

Is NICE too Optimistic about Savings from Normal Faecal Calprotectin Results?

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ABSTRACT

BACKGROUND: A recent systematic review confirmed the utility of faecal calprotectin (FC) in distinguishing organic (inflammatory bowel disease) from non-organic gastrointestinal disease (irritable bowel syndrome). FC levels <50 mcg/g have a negative predictive value >92% to exclude organic GI disease. Levels >250mcg/g correlate with endoscopic IBD disease activity; sensitivity 90%. This study aimed to determine clinical outcomes in those with a normal FC result. A retrospective study of FC testing in primary and secondary care.

METHOD: Adults (>16 years old) with FC results between July 2012 - October 2013 were reviewed. Clinical data was collected from hospital databases and General Practitioners (GPs). GPs were

provided with a referral pathway prior introduction of FC in 2012. Clinical data at 12 months post index FC test was available in 275 patients; 208 normal, 41 intermediate and 26 raised results.

RESULTS: A new IBD diagnosis was made in only 1% of patients with a normal FC result. Conversely, a new IBS diagnosis was made in a further 40% of normal FC results referred to secondary care. Despite a normal FC and referral guidance, 40% of patients were still referred to secondary care.

CONCLUSIONS: Normal FC testing remains a useful test in excluding organic GI conditions, although 40% were still referred to secondary care despite a normal FC. Despite a normal FC, 6% still remained in secondary care at 12 months without a new diagnosis.

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Key Words: Faecal Calprotectin; IBD; NICE

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INTRODUCTION

Calprotectin is a calcium binding protein, of the S100 family, found in neutrophils and white blood cells^[1]. Inflammation of the bowel results in neutrophil activation and a subsequent release of calprotectin^[2,3]. The use of faecal calprotectin (FC) as a non-invasive biomarker in the initial screening, and monitoring of patients with suspected or known inflammatory bowel disease (IBD) has come to the fore in recent years^[4]. It is of particular use in the distinction between inflammatory GI conditions such as IBD, from non-organic conditions such as irritable bowel syndrome (IBS)^[5].

Current NICE and manufacturer guidelines for the cut of levels of FC in assays are that levels of less than 50mcg/g of faeces suggest that there is no active inflammation present within the GI mucosa^[5,7]. NICE reported that for most of the studies that they reviewed sensitivity and specificity were over 80%, where a cut-off of 50mcg/g was used, and most positive and negative predictive values were 70-90%^[7]. One recent study found that a cut-off of 50mcg/g gives a sensitivity and specificity of 88% and 78% respectively, with a negative predictive value of >92% to exclude organic GI disease^[8]. A cohort study involving consecutively referred new patients with chronic diarrhoea proposed that a cut-off of 8mcg/g provides 100% sensitivity in detecting organic disease but at the cost of poor specificity^[9]. In this study, no patients were diagnosed with IBD with FC levels of 50ug/g or less, although this was a small study hence few patients with IBD. A systematic review of the use of FC, which informed the National Institute of Health and Care Excellence diagnostic assessment group, found that most of the available evidence for FC use in IBD is based on a cut-off value of 50mcg/g which reduces the number of false negatives whilst maintaining cost effectiveness^[5,7].

NICE's guidance states that a small subgroup of patients with a normal FC result with ongoing symptoms, may need exclusion of other causes such as bile salt malabsorption (BSM). The aim of this study was to determine the 12 month clinical outcomes of patients with a normal FC value.

MATERIALS AND METHODS

FC samples

FC test results from July 2012 to October 2013 in the University Hospital Coventry & Warwickshire (UHCW) pathology database were reviewed. 495 patients were identified; 52 paediatric patients (aged < 16 years) were excluded. Of the remaining, there were 365 (82%) with a normal FC result (<50mcg/g).

Clinical data collection

Clinical information was collected from review of the UHCW clinical results reporting system and the corresponding systems in Warwick and George Eliot Hospitals. If no information was found then general practitioners (GPs) were contacted for further details.

Due to the heterogenous nature of the data collection sources, clinical details such as symptoms and medication which may affect FC values (e.g. NSAIDs or PPIs) were often unavailable or poorly recorded. These factors were not considered here due to paucity of data.

No long term clinical information could be found for 157 of the 365 normal result. This left a population of 208 normal results from our initial cohort (Figure 1).

FC sample analysis

Standardised laboratory protocol at UHCW for FC analysis was used. 100mg of stool was weighed and dispensed into an analysis pot using a 10uL inoculation loop. As per local protocol, first morning sample was requested. The exact weight was recorded and 5ml of extraction buffer added. The samples were then vortexed for 30 minutes in order to ensure complete dissolution, and then centrifuged using an Eppendorf centrifuge. The supernatant was then removed for analysis using the Immunodiagnostik PhilCal ELISA method.

