

MSAC Application 1761

Faecal calprotectin for the monitoring of disease activity in patients with inflammatory bowel disease

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for the use of faecal calprotectin in monitoring disease activity in patients with known inflammatory bowel disease

Component	Description
Population	Patients with known inflammatory bowel disease (IBD) managed by a gastroenterologist.
Prior tests	None
Intervention	Quantitative enzyme-linked immunosorbent assay (ELISA) of Faecal Calprotectin (FC) (new MBS Item)
Comparator/s	Primary comparator in both symptomatic and asymptomatic patients: Colonoscopy and biopsy Secondary comparator in asymptomatic patients: Standard medical management (i.e., clinical history/examination, routine blood tests including C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)) ¹
Reference standard	Colonoscopy and biopsy
Outcomes	<p>Safety:</p> <ul style="list-style-type: none"> Potential harms avoided due to unnecessary colonoscopies avoided if FC is MBS listed <p>Effectiveness:</p> <ul style="list-style-type: none"> Concordance of results between FC and colonoscopy/biopsy Diagnostic and prognostic accuracy of FC compared to colonoscopy/biopsy <p>Patient management outcomes:</p> <ul style="list-style-type: none"> Prognostic utility: informed change in prognosis without change in treatment Predictive utility: change in treatment pathway (treatments ceased, modified or avoided) Complications and hospitalisations associated with IBD avoided <p>Cost offsets:</p> <ul style="list-style-type: none"> Cost offsets per FC test Reduction in number of colonoscopies and associated perforations/complications, biopsies, and imaging tests

Component	Description
	<p>Healthcare resources:</p> <ul style="list-style-type: none"> • Cost to deliver FC test • Cost to deliver colonoscopy (\pm biopsy) • Cost associated with change in management (i.e., change in therapy, addition or reduction of tests required, etc.) • Costs associated with other healthcare resources (associated tests due to false positive or intermediate results, costs of treatment, including of side effects). <p>Total Australian Government healthcare costs:</p> <ul style="list-style-type: none"> • Total cost to Medicare Benefits Schedule (MBS) • Total cost to other healthcare services
Assessment questions	<p>What is the safety and effectiveness of FC testing versus colonoscopy/biopsy in monitoring of disease activity in patients with known IBD managed by a gastroenterologist?</p> <p>What are the potential cost offsets associated with current approaches to disease management arising from the listing of FC testing?</p>

¹ FC test would not replace but rather be added to standard medical management

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of faecal calprotectin (FC) testing for monitoring disease activity in patients with known inflammatory bowel disease (IBD) managed by a gastroenterologist was received from Gastroenterological Society of Australia (GESA) by the Department of Health and Aged Care.

The rationale for this application is that FC testing is cheaper, safer, and clinically non-inferior compared to current alternatives i.e., colonoscopy and biopsy.

Background

In March 2018, MSAC considered but did not support [MSAC application 1353](#), which requested public funding for FC testing for monitoring disease activity in patients with known IBD. MSAC advised that a resubmission for monitoring IBD should provide:

- a definition of current Australian practice to monitor IBD (e.g., frequency of colonoscopies), together with supportive data on the clinical utility of this practice both to establish any clinical need for FC monitoring in the first place, and then also to better identify the downstream management practices and health outcomes which might be improved by introducing FC monitoring;
- further information on the biological variability of inflammation in the stable IBD patient cohort in order to provide a better basis for when to initiate a change in clinical management and also a better basis for the requested frequency of FC testing for this purpose.

PICO criteria

Population

The application is for the use of FC testing in monitoring of disease activity in patients with known IBD managed by a gastroenterologist.

IBD is comprised of two chronic inflammatory conditions of the gastrointestinal (GI) tract:

- Ulcerative colitis (UC) classically shows a diffuse, continuous, chronic inflammation that originates in the rectum and spreads proximally towards the caecum, gradually decreasing in severity. Disease is limited to the colon and rectum, and presents with initially superficial ulcers, which in severe or longstanding disease may penetrate into the most superficial muscular layer (muscularis mucosae). The rectum may be spared of ulceration in children (30%), in adults with fulminant colitis (13%) or in patients receiving topical and/or systemic treatment (44%). Discontinuous inflammation manifesting as caecal patches and inflammation surrounding the appendiceal orifice are associated with left-sided colitis, diagnosed in up to 75% of patients with distal disease (Villanacci et al. 2021).
- Crohn's disease (CD) can affect any part of the GI tract, from the mouth to the anus. The localisation of CD usually remains stable over time, with approximately one third of patients presenting with colonic disease, one third with ileo-colic and one third with small-bowel limited disease (Roda et al. 2020). Macroscopic examination of a resection specimen typically shows a discontinuous pattern of inflammation, with diseased segments frequently and abruptly separated by areas of uninvolved bowel (skip lesions). The earliest grossly visible mucosal lesions are small aphthous ulcers that typically develop along the mesenteric margin of the bowel wall (over lymphoid follicles) and are bordered by normal mucosa. As aphthous ulcers coalesce, they form large deep serpiginous or linear ulcers with overhanging oedematous mucosal edges giving rise to the classic 'cobblestone' appearance. Fistulae are more frequent in the small bowel but, though relatively rare, can also occur in the colon. The bowel wall becomes thickened and increasingly rigid as a consequence of transmural inflammation with fibrosis and fibromuscular proliferation (Villanacci et al. 2021).

An observational study performed on IBD patients in Victoria in 2011 reported an age-standardised incidence rate of 24.7 per 100,000 (Studd et al. 2016) while a study in the Mackay-Isaac-Whitsunday region in Northern Queensland performed in 2017-2018 reported an age-standardised incidence of 32.38 per 100,000 individuals (Flanagan et al. 2023). A cross-sectional study performed on a national database of general practice electronic health records (MedicineInsight) analysed 2,428,461 Australian patients from July 2017 to June 2019, and estimated the crude prevalence of IBD is 653 per 100,000 people (CD: 306 per 100,000 and UC: 334 per 100,000) (Busingye et al. 2021). These data support global trends of increasing prevalence in Western countries. The application proposed an incidence of 24.7 to 32.4 cases per 100,000 people, with a prevalence of approximately 100,000 Australians living with IBD based on a report from 2013 (PwC 2013). The application's range of incidence is reasonable, however based on more recent epidemiological data, prevalence may be as high as 93,000 people in Australia (based on a prevalence of 653 per 100,000 people and a projected 27,824,827 Australians in 2024) (Australian Bureau of Statistics 2023).

