200 µg/g) and 50% will have a result indicating inflammation is present (defined as >200 µg/g).

It is apparent that many different cut-offs are being recommended by manufacturers, are used by clinicians and are supported by published

evidence. Therefore, the EAG should aim to recommend appropriate cut-offs for the interpretation of fully quantitative FC tests in both primary and secondary care. Such recommendations should take into account the differential aims of testing in each of these environments (stated in section 4.1) and should be based on the most cost-effective use of NHS resources.

Pilot projects – given the potential of FC tests to reduce referrals to secondary care, a number of primary care pilot projects are under way. An example of this can be seen in the support provided by the NHS Technology Adoption Centre (NTAC) for the implementation of FC testing in routine clinical practice in West Northumberland and Durham Dales Clinical Commissioning Groups (CCGs). NTAC has provided NICE with the following information:

West Northumberland CCG is using a fully quantitative test (Quantum Blue) with samples being analysed in the laboratory. It is technically possible to use this equipment as a point of care test in primary care, although it is thought unlikely that this would ever be economical in practice.

Durham Dales CCG is using a semi-quantitative point of care test (CalDetect, version 1), with the analysis being carried out in the GP Practice.

In both cases there is a high cut-off value above which the patient should be referred to secondary care, and a low cut-off value below which there is a low probability of organic disease. Between the high and low cut-off values there is an intermediate range, in which case the patient should be retested. Due to differences in the assays used there is a difference in the cut-off values used in the project sites.

A cost-consequence analysis will be performed (*by NTAC*).

Patient level data on endoscopies performed and final diagnosis is currently being collected for each result which will be used in the analysis and development of the NTAC model. Considering the lack of primary care data, in general for the tests considered above, patient level data collected by NTAC may be helpful in informing the analysis conducted for this evaluation. Although sample sizes are likely to be small, these data may help to overcome spectrum bias associated with the application of data generated in secondary care to a primary care analysis of the FC tests. It should be noted that given the nature of the patient pathway and the heterogeneity of diagnostic testing (for example, endoscopy vs. flexible sigmoidoscopy) these data may be subject to other forms of bias, such as partial and differential

verification bias, which should be considered and documented in the analysis if these data are used.

The EAG should monitor NTAC's progress (and any other suitable pilot projects/audits) during the assessment phase and, if appropriate, use their data to inform the NICE assessment.

5.3 Comparators

Markers of inflammation currently used in the NHS for individuals suspected of gastrointestinal disorders are erythrocyte sedimentation rate (ESR)/plasma viscosity and C-reactive protein (CRP). These are used in both primary and secondary care. It has been suggested that FC tests could be used instead of existing inflammatory markers.

5.4 Outcomes

Given that FC tests have been shown to lead to improved diagnostic accuracy when compared to currently used inflammatory markers (therefore, reducing the need for further, potentially expensive, investigation), short-term costs and cost-savings are likely to be of importance in this evaluation.

The health outcomes of interest are the morbidity and mortality associated with inflammatory and non-inflammatory diseases of the bowel, and their diagnosis and management. Outcomes associated with health-related quality of life, such as, adverse events associated with endoscopy or inappropriate treatment are likely to be relevant in this assessment given the chronic nature of the conditions considered.

5.5 Healthcare setting

These tests may be used in both primary and secondary care.

Although FC testing is anticipated for use as an initial laboratory investigation in both primary and secondary care, the exact place of FC testing and support for a primary care service is not well established. Equally, the role of FC testing in secondary care for an individual who has already received an FC test in primary care requires careful consideration. FC service delivery strategies are considered further in section 6.

6 Modelling approach

6.1 Existing Models

Very few models assessing the use of FC tests have been identified. Many are basic anecdotal assessments conducted at a local level, often in a secondary care gastroenterology clinic. An economic analysis on the value of

calprotectin in screening out irritable bowel syndrome in primary care (CEP09041 [2010]) was commissioned by the Centre for Evidence-based Purchasing (CEP). This analysis evaluated the use of FC compared with ESR and CRP. In addition, a comparison of laboratory-based FC testing with POC FC testing was undertaken. This was a cost-effectiveness analysis that reported the incremental cost per correctly diagnosed IBD and IBS patient. A poster was forwarded by Thermo Fisher Scientific detailing a cost-effectiveness analysis based on amendments to the CEP economic analysis.