Ethics

Ethical guidance was obtained from the Coventry and Warwick NRES

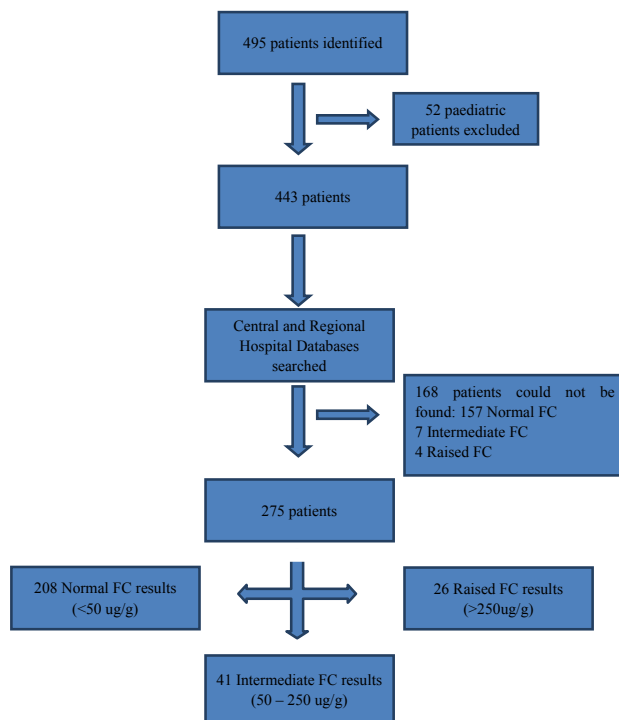


Figure 1 Flow chart of FC test patients.

Table 1 Patient demographics of normal FC results.

	FC <50mcg/g
Mean Age (SD)	38 (13)
Male:Female (%)	35:65
Mean FC mcg/g (SD)	22 (5.0)
Referred to secondary care (%)	66
Remain in secondary care at 12 months post index FC (%)	9.1
Pre-existing IBD (%)	3.4
New diagnosis IBD (%)	1.0
Other organic GI diagnosis (%)	13
Diagnosis IBS (%)	40
Undiagnosed or awaiting diagnosis (%)	42

Committee. As this study was evaluating a test already in clinical practice, no further ethical approval was required.

RESULTS

The mean age of the cohort with normal FCs was 37.8 years (SD 13.4) with a range of 18 to 84 years of age. There were 73 males (35%) and 135 females (65%). 40% of patients who underwent FC testing were aged 40 years or older; not in accordance with local prescribed guidelines (Figure 2). NICE recommends an age of 50 years as a red flag for change in bowel habit in their IBS guidelines, taking this into account, 19% of patients undergoing FC testing within our cohort were aged 50 or over. See table 1 for a full description of the results.

The lowest value the FC ELISA assay can detect is 20mcg/g, with lower results reported as <20mcg/g. For the purpose of data analysis any result recorded as this was taken to equal 20mcg/g. The mean FC for the normal cohort was 22mcg/g (SD 5.0).

Of the 208 with normal FC results, 77 (37%) patients underwent a colonoscopy, 37 (18%) a CT scan and 46 (22%) an MRI. In total, 46% underwent investigations with normal FC, some having more than one investigation.

66% of patients with a normal FC result were still referred to secondary/tertiary gastroenterology care by their primary care

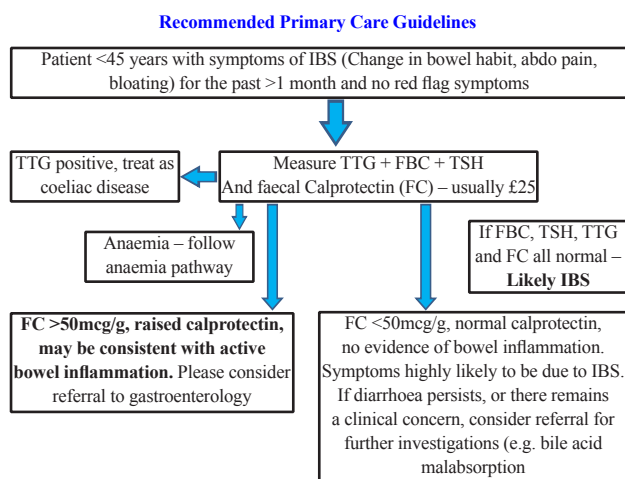


Figure 2 Local Guidance for GPs to determine utility of FC in those with chronic diarrhoea. Faecal Calprotectin – a new test for bowel inflammation.

- Do NOT use FC for ?bowel cancer
- Do NOT use FC for ?infection
- DO give your patient a stool pot; a 2p sized amount of sample is sufficient (solid stool best if possible)
- DO ask them to bring it to their local hospital/GP to send to BIOCHEMISTRY (not microbiology) – stable at room temp
- DO fill in as much clinical info as you can, incl. symptoms and duration
- DO send a SEPARATE sample to microbiology for M,C+S unless infection has already been excluded

physicians, with only 26% managed in primary care. 3.4% were known IBD patients (in remission) under ongoing secondary care for their condition.