The aetiology of IBD is unknown, with the disease arising through a combination of genetic and environmental factors. Both CD and UC carry enormous morbidity, neither is curable (unless a colectomy is performed in those with disease confined to the large bowel only), and both increase the risk of GI and extra-intestinal malignancies, which may be due to repeated mucosal inflammation causing cellular/DNA damage, combined with medical therapies (e.g. anti-tumour necrosis factor (TNF) therapies, anti-interleukin (IL)-12/23 agents, sphingosine-1-phosphate (S1P) receptor inhibitors and small molecule therapies) which lead to prolonged periods of immune-suppression (McDowell et al. 2023; Axelrad et al. 2016).

Males have a lower risk of CD (OR: 0.86; 95% CI: 0.81, 0.90) but a greater risk of UC (OR: 1.12; 95% CI: 1.06, 1.17) compared to females. Compared to non-smokers, patients who were current smokers were associated with a greater risk of CD (OR: 1.13; 95% CI: 1.04, 1.23) but a lower risk of UC (OR: 0.52; 95% CI: 0.47, 0.57). Other factors positively associated with both CD and UC are age (≥ 25 years), non-Indigenous status and socioeconomic advantage (Busingye et al. 2021).

Patients with an established IBD diagnosis are managed by a gastroenterologist, with a minimum of one annual appointment. Access to biological disease modifying drugs (bDMDs), such as adalimumab, infliximab and vedolizumab, via the PBS is restricted to patients with severe CD, and moderate-to-severe UC, and endoscopy results demonstrating this severity of disease may expedite access to these treatments during acute disease relapses. Disease severity and clinical presentations for CD and UC are summarised below.

Crohn's Disease

Two commonly used systems for disease severity evaluation are the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index (HBI). Both indexes are primarily based on clinically evaluable symptoms/history, however the CDAI also requires the patient's haematocrit (a blood test). In clinical practice, the following working definitions in relation to the CDAI may be useful (Lichtenstein et al. 2018):

- Clinical remission (patients with a CDAI <150) – These patients are asymptomatic and without symptomatic inflammatory sequelae. This status is achieved either spontaneously or after medical or surgical intervention. Patients requiring glucocorticoids to remain asymptomatic are not considered to be in remission and are referred to as being 'steroid-dependent'.
- Mild CD (patients with a CDAI 150-220) – These patients are typically ambulatory and tolerate an oral diet. They have <10 percent weight loss and no symptoms of systemic disease such as fever, tachycardia, abdominal tenderness, and no signs or symptoms of intestinal obstruction. They may have some soft stools, abdominal pain, or modest declines in their general wellbeing.
- Moderate to severe CD (patients with a CDAI 220-450) – This group comprises patients who have failed treatment for mild to moderate disease or those patients with prominent symptoms such as fever, weight loss, abdominal pain and tenderness, intermittent nausea or vomiting, or anaemia.
- Severe-fulminant disease (patients with a CDAI >450) – Patients with persistent symptoms despite glucocorticoids or biologic agents (infliximab, adalimumab, certolizumab pegol, natalizumab, vedolizumab, or ustekinumab) as outpatients, or individuals presenting with high fever, persistent vomiting, intestinal obstruction, peritoneal signs, cachexia, or evidence of an abscess.

In addition to the clinical parameters, the American Gastroenterological Association (AGA) stratifies patients into either a low-risk or moderate-to-high-risk category by assessing inflammatory status with the following tests (Sandborn 2014):

- Endoscopic evaluation for mucosal ulcerations, stricturing and disease extent
- Laboratory parameters: C-reactive protein (CRP) and/or FC
- Presence or absence of upper GI involvement

Ulcerative Colitis

Clinical trials of UC often use formal grading systems to describe disease activity. The severity of UC is generally classified as mild, moderate, or severe disease; however, the definition of mild to moderate disease activity may vary in the literature depending on the specific index or score being used (e.g., Truelove and Witts severity index, Mayo Clinic score, Montreal classification). In clinical practice, the following definitions may be useful (Al Hashash 2023):

- Mild – Patients with mild clinical disease have ≤ 4 stools per day with or without small amounts of blood, no signs of systemic toxicity (e.g., no tachycardia), and a normal CRP and/or erythrocyte sedimentation rate (ESR). Mild crampy abdominal pain, tenesmus, and periods of constipation are also common, but severe abdominal pain, profuse rectal bleeding, fever, and weight loss are not part of the spectrum of mild disease.
- Moderate – Patients with moderate clinical disease may have frequent, loose, bloody stools (4-6 per day), mild anaemia not requiring blood transfusions (haemoglobin >10 g/dL), and abdominal pain that is not severe. Patients have no or minimal signs of systemic toxicity. Adequate nutrition is usually maintained and weight loss is not associated with moderate clinical disease.
- Severe – Patients with a severe clinical disease typically have frequent, loose, bloody stools (≥ 6 per day) with severe cramps and evidence of systemic toxicity as demonstrated by fever (temperature $\geq 37.8^\circ\text{C}$), tachycardia (heart rate ≥ 90 beats per minute), anaemia (haemoglobin <10 g/dL), and/or an elevated CRP or ESR. Patients may have weight loss.

Within the context of this application, patients can be considered to be in one of four health states:

- Asymptomatic, no biochemical evidence (e.g., elevated FC levels) of impending IBD relapse.
- Asymptomatic, with biochemical evidence of impending IBD relapse.
- Symptomatic, with no evidence of IBD relapse (as demonstrated by the results of blood tests, FC levels and/or imaging).
- Symptomatic, with evidence of IBD relapse.

Due to the variable, relapsing/remitting nature of IBD, a single patient may transition between all four of these health states in a given year. Furthermore, the applicant has noted that even an asymptomatic patient may be at high risk of IBD relapse (e.g., patients with recent flare or surgery but currently asymptomatic). The symptomatic patient with UC or CD may present within a range of clinical severity, as described above, although this has poor correlation with mucosal disease activity (Cellier et al. 1994, Walsh et al. 2016). Also, some patients may be placed on long-term treatments (e.g., immunosuppression), and have their disease state and dosing monitored during regular gastroenterologist reviews.

PASC discussed whether the asymptomatic and symptomatic populations should be split into two PICO sets, given that the test frequency, comparators, clinical management algorithms and outcomes were likely to be different for each of these groups. PASC proposed that this would likely be for assessment purposes only. If this application were supported by MSAC, then it would be likely that only one item number would be created that would encompass both the asymptomatic and symptomatic populations. The applicant agreed with this approach.