6.2 Model structure

Published studies that measure the clinical utility of FC tests using a prospective study design that follow patients from initial diagnosis through to final health outcomes have not been identified during the scoping phase. Consequently, it is likely that a linked evidence approach will need to be used in the modelling. That is, outcomes of the diagnostic tests to be assessed will need to be related to changes in final health outcomes.

6.3 Diagnostic strategy/Service delivery framework

Although FC testing is anticipated for use as an initial laboratory investigation in both primary and secondary care, the exact place of FC testing and support for a primary care service is not well established. Clinical experts suggest that 2 main models may be used:

- 1) primary care to use rapid POC FC tests independently of any input from secondary care/labs
- 2) primary care led strategies supported by specialist input (for example, clinical biochemists who process and interpret the test in the lab, and gastroenterologists).

It is anticipated that there will be important trade-offs between these 2 models. For example, model 1 is likely to cost less than model 2, but, the specialist support provided in model 2 may lead to improved diagnostic performance of FC tests when compared to model 1.

Equally, the role of FC testing in secondary care for an individual who has already received an FC test in primary care requires careful consideration. While acknowledging the variation in clinical expert opinion it has been suggested that individuals with an indeterminate FC test result from primary care will be retested for FC in secondary care to ensure further invasive/costly investigations are justified. Those individuals with a negative or positive FC test would not likely be retested in secondary care. In addition, those individuals who received a rapid FC test would have a repeat FC test using a fully quantitative technology to better understand the level of bowel

inflammation. Given the variation in clinical opinion, the EAG should explore the optimal role of FC testing in secondary care for individuals who have previously been tested for FC in primary care.

A variety of plausible diagnostic strategies/service delivery frameworks emerge and should be investigated in the assessment with a view to allowing recommendations to be formulated on optimal set-ups. Such strategies include:

Strategy 1

- a. GP/Nurse identifies appropriate patients and independently uses a rapid POC FC test.
- b. GP/Nurse refers patients as appropriate to secondary care (gastroenterologist) based on the FC test result and other clinical factors. Majority of FC test negative (indicative of non-inflammatory diseases of the bowel) patients are managed in primary care; those with inadequate symptom control are eventually referred to secondary care. Individuals with an indeterminate test result are retested within 6 weeks by the GP/nurse, if result is still indeterminate then the individual is referred to secondary care.
- c. Hospital consultant repeats the FC test where appropriate (to be explored by the EAG). FC tests are used to confirm the need for further investigation or aid diagnosis.

Strategy 2

- d. GP/Nurse identifies appropriate patients and independently uses a rapid POC FC test
- e. Where there is uncertainty in the diagnosis, the GP/Nurse refers the case (for example, using 'choose and book'), to a clinical biochemist for assistance in interpreting the result.
- f. GP/Nurse refers patients as appropriate to secondary care based on FC test result and other clinical factors. Majority of FC test negative (indicative of non-inflammatory diseases of the bowel) patients are managed in primary care; those with inadequate symptom control are eventually referred to secondary care. Individuals with an indeterminate test result are retested within 6 weeks by the GP/nurse, if result is still indeterminate then the individual is referred to secondary care.

- g. Hospital consultant repeats the FC test where appropriate (to be explored by the EAG). FC tests are used to confirm the need for further investigation or aid diagnosis.

Strategy 3

Same as strategy 2, but, in bullet point 'b' the GP/Nurse refers the case (for example, using 'choose and book') to a gastroenterologist for assistance in interpreting the FC test result in a clinical context.

Strategy 4

- a. GP/Nurse identifies appropriate patients and sends samples to a laboratory for a fully quantitative or rapid FC test to be conducted.
- b. The lab processes the test and results are interpreted by a clinical biochemist - a report is sent to the GP/nurse.
- c. GP/Nurse refers patients as appropriate to secondary care based on the report. Majority of FC test negative (indicative of non-inflammatory diseases of the bowel) patients are managed in primary care; those with inadequate symptom control are eventually referred to secondary care. Individuals with an indeterminate test result are retested within 6 weeks by the GP/nurse, if result is still indeterminate then the individual is referred to secondary care.
- d. Hospital consultant repeats the FC test where appropriate (to be explored by the EAG). FC tests are used to confirm the need for further investigation or aid diagnosis.

Strategy 5

Same as strategy 4, but, in between bullet points 'b' and 'c' the following step is included - GP/Nurse has the option to refer the case (for example, using 'choose and book'), where there is uncertainty in the diagnosis, to a gastroenterologist for assistance in interpreting the result in a clinical context.