8% of patients ($n=17$) with a normal FC result did not have clinical details provided by their GP practice. There was no additional information derived from central and regional hospitals and so it was assumed these patients were not referred to secondary/tertiary care. Their diagnoses are not known, although as they have not required further investigations or specialist care, it could be assumed that they are likely to have had a non-organic diagnosis such as IBS.

Twelve months after their initial FC test only 9.1% of the cohort were still under secondary gastroenterology care for their conditions, of which 7 (3.4%) were known IBD patients in remission.

There were two new diagnoses of IBD in the normal FC cohort (1.0%). A further 40% were diagnosed with IBS in secondary care, 13% with other organic GI conditions including BSM, Diverticular Disease and infectious gastroenteritis. A final diagnosis was not available in 42% due to either no information being returned by the contacted GPs (8.2%) or no formal diagnosis being made in secondary care (34%).

DISCUSSION

NICE guidelines on FC usage do not currently set an age cut-off for FC testing. The NICE IBS guidelines uses an age cut-off >50 as a red flag for change in bowel habit. Local guidelines are that FC testing should not be used over the age of 40 due to the rising incidence of bowel cancer. Rather, such patients with a change in bowel habit or diarrhoea should undergo endoscopic investigation.

In this study, over 90% of those without data from GPs had normal FC results (157 out of 168). If we carry out a sensitivity analysis by adding those to the numbers in section 3, that would suggest that the proportion referred with normal FC would be about 40% rather than 66% - still higher than anticipated by NICE. Of the 208 patients with

a normal FC result one third went on to have a colonoscopy, whereas NICE would not expect any with normal FC to have that. Our regional guideline states that if symptoms persist despite a normal FC result conditions such as bile salt malabsorption (BSM) may require exclusion. Of those referred to secondary care with a normal FC, 40% had a new diagnosis of IBS and 13% with an organic bowel condition (including BSM and diverticular disease), 42% received no formal diagnosis and 4% were known IBD patients.

The mean age of patients undergoing FC testing was 39 years, with 40% older than 40 years and 19% older than 50 years (4 patients (1.5%) were those with IBD, monitored by FC testing). The oldest patient to undergo FC testing was 89 years. This would suggest that there needs to be greater education and awareness about the strengths and limitations of FC testing in aiding with diagnosis or exclusion of organic GI diseases, principally IBD.

This study lends further support to the potential utility of FC as an initial screening tool to aid in excluding organic GI conditions, principally IBD, when testing is performed in accordance with guidance (local or national). By 12 months, only two patients (1%) with a FC value of <50 mcg/g had a new histologically proven diagnosis of IBD, compared to 19% of those with an intermediate result (50-250mcg/g) and 38% of those with levels >250 mcg/g. It also shows that ~6% of patients with a normal FC result are in secondary care 12 months post index FC – but without a new diagnosis. Those with an intermediate result have an approximately threefold increase in ongoing secondary care at 12 months (34%) and an eight fold increase for raised results (73%).

A limitation in this study is the heterogenous clinical data collected across three different sites which led to no long-term clinical information being available for 157 individuals, with a normal FC result, who did not seem to have been referred to secondary care. Another limitation was that FC tests were requested from both primary and secondary care. During the NICE appraisal the issue of spectrum bias was raised because most of the studies in the assessment report^[5] came from secondary care settings. Unfortunately the numbers of patients in our study, and the lack of data on long-term outcomes on a substantial number of those with normal results, make it impossible for us to analyse screening parameters such as NPV, separately by source.

The high proportion referred to secondary care despite a normal FC, whether the observed 66% or the 40% from the sensitivity analysis, must cast doubt on the assumption made in the NICE appraisal that if GPs had access to FC testing to help distinguish IBS from organic disease, referrals to secondary care would be considerably reduced, resulting in savings. Our data suggest that savings might be less than expected.

Further studies with adherence to a protocol for testing would be needed to determine the long term clinical outcomes in patients undergoing FC testing in both primary and secondary care, particularly intermediate results. Considerable numbers of investigations were undertaken in patients with normal FC possibly suggesting that physicians are uncertain of the merits of FC in screening out organic disease despite the 1% pick up rate of IBD in our series.

The analytical technique to measure FC such as the ELiA method may also influence long term clinical outcome. This study however suggests that at 1 year the chance of developing IBD with a normal FC is 1% compared with 19% and 38% with intermediate and high FC values respectively. It also further affirms that those with a normal FC can be managed in primary care once other causes of diarrhoea such as bile acid diarrhoea have been excluded (in those with persisting symptoms).

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