Intervention

The application has proposed MBS listing of a quantitative ELISA test of FC. Calprotectin, also known as MRP8/14 and S100A8/A9, is a calcium- and zinc-binding protein of the S-100 protein family, and accounts for 60% of the cytosolic protein in neutrophils, and, to a lesser extent, in monocytes and macrophages. Calprotectin is considered to be a positive acute phase protein. The presence of calprotectin in faeces is a consequence of migration of neutrophils into the GI lumen due to an infection or inflammatory process (Pathirana et al. 2018). To ensure accuracy, the FC test must be performed within 72 hours of specimen collection. The existing MBS item numbers for use of the FC test (66522 and 66523) are used at the diagnostic stage in patients without diagnosed IBD.

The FC test is applicable to both CD and UC (Corewell Health 2023), however, it is a stronger predictor of clinical relapse in UC than in CD, likely due to fact that CD may be limited in some instances to the upper GI tract (and thus subject to degradation/dilution of calprotectin by the time it is measured in faeces), while UC is confined to the colon/rectum (Costa et al. 2005).

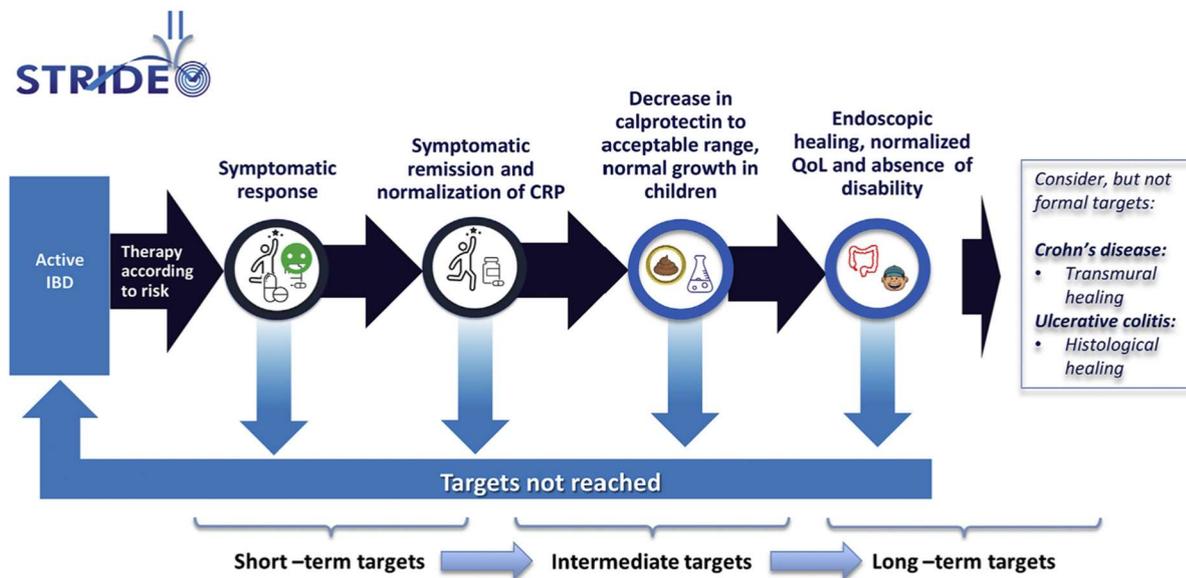
Tight control of IBD related inflammation is the current best practice management paradigm to optimise outcomes, improve the long-term prognosis of patients with IBD and avoid complications and hospitalisations. The STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease)-II guidelines (summarised in Figure 1 below) provide recommendations for achieving and maintaining tight control in IBD management and have been adopted by major Australian and international gastrointestinal societies. These guidelines emphasize the importance of “treating to target”, which involves setting specific treatment goals and regularly assessing disease activity to ensure those goals are met. The guidelines highlight the use of objective measures, such as clinical indices, biomarkers (including FC), and endoscopic evaluation, to monitor disease activity. Although symptomatic relief is one of the primary goals of treatment in IBD, there is a poor correlation between clinical symptoms alone and mucosal inflammatory burden (Cellier et al. 1994, Walsh et al. 2016). The STRIDE-II guidelines state that “it is not infrequent to discover significant mucosal inflammation during complete clinical remission” (Turner et al. 2021: 1574). In line with this, STRIDE-II guidelines consider symptomatic remission a short-intermediate target, while long-term targets include endoscopic healing, normalised quality of life and absence of disability. Therefore, patients who are yet to achieve endoscopic healing may continue to receive treatment despite the absence of symptoms. Frequent and regular assessment allows for early detection of inflammation and prompt adjustment of treatment to achieve mucosal healing and symptom control.

The proposed FC testing may be divided into two broad categories of use for disease activity monitoring in patients with previously diagnosed IBD:

- In patients who have symptoms consistent with a flare of IBD
- In asymptomatic patients to assess for latent (subclinical) IBD relapse

In either of these settings, FC testing may also be used as a monitoring tool to evaluate response to therapies (medical or surgical) or during post-flare management. In this capacity, the quantitative FC result may inform gastroenterologists if a patient needs a change (escalation or de-escalation) in therapy. It is also an intermediate target in the 'treat to target' approach to IBD management, as described in the STRIDE-II guidelines summarised in Figure 1 below.

Figure 1 STRIDE-II guidelines by the International Organization for the Study of Inflammatory Bowel Diseases.



Source: Figure 1, p 8 of the application.

CRP = C-reactive protein; IBD = inflammatory bowel disease; QoL = quality of life; STRIDE = selecting therapeutic targets in inflammatory bowel disease

Note: 'Crohn's disease' is legacy nomenclature.

The proposed intervention relies on the quantitative determination of FC to guide clinical management of IBD. The application delineated three broad results categories, summarised in Table 2 below.

Table 2 Proposed faecal calprotectin result categories, and corresponding interpretations in an asymptomatic and symptomatic patient.

FC Level	Asymptomatic patient	Symptomatic patient
<100 µg/g	Indicative of mucosal healing / absence of disease.	Indicative of a non-inflammatory cause for symptoms (such as functional gut disorders). In this situation, colonoscopy may be avoided.
100-250 µg/g	An intermediate result which needs to be interpreted in the clinical context including checking of adherence to therapy, consideration of change from baseline/trends in FC in the patient and other factors which may contribute to an increased FC e.g., diverticulitis and medications such as non-steroidal anti-inflammatory drugs. Repeating the FC test in 4 to 6 weeks may be required to establish trend, and investigation with imaging and/or colonoscopy may be warranted.	Needs to be interpreted in the clinical context including checking of adherence to therapy, consideration of change from baseline/trends in FC in the patient and other factors which may contribute to an increased FC. Repeating the FC test in 4 to 6 weeks may be required to establish trend, and investigation with imaging and/or colonoscopy may be warranted.
>250 µg/g	Indicative of intestinal inflammation and may warrant escalation of therapy and/or further evaluation such as colonoscopy/imaging. Timely and appropriate therapeutic	Indicative of active disease and would generally warrant adjustment to therapy. In this situation, colonoscopy may be avoided.

