

Faecal calprotectin delivers on convenience, cost reduction and clinical decision-making in inflammatory bowel disease: a real-world cohort study

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Key words

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Abstract

Background: Faecal calprotectin (FC) is an accurate biomarker of disease activity in inflammatory bowel disease (IBD), yet the cost/resource implications of incorporating FC into 'real-world' practice remain uncertain.

Aim: To evaluate the utility of FC in clinical decision-making and on healthcare costs in IBD.

Methods: Retrospective data, including colonoscopy/other investigations, medication, admission and surgical data, were collected from hospital records and compared between two groups: pre-FC historical cohort (2005–2009) where colonoscopy was used to assess IBD activity versus the cohort where FC was used first instead (2010–2014). Post-test costs were also compared.

Results: A total of 357 FC tests (246 patients, 2010–2014) and 450 colonoscopies (268 patients, 2005–2009) were performed. On subsequent review, both FC and colonoscopy (in their respective cohorts) were associated with changes in management in 50.7 versus 56.2% ($P = 0.14$), respectively, with similar proportions of subsequent IBD-related investigations within 6 months (21.8 vs 21.9%, $P = 1.0$).

Prior to FC availability (2005–2009), a colonoscopy for disease reassessment cost AU\$606 578 (cost per patient-year \$1887.34) versus AU\$282 048 (cost per patient-year \$968.60) when FC ± colonoscopy was used (2010–2014). Within the FC cohort, 73.6% did not proceed to colonoscopy within 6 months post-FC, and 60.6% had not undergone colonoscopy post-FC by the end of follow up (median 1.8 years (0.1, 4.6) post-FC). Those with FC ≥ 250 were scoped earlier than those with FC < 100 $\mu\text{g/mL}$ (median 0.49 vs 1.0 years, $P = 0.03$).

Conclusion: Introduction of FC into routine IBD care aided changes in clinical management in a similar proportion, yet at potentially half the total cost, compared to a historical colonoscopy-only cohort at the same centre.

Introduction

Faecal calprotectin (FC) is the most widely used, neutrophil-derived protein biomarker of intestinal inflammation worldwide. It is highly sensitive, reliable and non-invasive,¹ with demonstrated utility in differentiating inflammatory versus non-inflammatory causes of diarrhoea (e.g. inflammatory bowel disease (IBD) vs irritable bowel syndrome),^{2,3} monitoring response of patients with IBD on therapy (i.e. disease activity, risk of

relapse)^{4,5} and as a surrogate assessment of mucosal healing and/or post-operative recurrence.^{4,6}

Recently, FC has also been shown to correlate strongly with histological activity;^{7,8} nevertheless, colonoscopy remains the gold-standard assessment tool in IBD.⁹ The evolving mantra of 'treat to target' in IBD necessitates regular and frequent disease assessment to ensure that treatment is optimised and delays are minimised wherever possible. For instance, recent expert guidelines, such as STRIDE,¹⁰ suggest that disease activity should be reassessed as frequently as every 3–6 months. Apart from the imposition on patients with the inherent risks, inconvenience and invasiveness of colonoscopy, there are increasing concerns over access and cost in many countries given the growing numbers of colonoscopy procedures required for bowel cancer screening

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programmes in ageing populations, together with increasingly strained healthcare budgets.^{11,12}

Therefore, in this study, we aimed to evaluate the utility of FC in patients attending a specialist IBD clinic over the first 5 years of its availability in comparison to a historical 5-year cohort of patients attending the same clinic before calprotectin testing was available, when colonoscopy was the primary disease activity assessment tool used. Moreover, the study aimed to assess the effect of FC testing on subsequent investigations undertaken, with particular reference to colonoscopy and the potential cost savings availed by FC in a routine, real-world IBD clinic setting.

Methods

Setting

Prospectively acquired databases for all colonoscopies and FC tests conducted in confirmed IBD patients at Eastern Health, Melbourne – a network of metropolitan hospitals serving a catchment population of nearly one million with a specialist IBD service – were interviewed retrospectively for this study.

Data collection

Two patient groups were therefore captured and then compared from the same centre. The study group of interest was all patients with confirmed IBD who had FC performed for disease activity (re)assessment during a 5-year period, the first 5 years that FC was available at our centre (between 1 January 2010 and 31 December 2014 inclusive). The second comparator group was a historical cohort of all patients with confirmed IBD who had colonoscopy performed for disease activity (re)assessment in the preceding 5-year period (between 1 January 2005 and 31 December 2009 inclusive) prior to the availability of FC at the study centre.