Strategy 6

- a. GP/Nurse identifies appropriate patients and refers cases to a gastroenterologist (for example, using 'choose and book').

- b. The gastroenterologist reviews the case and, if appropriate, forwards a stool sample collection kit to the GP/patient.
- c. A sample is sent to the gastroenterologist/lab for processing. Test results are initially interpreted by a clinical biochemist in the lab and then by a gastroenterologist (who provides clinical context). The gastroenterologist sends a report to the GP/nurse.
- d. GP/Nurse refers patients as appropriate to secondary care based on the report. Majority of FC test negative (indicative of non-inflammatory diseases of the bowel) patients are managed in primary care; those with inadequate symptom control are eventually referred to secondary care. Individuals with an indeterminate test result are retested within 6 weeks by the GP/nurse, if result is still indeterminate then the individual is referred to secondary care.
- e. Hospital consultant repeats the FC test where appropriate (to be explored by the EAG). FC tests are used to confirm the need for further investigation or aid diagnosis.

The EAG may amend/add to the strategies identified above. While the strategies above focus on primary care, the EAG will also need to explicitly model the impact of FC testing in secondary care.

6.4 Cost considerations

It is assumed that the capital equipment required to process the fully quantitative laboratory-based FC tests is readily available for ELISA based tests in the majority of NHS laboratories or supplied free of charge by the manufacturer for ELiA based tests. Where there are significant fixed costs associated with a test these should be accounted for in the analysis. For example, the Quantum Blue and CalFast tests require a reader to process the test; this is likely to impact the use and resulting cost-effectiveness of these test. The NICE costing team estimate the average cost of a faecal calprotectin test to be between £14.37 and £17.28 (excluding labour).

6.5 Health outcomes

Health outcomes will need to be calculated as QALYs in the economic modelling.

7 *Equality issues*

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

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

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

8 *Implementation*

Support tools are developed by the implementation team at NICE. The implementation team does not get involved in developing the guidance recommendations but works alongside the guidance-producing programme, the communications team and field based teams to, amongst other things, ensure intelligent dissemination of NICE guidance to the appropriate target audiences.

Commissioners will need to know whether there are significant non-recurrent set-up costs associated with the introduction of the interventions listed in Table 1, particularly where these are likely to influence the location of services or the size of population they would need to serve. They are also likely to be interested in implementation advice that describes and supports the optimal diagnostic strategies/service delivery frameworks emerging from the evaluation.

Appendix A Related NICE Guidance

Published

- Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. NICE clinical guideline CG61 (2008). Available from: <http://guidance.nice.org.uk/CG61> Date for review: July 2014.
- Faecal incontinence: the management of faecal incontinence in adults. NICE clinical guideline CG49 (2007). Available from: <http://guidance.nice.org.uk/CG49> Date for review: July 2013.

Under development

- SeHCAT (Tauroselcholic [75Selenium] acid) for the investigation of bile acid malabsorption (BAM) and measurement of bile acid pool loss. NICE diagnostics guidance. Expected: November 2012. <http://guidance.nice.org.uk/DT/8>
- Ulcerative colitis (referred to NICE for Quality Standard development)

Appendix B References

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**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE**

DIAGNOSTICS ASSESSMENT PROGRAMME

Equality impact assessment – Scoping

**Faecal calprotectin diagnostic tests for inflammatory
diseases of the bowel**

The impact on equality has been assessed during this assessment according to the principles of the NICE Equality scheme.

1. Have any potential equality issues been identified during the scoping process (scoping workshop discussion, assessment subgroup discussion), and, if so, what are they?

Yes. The following has been listed in section 7 of the scope:

‘People with chronic diarrhoea may be classified as having a disability and therefore be protected under the Equality Act 2010.

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

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

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

2. What is the preliminary view as to what extent these potential equality issues need addressing by the Committee?

The clinical effectiveness of the faecal calprotection tests is unlikely to be affected by the sex or family origin of the patient and therefore, no population sub-groups relevant to these protected characteristics were included in the scope.

3. Has any change to the draft scope been agreed to highlight potential equality issues?

The scope has not been amended.

4. Have any additional stakeholders related to potential equality issues been identified during the scoping process, and, if so, have changes to the stakeholder list been made?

None identified.

Approved by Associate Director (name): ...Nick Crabb.....

Date: 21/09/2012