FC Level	Asymptomatic patient	Symptomatic patient
	escalation may avoid complications emerging and progression to hospitalisation and/or surgery.	Repeated FC in 2-3 weeks likely required to assess response to treatment.

Source: Constructed during the evaluation, based on information extracted from pp 21-22 of the application.

FC = faecal calprotectin.

The FC trend over time is more valuable than any single FC result, and single observations of FC results should not be interpreted in isolation, but rather used in combination with patient history, examination, laboratory investigation ± imaging to construct a comprehensive clinical picture and inform specialist decision-making.

CRP results, an inflammatory marker commonly tested in blood samples, provides added value when interpreted in concert with FC. According to the recent STRIDE-II guidelines, FC has a high sensitivity and lower specificity in identifying mucosal inflammation while CRP has the opposite characteristics: higher specificity but lower sensitivity in the context of monitoring of disease activity in IBD (Turner et al. 2021). Interpreting FC results in isolation can be unreliable and misleading, as FC values <600 µg/g can still be associated with minimal inflammation. Low CRP values have been associated with a reduced risk of clinical relapse, while high CRP values determined after the discontinuation of anti-TNF treatments are associated with a higher risk of relapse (Gisbert et al. 2015) (anti-TNF treatments (e.g. infliximab, adalimumab) are well established, PBS-listed treatments for moderate/severe IBD).

During the pre-PASC teleconference, specialist gastroenterologists suggested intermediate results are interpreted in the clinical context, and that a trend in FC is more important than a single result. It was also acknowledged that on occasion FC tests may lead to additional colonoscopies, but proposed that they believe the overarching impact of FC testing in IBD would be to reduce colonoscopy rates. A better understanding of the impact on the Australian population may be provided from data that are forthcoming from the Monash Health clinical database (to be provided by the applicant).

FC levels may be increased by any process which increases neutrophil infiltration into the gut lumen. Other than IBD, the following may lead to 'falsely increased' FC levels (Corewell Health 2023):

- Proton pump inhibitor use
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Enteropathological microorganisms, such as parasites (including ova) and bacteria

The manufacturer-quoted cut-off values for detecting IBD for different FC assays are generally similar. However, the sensitivities and specificities at a given cut-off, and therefore the optimum cut-off values, are different between assays, and a reference standard for calprotectin is lacking (Pathirana et al. 2018). In a comparison of six different calprotectin assays, the kits yielded significant correlation, however up to a 5-fold quantitative difference was found between assays, noting that the study included two ELISA tests and four alternative techniques (Labaere et al. 2014). These differences may need to be considered in interpreting FC results; over the past few decades, several FC assays and extraction devices have been introduced by manufacturers.

PASC noted that the manufacturer-quoted cut-off values varied between different brands of test kits which raises issues for standardisation/comparability between assays. PASC also noted the discrepancy in the clinically validated test thresholds compared to that which is published. For example, PASC noted that FC

results of <50 µg/g are considered negative according to the published test threshold, whereas in clinical practice an FC result of <100 µg/g would generally be considered negative. This could be a source of confusion for clinicians and make test interpretation difficult.

Furthermore, PASC noted that how FC test results are interpreted by clinicians and the subsequent management decisions made will vary depending on the clinical context. For example, a FC test result in the intermediate range will lead to different management plans depending on whether the patient is asymptomatic (likely 'watch and wait' along with repeat FC test) vs symptomatic (patient may require a colonoscopy). The applicant noted that while reference ranges are important when interpreting FC test results, the trend in FC results are more important in determining clinical management. While this may require several FC tests being undertaken to determine the trend, the applicant confirmed that only a small proportion of patients would require more than 4 FC tests per year.

PASC agreed that additional advice should be sought from pathology organisations (eg. Royal College of Pathologists of Australasia) regarding the issues surrounding test thresholds/reference ranges outlined above. Their advice should also be sought regarding how the appropriate test thresholds and reference ranges should be communicated to clinicians, in particular the choice of reference range to report.

The application proposed 6-monthly FC monitoring for IBD relapse in asymptomatic patients, citing national and international guidelines. The early identification of IBD relapse allows for timely and appropriate therapy escalation, avoiding unnecessary inflammation and the sequelae associated with overt, symptomatic disease relapse, including hospitalisation and/or surgery. The cited STRIDE-II guidelines do not appear to advocate for 6-monthly testing in patients with UC, stating that:

“Few studies have indicated that [FC] can be useful in predicting relapses in UC, but its added predictive value while in complete clinical remission is less clear. Two measurements of FC, 1 month apart, may best predict flares before clinical symptoms.” (Turner et al. 2021: 1578)

The national guideline cited by the applicant, NPS MedicineWise (MedicineWise 2021), advocates for 6-monthly testing citing one paper, the ECCO-ESGAR Guideline for Diagnostic Assessment in Inflammatory Bowel Disease, which states that:

“Two consecutively elevated FC levels were the best predictor for clinical relapse, but this was investigated systematically in only one study. In one of the more recently published studies, patients with both UC and CD provided faecal samples every third month and were prospectively followed until the first clinical relapse. This study revealed that FC levels start rising approximately 3 months before a relapse becomes clinically apparent, and confirmed the observations of the aforementioned systematic review...When the FC concentration is in the target range, the patient is reassured and advised to retest in 3 months. When the FC concentration is in the action range, the treatment plan is adjusted and re-testing is advised for the next month. In the uncertain range, a test interval of 1 month is advised before progressing to a treatment decision.” (Maaser et al. 2019: 153)

The application did not present additional evidence on the efficacy of FC as a monitoring tool in asymptomatic patients with IBD (e.g., number needed to test), and it is unclear whether 6-monthly testing would be adequate to provide timely identification of asymptomatic IBD relapses. It is unclear what proportion of patients might experience relapses between testing intervals and therefore the number of relapses that may be missed (i.e., occur in between the 6-monthly monitoring). During the pre-PASC

teleconference, gastroenterologists stated that most patients with IBD would be reviewed with 3-6 monthly appointments and patients with active disease/flare will often have more frequent follow-up (4-6 weekly until flare controlled). Some asymptomatic patients with very mild disease phenotype and not on any immunosuppressive medication may be seen every 12 months. It is unclear if this means that if asymptomatic patients receive 6-monthly monitoring FC tests, some of these patients may require additional gastroenterologist consultations which they otherwise would not have had. It was noted in the applicant's response to questions for targeted consultation, the applicant suggested that FC testing can be performed between review appointments, co-ordinated through gastroenterologists via nursing or administration staff if the treating gastroenterologist feels this would be of benefit.