Data extracted also included patient demographics and baseline clinical and treatment data at the time of index FC or colonoscopy examination in the aforementioned periods. Thereafter, the clinical course was analysed for occurrence of IBD flares, hospitalisation(s) and surgery(ies) but also for changes in management and/or further investigations (including any gastrointestinal imaging, such as computed tomography, magnetic resonance imaging, X-ray or contrast enema/follow-through and/or capsule endoscopy), plus colonoscopy for disease activity assessment post-FC, until the end of the respective 5-year period.

Faecal calprotectin, colonoscopy assessment and/or other investigation data

FC concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (*Buhlmann EK-Cal*, Schönenbuch, Switzerland). Local laboratory cut-off values comparable with those reported elsewhere in IBD cohorts were applied, with a result deemed 'negative/normal' if FC <100 µg/mL, 'positive' if FC ≥100 µg/mL and 'definitely/highly positive' if FC ≥250 µg/mL.^{13–16}

Colonoscopic assessment of disease activity was deemed 'active' when there was macroscopic evidence for inflammation consistent with the underlying IBD diagnosis, that is, a simple endoscopy score ≥ 3 or Mayo endoscopy score ≥ 1 for Crohn disease (CD) and ulcerative colitis (UC) respectively. In each case, for both colonoscopy and FC data, patients with antecedent causes for inflammation, such as concurrent infections (either suspected or confirmed microbiologically) or gastrointestinal malignancy, were excluded from the study. Also in relation to colonoscopy use data in both the 2005–2009 and 2010–2014 cohorts, only colonoscopies performed for disease activity assessment, not those performed solely for dysplasia/cancer surveillance or other indications, were included in the study. If a colonoscopy was determined to have been performed for multiple indications, including disease activity assessment, this was included.

Impact of faecal calprotectin on subsequent clinical decision-making

The effect of FC testing on contemporaneous clinical decision-making was assessed by the study investigators who determined whether any 'change in management' was initiated at each patient's next clinic visit at the study institution as long as this visit occurred within 3 months of the date of FC testing. Both escalation(s) of therapy, defined as one or more of an increased treatment dose/frequency, additional therapy or step-up in therapy, and de-escalation(s), defined as reduction in dose/frequency, step down or cessation of therapy, were counted as a change in management, as was the decision to refer for a surgical intervention (i.e. resection).

Cost analysis

Cost analyses were conducted by examining the costs directly associated with FC at the study centre (AU\$ 50.00 as of 31 December 2014) and the total reimbursement amount payable for a colonoscopy as a day procedure at a government-funded (public) hospital in the

study city (AU\$1347.95 as per Department of Health Victoria's weighted inlier equivalent separation reimbursement amount as of 31 December 2014).¹⁷

Furthermore, in relation to the cost comparison between the two cohorts, in order to assess whether any confounding due to the differential 5-year periods existed, a sensitivity analysis was performed

independently by one study investigator (DvL). By reviewing each case at the time of FC testing and incorporating the clinical context for each patient when FC was recommended, a decision was made whether, in the absence of availability of FC, a colonoscopy for disease activity assessment would have been performed, with a high degree of certainty. This provided an additional,

Table 1 Patient characteristics

Baseline demographics	Colonoscopy cohort (2005–2009)	Calprotectin cohort (2010–2014)	P value
<i>n</i> (per patient)	268	246	
Male gender, <i>n</i> (%)	145 (54.1)	112 (45.5)	NS
Median age (range) (years)	38.6 (18, 80)	46.4 (18, 94)	<0.01
CD as IBD subtype	148 (55.2)	178 (72.3)	<0.01
Median disease duration (range) (years)	5.3 (0.1, 41)	10.0 (1, 47)	<0.01
Montreal classification (CD)			
Disease location			
Ileal (L1)	30 (20.3)	56 (31.5)	NS
Colonic (L2)	59 (39.9)	66 (24.7)	NS
Ileocolonic (L3)	59 (39.9)	123 (46.1)	NS
Isolated UGI (L4)	10 (6.8)	12 (4.5)	NS
Disease behaviour			
Non-stricturing, non-penetrating (B1)	76 (51.4)	156 (58.4)	NS
Stricturing (B2)	38 (25.7)	63 (23.6)	NS
Penetrating (B3)	34 (23.0)	48 (18.0)	NS
Montreal classification (UC)			
Disease location			
Proctitis (E1)	17 (14.3)	13 (14.4)	NS
Left-sided colitis (E2)	54 (45.4)	32 (35.5)	NS
Extensive colitis (E3)	48 (40.3)	45 (50.0)	NS
Disease severity			
Inactive (S0)	17 (14.3)	21 (23.3)	NS
Mild (S1)	45 (37.8)	29 (32.2)	NS
Moderate (S2)	36 (30.3)	21 (23.3)	NS
Severe (S3)	21 (17.6)	19 (21.1)	NS
<i>n</i> (per test)	450	357	
Medication at time of FC/colonoscopy			
Aminosalicylate	210 (46.7)	139 (38.9)	NS
Immunomodulator	182 (40.4)	204 (57.1)	<0.01
Systemic corticosteroid	109 (24.2)	47 (13.2)	<0.01
Anti-TNF biological	48 (10.7)	91 (25.5)	0.03
C-reactive protein ≥ 3 mg/L at time of FC or colonoscopy (%)	219 (48.9)	168 (47.1)	NS
Further investigation(s) within 6 months post-FC or colonoscopy (excluding colonoscopy) [†]	26/210 (13.1)	24/354 (6.3)	0.03
Further investigation(s) within 6 months post-FC or colonoscopy (including colonoscopy) [†]	46/210 (21.9)	77/354 (21.8)	NS
Change in management occurred at next clinic review post-FC or colonoscopy [†]	253 (56.2)	181 (50.7)	NS
Median follow up (years) to end of respective 5-year period post-FC or colonoscopy	1.7 (0.1, 5.0)	1.8 (0.1, 4.6)	NS