PASC considered that more evidence is required for the proposed testing frequency of asymptomatic patients as it is not evident from the application the proportion of IBD relapses that may be missed in the periods between testing.

The application proposed a maximum of 4 FC tests per IBD patient per year, which included both monitoring asymptomatic patients 6-monthly and evaluating response to therapy in patients with active disease. This is likely to be inadequate for some patients. During the pre-PASC teleconference, consultant gastroenterologists stated that depending on disease severity of an acute relapse, a patient may need 2 to 4 FC tests per year to evaluate response to therapy and establish a downward trend (in FC), noting that discordance between the FC trend and symptoms is a setting where additional FC testing may be needed. For patients who remain asymptomatic, 6-monthly monitoring will require at least 2 FC tests per year, but potentially more as re-testing for confirmation is required after an elevated FC result. Therefore, a patient with one relapse in a year may require 4 to 6 FC tests in that year (assuming both monitoring tests were negative); patients with multiple relapses or prolonged disease activity or an elevated FC monitoring result may require ≥ 6 FC tests. During the pre-PASC meeting, the applicant acknowledged that four FC tests per year might not be sufficient for some patients and expressed a willingness to explore a higher number. The applicant is asked to confirm that based on preliminary data from Crohn's Colitis Care (CCCare) and Monash Health, less than 1% of patients required more than 4 FC tests per year. The applicant is also intending to provide preliminary information from Australia and Scotland with regard to the actual number of FC tests required per IBD patient.

In addition, as patients are likely to move between being asymptomatic, symptomatic and having relapsed disease, the number of tests required by any given patient in a year is likely to fluctuate.

Comparator(s)

PASC considered that the applicant had proposed that the comparator should be colonoscopy/biopsy for both the asymptomatic and symptomatic populations. PASC considered that the comparators are likely to be different for asymptomatic vs symptomatic patients.

PASC considered that the best way to assess the proposed intervention would be to split the population into two separate PICO sets (asymptomatic and symptomatic populations to be considered separately) given that among other considerations, the comparators are different for the two proposed sub-populations.

Comparator in asymptomatic patients

The comparator proposed by the applicant is colonoscopy and biopsy. The current management of asymptomatic IBD in Australia involves regular visits to a specialist gastroenterologist to monitor disease progress. The frequency of reviews depends on a number of factors including severity of disease phenotype, current and/or recent disease activity, recent disease diagnosis, treatments used, recent surgery, complications of disease (e.g. fistula, strictures, short gut), and recent change in therapy. During reviews, the gastroenterologist may monitor patients through a combination of clinical, biochemical, endoscopic and radiological investigations. During the pre-PASC teleconference, consultant gastroenterologists stated that while colonoscopies would not be performed every six months on asymptomatic patients to assess for disease relapse, they elected to retain colonoscopy as the chosen comparator in this setting. The applicant's rationale is that, while colonoscopy is not routinely performed 6-monthly in asymptomatic patients, it may be needed to assess for mucosal/endoscopic healing (a target outlined in the STRIDE II guidelines) in such patients. Apart from FC testing, the applicant considered imaging a suitable surrogate test to colonoscopy to assess mucosal healing. However, imaging was not considered an appropriate comparator due to the potential radiation exposure to patients, the cost of the intervention and the time taken for the test to be performed due to access issues (often weeks or months). The applicant's further rationale is that in the absence of FC testing in these patients, colonoscopy would be performed more regularly (with frequency dependent on several clinical factors), given the poor correlation between disease activity and clinical assessment alone. The applicant intends to provide further information with data from the Monash Health database. Standard medical management (i.e., clinical history/examination, routine blood tests including ESR and/or CRP \pm imaging) may be considered an alternative comparator in the asymptomatic patient, noting that were it approved for MBS reimbursement, FC testing would not replace but rather be added to standard medical management.

PASC considered that for asymptomatic patients, in addition to colonoscopy, an appropriate secondary comparator would be standard medical care including clinical assessment consisting of routine blood tests and inflammatory markers. PASC noted that bowel imaging is not typically used for monitoring purposes in clinical practice and is not widely available in Australia. Therefore, PASC did not consider bowel imaging to be an appropriate comparator for either the asymptomatic or symptomatic populations.

Comparator in symptomatic patients

Symptomatic patients are often investigated using colonoscopy/biopsy for evidence of IBD relapse. The introduction of FC testing would likely replace the need for some of these colonoscopies. Therefore, colonoscopy/biopsy may be an appropriate comparator in the symptomatic IBD patient, as described in the treatment algorithm (Figure 3). *PASC agreed that colonoscopy/biopsy was an appropriate comparator for symptomatic populations.*

The applicant stated that over 50% of colonoscopies may be substituted following MBS listing of FC testing for monitoring of IBD in both symptomatic and asymptomatic patients, based on an Australian real-world study (Motaganahalli et al. 2019). Another study from Scotland showed a 36% drop in colonoscopy and flexible sigmoidoscopy after introduction of FC testing for monitoring of IBD as part of practice in the NHS (Plevris et al. 2022). During the pre-PASC teleconference, the applicant noted they would provide granular data (from a Monash Health clinical database) to inform the likely frequency of FC testing and colonoscopies, which is likely to vary based on the severity of the disease and presentation of symptoms. FC testing may also prompt additional colonoscopies when FC test results are ambiguous (i.e. intermediate FC results).

PASC considered that the number of colonoscopies undertaken in Australia may already be low given that FC testing is currently available for monitoring purposes in some locations in Australia where it is funded by some hospitals and privately by some patients. PASC noted that publicly funding FC testing has the potential to increase the number of colonoscopies undertaken, as patients with false positive FC results and asymptomatic patients with intermediate FC results may proceed to colonoscopy for further investigation. The applicant asserted that published data from Scotland and Australia have shown that introducing FC testing has reduced the number of colonoscopies performed by up to 50%. The applicant clarified that an intermediate FC test result would likely lead to a repeat FC test being performed rather than a colonoscopy. PASC considered that a post-implementation study should be undertaken to determine whether MBS listing of FC testing for monitoring in IBD patients has the effect of reducing the number of colonoscopies undertaken, as originally intended. PASC queried whether colonoscopies would still be performed to confirm IBD flare resolutions, despite the availability of FC, as endoscopic healing has been specified as an endpoint in the STRIDE-II guidelines. The applicant confirmed that if FC testing were publicly funded, then colonoscopies would be performed less frequently given that FC testing would be an appropriate surrogate for colonoscopy to monitor endoscopic healing. Once a patient's FC levels had normalised following an IBD flare, then colonoscopy would not be required. The applicant stated that FC test results could be solely used to guide IBD therapy in this context, without the need for colonoscopies.

MBS item numbers relevant for the nominated comparator include colonoscopy/endoscopy (MBS item number 32222-32228), biopsy (histopathology: MBS item numbers 72823, 72824). Delivery of colonoscopies also require other healthcare resources. These include anaesthetic services relating to colonoscopy (MBS item numbers 20810, 17610 and 23025).

Future technology

The STRIDE-II guidelines state that colonoscopy has a limited role in tight monitoring strategies, because it cannot be performed repeatedly within short timeframes (e.g. every 3-6 months) due to its invasive nature and economic concerns. In addition, mucosal assessments may not be feasible in certain scenarios, such as for proximal small bowel disease, and in children (where mismatch between endoscopic healing and transmural healing is not uncommon)¹ (Turner et al. 2021). Consequently, the use of bedside intestinal ultrasound (IUS) has revolutionised the ability to assess the degree of inflammation in IBD (Kucharzik et al. 2017); it allows for frequent assessments and has the advantage of assessing the entire GI tract, including transmural healing. IUS has proven to be a useful tool to check IBD disease activity, extent of disease, bowel damage, complications, and the response to treatment. It is performed with equipment that is standard and readily available in most hospitals. Unlike computed tomography imaging, or endoscopy, which require specialist equipment or advanced preparation by the patient, IUS can be performed at short notice during a clinical encounter, and is currently being used in Australia (Central Adelaide Local Health Network 2023), however it is currently not widely used/accessible in Australia due to rollout/training bottlenecks.

¹ Endoscopic healing may be visualised via endoscopy, however transmural disease activity/healing cannot be assessed through endoscopy and is generally assessed radiologically (Neurath and Vieth 2023). Children may have ongoing transmural disease, despite demonstrating endoscopic healing. The presence of transmural healing is associated with greater disease-free survival (Suárez Ferrer et al. 2021).

Reference standard (for investigative technologies only)

For patients previously diagnosed with IBD seeing a gastroenterologist for ongoing management, the gold standard for assessment of disease activity is colonoscopy and biopsy. Therefore, colonoscopy/biopsy is considered to be the reference standard to assess the test accuracy of FC testing. The MSAC has previously accepted colonoscopy and biopsy as the reference standard for FC testing (MSAC 2017).

For asymptomatic patients receiving FC testing to monitor for a potential future IBD relapse, there is no established reference standard. FC testing is the most established test to predict IBD flares. More recently, artificial intelligence (AI) monitoring has been proposed to be able to predict flares based on age, mean serum albumin, immunosuppressive medication use, and mean and highest platelet counts (Waljee et al. 2018). According to the applicant, IBD monitoring using AI is likely to include rather than replace FC testing.

PASC confirmed that the reference standard was appropriately defined in the PICO.

Outcomes

Safety outcomes:

- Harms associated with colonoscopy
- Harms associated with treatment

Clinical effectiveness outcomes:

- Test performance outcomes:
 - Diagnostic accuracy: sensitivity, specificity, additional true positives and additional true negatives
 - Concordance between tests

Patient management outcomes:

- Reduced disease activity (based on inflammation or biomarkers)
- Prognostic utility: informed change in prognosis without change in treatment
- Need for additional monitoring
- Predictive utility: change in treatment pathway (ceased, modified or avoided treatment)
- Duration and severity of flareups
- Complications and hospitalisations avoided
- Reduced risk of cancer

Health outcomes:

- Morbidity associated with IBD
- Health-related quality of life (HRQOL)

Cost offsets:

- Cost offsets per FC test
- Reduction in number of colonoscopies and associated perforations / complications, biopsies, and imaging tests

Healthcare resources:

- Cost to deliver FC test
- Cost to deliver colonoscopy (\pm biopsy)
- Cost associated with change in management (i.e., change in therapy, addition or reduction of tests required, etc.)
- Costs associated with other healthcare resources (associated tests, treatment, including of side effects, costs associated with additional colonoscopies (and associated biopsies and complications) due to false positive or intermediate FC results in asymptomatic patients).

Total Australian Government healthcare costs:

- Total cost to the MBS
- Total cost to other healthcare services

PASC confirmed that the outcomes were appropriately defined in the PICO.

Assessment framework (for investigative technologies)

The application claimed that FC testing is cheaper, safer, and clinically non-inferior compared with colonoscopy and biopsy/histopathology for routine assessment of disease activity in patients with established IBD. The application also claimed that FC testing would lead to tighter control of IBD, leading to better clinical outcomes and reductions in disease sequelae.

The FC test provides a quantitative result, which may indicate low, moderate or high levels of disease activity. It is proposed that this investigation can partially replace colonoscopy and biopsy to measure IBD activity. The application also claimed that through the use of FC to monitor for disease activity in asymptomatic patients, IBD relapses may be identified and treated earlier, minimising disease activity and reducing the sequelae of IBD, including disease-specific morbidity, disease progression, intestinal perforation, anaemia, hospital admission and surgery. In addition, tighter IBD control may reduce risk of colorectal cancer, noting that the FC test cannot screen for cancer whilst colonoscopy can.

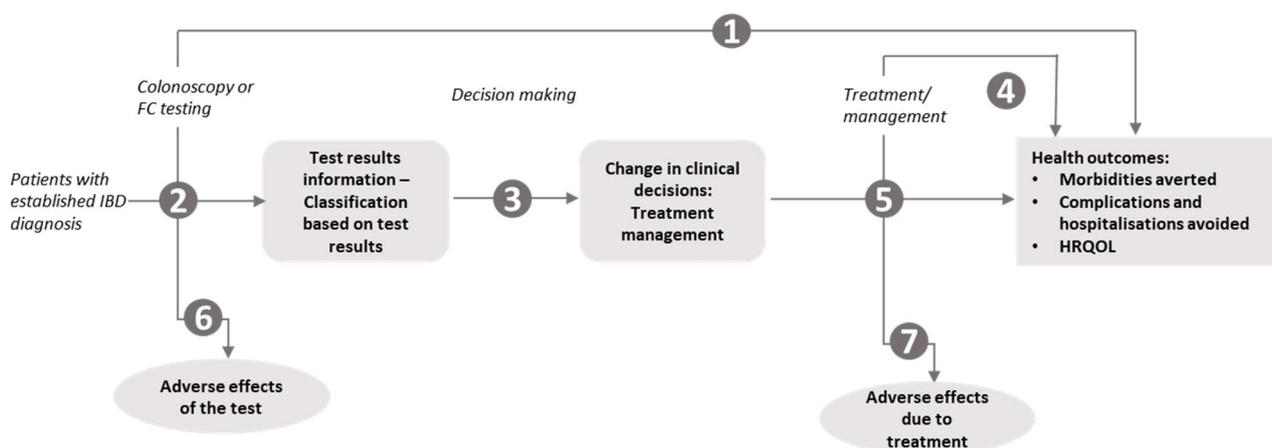
A linked evidence approach is the most appropriate as there is unlikely to be direct evidence of the impact of FC testing on health outcomes. Figure 2 describes the assessment framework for FC testing showing links to health outcomes.