[†]Including one or more of treatment escalation/de-escalation/cessation, switch to alternative IBD medication and/or decision to proceed to bowel resection. [‡]Including enteroscopy, capsule endoscopy, CT/MRI/IUS/contrast-enhanced imaging studies (\pm repeat) colonoscopy where indicated). CD, Crohn disease; CT, computed tomography; FC, faecal calprotectin; IBD, inflammatory bowel disease; IUS, intraoperative ultrasound; MRI, magnetic resonance imaging; NS, not significant; TNF, tumour necrosis factor; UC, ulcerative colitis.

conservative (albeit hypothetical) comparator group for assessing a potential cost difference between the utility of FC ± colonoscopy versus colonoscopy alone.

Statistical analysis

All statistical analyses were performed using IBM SPSS software version 20 (Chicago, IL, USA). Proportions were compared with Fisher's exact tests, and continuous variables were assumed to be non-parametric throughout, expressed as medians with ranges and compared with Mann–Whitney tests. Cost per patient-year was calculated as the total cost of investigations incurred across all patients in the cohort divided by the total cumulative years of follow up in which the investigation occurred. A *P*-value was deemed to be significant at the level of <0.05.

The study was approved by the Eastern Health Human Research Ethics committee.

Results

Characteristics of patient cohort

A total of 357 FC tests (in 246 patients) and 450 colonoscopies (in 268 patients) were performed implicitly for the assessment of IBD activity in the 5-year periods of 2010–2014 and 2005–2009 respectively. The characteristics of the two patient cohorts are shown in Table 1.

Overall, 136 (38.0%) FC tests were 'negative/normal' (<100 µg/mL), 221 (61.9%) were 'positive' (≥100 µg/mL) and, of these, a subgroup of 151 tests (42.2%) were in the 'definitely/ highly positive' (≥250 µg/mL) range.

Impact on clinical decision-making (FC vs colonoscopy)

Within the FC cohort (2010–2014), FC was associated with a similar proportion of changes in management at the subsequent clinic review compared to those associated with colonoscopic assessment (latter within the 2005–2009 cohort), (50.7 vs 56.2%, *P* = 0.14) and a similar proportion of subsequent IBD-related investigations within 6 months (21.8 vs 21.9% in the respective cohorts, including (repeat) colonoscopy, *P* = 1.0). However, when excluding colonoscopy as a subsequent investigation, there was a reduced proportion of other GI investigations performed within 6 months post-FC than post-colonoscopy in the respective cohorts (6.3 vs 13.1%, *P* = 0.03).

A detailed breakdown of the changes in management enacted at the subsequent clinic visit after FC was performed is shown in Figure 1.

Impact of FC on subsequent colonoscopy use

Of 246 patients in the FC cohort where complete colonoscopy data were available throughout the follow-up period, 181 (73.6%) did not proceed to colonoscopy for disease activity (re)assessment within 6 months of the FC test, and 149 (60.6%) had not proceeded to colonoscopy post-FC by the end of follow up (median 1.8 (0.1, 4.6) post-FC testing).

In addition, those with more active/definitive inflammation (as per FC ≥ 250 µg/mL) had a shorter median time to subsequent colonoscopy than those with normal/negative FC < 100 µg/mL (6.0 vs 12.1 months, *P* = 0.03).