Questions relevant to this assessment framework are as follows:

1. What are the direct health outcomes of colonoscopy or FC testing?
2. What is the accuracy of FC testing in identifying relapses in IBD? What is the concordance of FC testing in comparison to colonoscopy/biopsy in identifying relapses in IBD?

3. What is the prognostic and predictive value of FC testing in monitoring patients with IBD? Does the FC testing result in change in management? Impact on management includes further investigations, treatments and surveillance.
4. What is the impact on health outcomes due to change in treatment / management?
5. What is the direct impact on health outcomes due to change in clinical decisions?
6. Are there harms avoided due to FC testing and due to early prognostic information provided by FC testing?
7. Are there any adverse effects due change in clinical decisions (due to new treatments or change in clinical management).

Figure 2 Assessment framework for faecal calprotectin testing showing links to health outcomes



FC = faecal calprotectin; HRQOL = health-related quality of life; IBD = inflammatory bowel disease

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: adverse events due to testing; 7: adverse events due to treatment

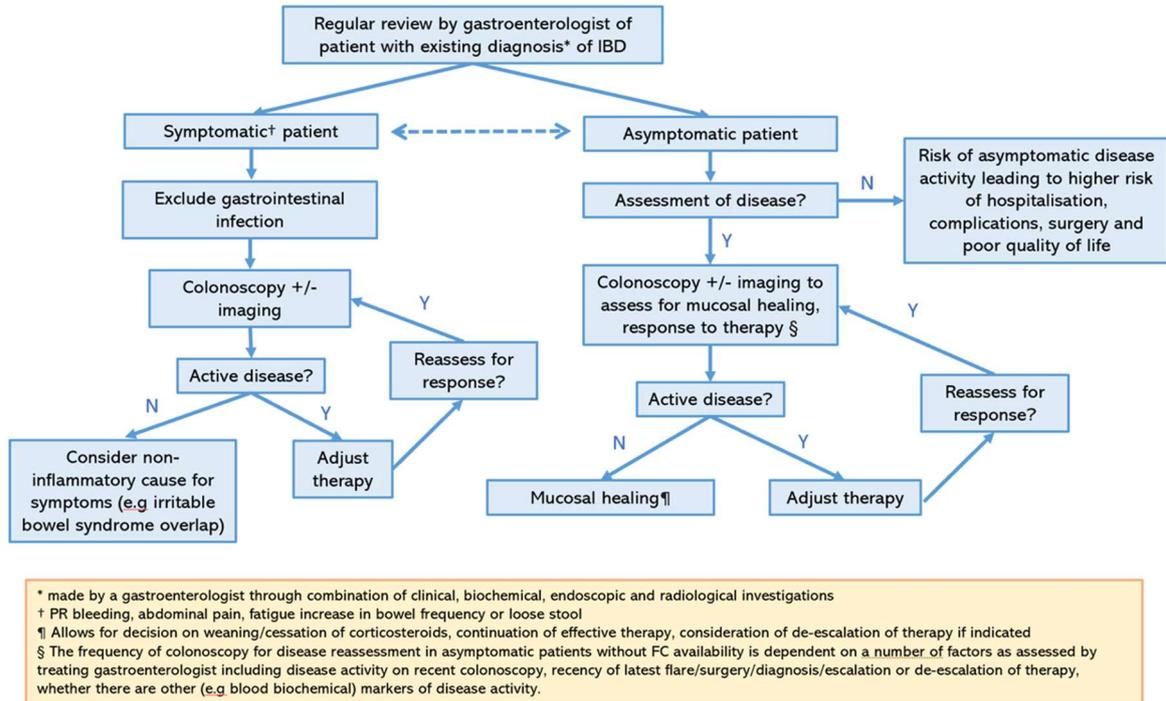
PASC confirmed that the assessment framework was appropriately described in the PICO.

Clinical management algorithms

Patients with an established IBD diagnosis are managed by gastroenterologists. A minimum of one annual appointment for review is appropriate management, however additional appointments are required for patients with symptoms and/or moderate/severe disease. During reviews, the gastroenterologist will monitor patients through a combination of clinical, biochemical, endoscopic and radiological investigations. The current and proposed treatment algorithms are provided in Figure 3 and Figure 4 below.