Cost comparison of colonoscopy-only use (2005–2009) versus FC ± colonoscopy use for disease assessment (2010–2014)

In the 5-year period of 2005–2009, 450 colonoscopies were performed for disease activity (re)assessment, that is, prior FC availability, at a total cost of AU\$606 577.50 or cost per patient-year of \$1887.34 (based on follow-up period per procedure per patient).

In comparison, in the 5-year period of 2010–2014 with availability of both FC and colonoscopy, 357 FC tests were performed that were then, as deemed appropriate by the treating clinician(s), followed by 196 colonoscopies for disease activity (re)assessment in the same cohort, at a total cost of AU\$282 048.20 or cost per patient-year of \$968.60. Therefore, as displayed in

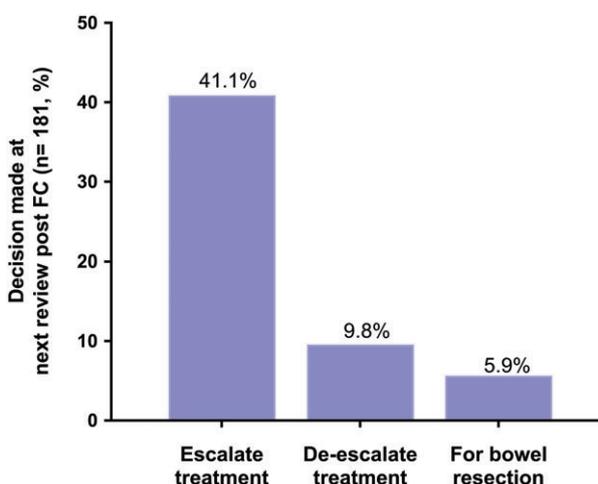


Figure 1 Breakdown of changes in management that occurred in 181 patients at the next clinic visit after faecal calprotectin (FC) testing. Escalation of therapy was defined as one or more of an increased treatment dose/frequency, additional therapy or step-up in therapy. De-escalation was defined as a reduction in dose/frequency, step down or cessation of therapy.

Figure 2, there was an apparent, overall cost reduction of 51% enabled by the introduction of FC testing between the two cohorts.

Furthermore, to reassess whether confounding due to the differential 5-year periods existed, a sensitivity analysis was performed where it was deemed that, hypothetically, in the absence of FC in the 2010–2014 cohort, a colonoscopy would have been performed with high (almost certain) likelihood in at least 239 of 357 (66.9%) cases where FC was tested for disease activity (re)assessment. The total cost of colonoscopies in this hypothetical cohort was \$322 160.10, which was an additional cost of 12.5% compared to the use of FC ± colonoscopy in the same patient cohort.

Discussion

This study provides valuable, real-world data evaluating the impact, both in terms of clinical decision-making and relative cost, of the introduction of FC testing to routine care at a single large IBD centre, in addition to previous standard decision support tools, including colonoscopy and symptom-based clinical assessment of disease activity. To date, this is the largest published study specifically evaluating the utility of FC in real-world practice. Given that many countries like Australia have struggled to convince government/payers of the beneficial role and cost implications in providing reimbursement for FC, there are several salient findings here.

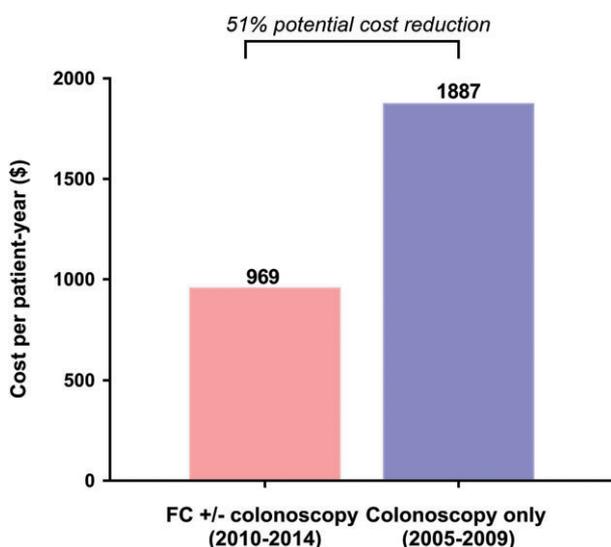


Figure 2 Cost comparison of colonoscopy-only use (2005–2009) versus faecal calprotectin (FC) ± colonoscopy use (2010–2014) for disease activity assessment.

First, the introduction and use of FC in routine care in this IBD cohort appears to have reduced the number of colonoscopies requested for disease activity (re)assessment, compared to both the preceding 5 years at the same centre (2005–2009) and to a conservative, hypothetical colonoscopy-only approach within the same 5-year cohort (2010–2014). The magnitude of cost savings is potentially significant – in this study the cost of FC ± colonoscopy was approximately one half that of the historical colonoscopy-only cohort for disease activity (re)assessment based on contemporaneous local costing data. This is consistent with that proposed or extrapolated elsewhere – for instance, in their prospective randomised trial, Wright *et al.* projected that the introduction of FC for monitoring post-operative recurrence in CD could reduce the number of colonoscopies performed for this indication by 47%.¹⁵ Although based solely on physicians' survey responses and thus open to bias, another study suggested that colonoscopy rates might be reduced by over 80% by using an FC-first approach.¹⁸ For payers, this emphasises that, despite the addition of a new test (with the associated expenditure) like FC, its routine application in appropriate contexts can be cost beneficial given that, in many cases, it supplants a higher-cost current investigation (e.g. colonoscopy). Furthermore, the cost differential would only be greater if indirect costs were also included given the relative convenience of FC for patients versus the loss of productivity and absenteeism caused by bowel preparation, sedation and attendance at a healthcare facility, as are typically required for colonoscopy – although this is beyond the scope of the present study.

Second, and in relation to above, testing FC appeared subsequently to assist clinicians in triaging colonoscopy as those with higher FC titres (≥ 250 ug/ml) had a shorter median time to colonoscopy than those with low FC titres. Moreover, the majority of patients with FC tested did not then proceed to colonoscopy at all within the follow-up period, providing real-world confirmatory data that have previously only been speculative.¹⁸ In addition, compared to the colonoscopy-only cohort, there was significantly reduced use of other imaging investigations for IBD assessment (typically also of high cost, e.g. magnetic resonance enterography) performed after FC testing during the follow-up period.

Third, approximately one-half of FC recipients had a change in management at their next clinic visit, which was almost identical to the proportions reported by Rosenfeld *et al.*,¹⁸ reinforcing the validity of these data. Moreover, we showed that the proportion of changes in management post-FC was similar to that of endoscopic activity assessment in the respective cohorts, indicating that, aside from potential cost benefits, importantly,

there was no apparent loss of fidelity in clinical decision-making with FC without colonoscopy. This also reiterates the observation by Abej *et al.* that, once available, clinicians quickly learn to put faith in FC and use the test in clinical decision-making.¹⁹ Indeed, in a recent study that surveyed Australian gastroenterologists, interestingly, both FC users (79%) and non-users (68%) reported that the use of FC would likely defer or avoid colonoscopies if the test was available under government reimbursement.²⁰ In addition, while some have raised concerns about the accuracy of FC in assessing small bowel CD,^{21,22} other studies have refuted this assertion.^{15,23–25} Indeed, in this study, FC was actually used in a higher proportion of CD than UC patients, and of those, approximately one third had isolated small bowel CD. As per these supportive data, we agree with others that this is rational and appropriate given the constraints of alternative small bowel investigations.^{15,26}

Although this is the largest study to our knowledge to evaluate FC compared to colonoscopy disease activity assessment in relation to clinical decision-making and cost analysis in a real-world IBD cohort, there are several limitations with this type of retrospective methodology. This also includes inherent differences between the FC and colonoscopy only cohorts, especially as the latter is from an earlier time period – this is reflected in a more aggressive treatment profile seen in the FC cohort. By the same token, the higher median age and disease duration reflect that these cohorts are essentially a similar patient group, yet the FC cohort is 5 years ahead chronologically, and all other disease characteristics are similar. To address this potential time-related bias further, we performed a sensitivity analysis within the same time period of the FC cohort, reconfirming that, even on conservative estimation, there was still a significant potential reduction in colonoscopies performed for disease activity

assessment, and thus cost savings, with the introduction and use of FC as first-line therapy. In addition, while one may question the inherent heterogeneity of measuring the utility of FC in a real-world, uncontrolled cohort as this is, conversely, it is also a strength of the study given that this approach allows the ability to generalise these data and the application of FC in a context similar to IBD centres elsewhere.

Conclusion

While previous research and cumulative experience have already established the capability of FC as a reliable, sensitive and reproducible marker of mucosal inflammatory activity, this study has further demonstrated its utility and potential cost savings, compared to colonoscopy in disease activity assessment, in a real-world context. With the growing imperative of cost containment and resource rationalisation, FC has been shown to have gained the trust and confidence of clinicians within a short timeframe, become a useful tool in triaging colonoscopy and enhance treatment decision-making. Moreover, this study has demonstrated the potential for FC to reduce significantly the burden of costs for payers and the inconvenience of alternative investigations for patients alike, without compromising the provision of quality care in IBD.

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