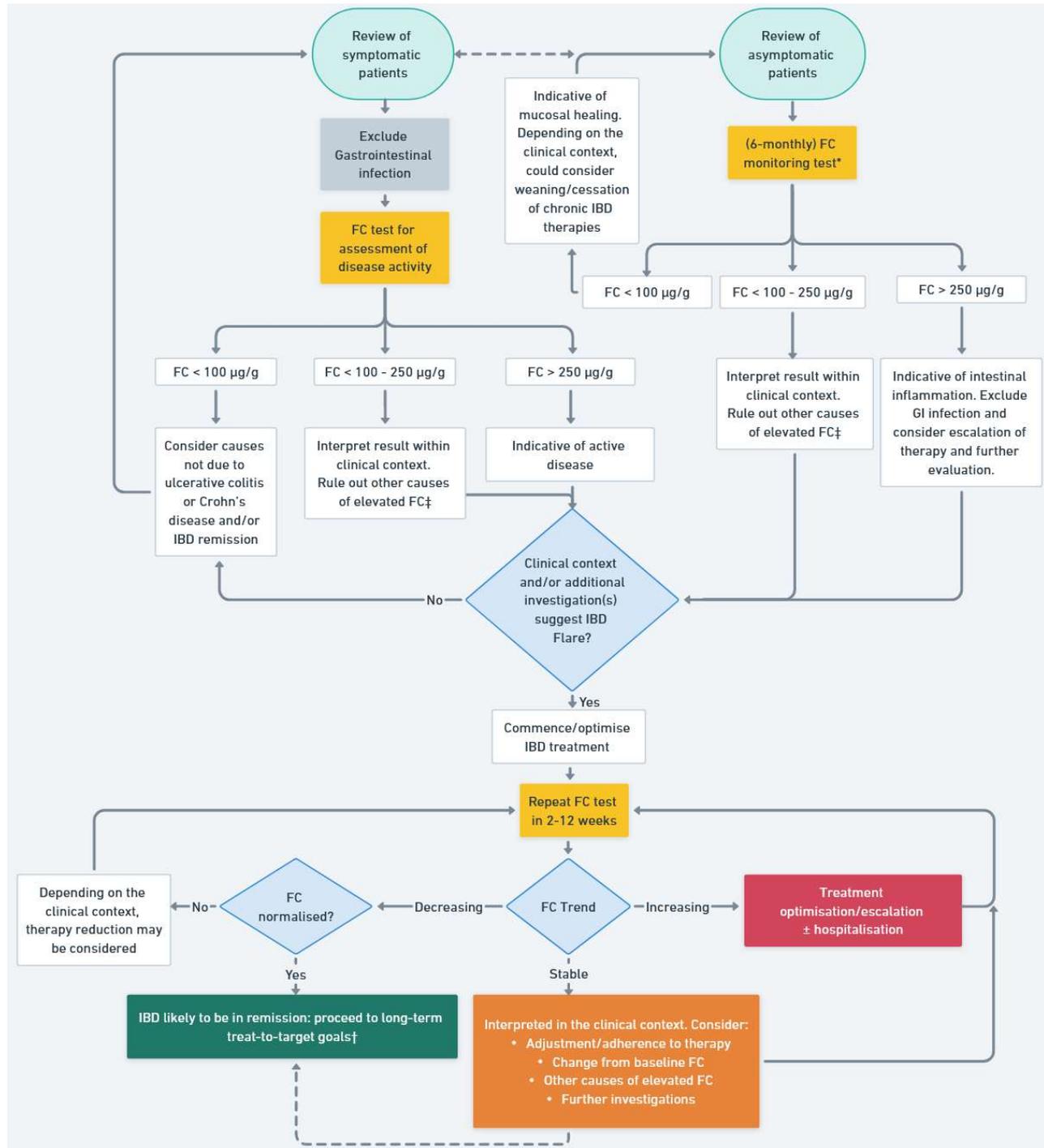
Figure 3 Treatment algorithm without faecal calprotectin testing

Usual Care



Source: Additional information provided by the applicant at the pre-PASC stage.

Figure 4 Proposed treatment algorithm with faecal calprotectin testing.



Source: Developed during the evaluation.

IBD = inflammatory bowel disease; FC = faecal calprotectin

* The frequency of FC reassessment in asymptomatic patients is dependent on a number of factors as assessed by the treating gastroenterologist including the result of latest FC/trend, disease activity on recent colonoscopy, recency of latest flare/surgery/diagnosis/escalation or de-escalation of therapy, whether there are other (e.g. blood biochemical) markers of disease activity. For example, after alteration of therapy, routine FC at 3-6 months would be standard practice.

‡ Rule out other causes of elevated FC (e.g. diverticulitis, medications, infection). Consider: Checking of adherence to therapy, Change from baseline/trends in FC; Further investigations (e.g. colonoscopy, imaging).

† Mucosal healing as assessed by colonoscopy is a long-term treatment target. The frequency of colonoscopy assessment will depend on the clinical context.

Dashed lines represent potential pathways, reflecting flexibility in the clinical dynamic.

During the pre-PASC teleconference, consultant gastroenterologists stated that they would not generally use colonoscopies to assess asymptomatic patients for disease activity on a 6 monthly basis. They contend that prior to the availability of FC tests, regular colonoscopy was performed even in asymptomatic patients, but the frequency depended on a number of clinical factors. The applicants elected to retain colonoscopy as the chosen comparator in this setting. The introduction of FC testing is proposed to primarily reduce the number of colonoscopies performed by ruling out IBD flares in symptomatic patients and confirming the presence of an IBD flare in symptomatic patients. The application also suggests that FC results which indicate IBD flare resolution may also reduce the number of colonoscopies performed, however the extent of reduction may be less than expected. This is due to the need for colonoscopies in patients following IBD flares to assess that endoscopic healing has occurred once FC results have normalised, as stated in the STRIDE-II treat-to-target guidelines provided in the application (Figure 1).

Proposed economic evaluation

The application claimed the proposed intervention (FC testing) is non-inferior in terms of comparative benefits and harms to colonoscopy/biopsy. The comparative effectiveness of FC testing relative to colonoscopy/biopsy needs to be assessed based on sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), additional true positives and additional true negatives to assess the clinical claim. Results of a preliminary literature search of non-comparative results for FC testing are summarised in Table 3 and indicate that FC is a good surrogate marker in detecting mucosal healing and predicting relapse with high accuracy. However, accuracy estimates vary by the FC cut-off levels. FC was also found to be more sensitive in UC than CD.

While there has been no evidence submitted of the comparative safety for FC testing, it may lead to a reduction in colonoscopy related adverse events (e.g., perforations) where colonoscopies are avoided in some patients.

Table 3 Available evidence to inform an economic evaluation

Reference	Description
(Bohra et al. 2023)	Assessed the utility of FC in CD comparing it to endoscopic activity. Pooled sensitivity was 81% (95% CI, 77-84%) with specificity of 74% (95% CI, 70-80%) and an AUC of 0.85. Subanalysis for mucosal healing: DOR of 18.17 (95% CI [11.08-29.82]) and a negative likelihood ratio of 0.19 [0.14-0.26].
(Rokkas et al. 2018)	FC in IBD (CD and UC) showed a pooled sensitivity of 85%, specificity of 75%, DOR of 16.3 and AUC of 0.88, in diagnosing active disease. The sub-group analysis revealed that FC performed better in UC than in CD (pooled sensitivity 87.3% vs 82.4%, specificity 77.1% vs 72.1% and AUC 0.91 vs 0.84). Examining the optimum FC cut-off levels, the best sensitivity (90.6%) was achieved at 50 µg/g, whereas the best specificity (78.2%) was found at levels >100 µg/g.
(Bromke et al. 2021)	Presents results of two meta-analyses. CD: 16 studies with 1333 patients. FC had a diagnostic OR of 13.8 in detecting mucosal healing. Summary sensitivity was 82.8% (76.9-87.4), specificity was 75.9% (68.3-82.1). AUC was 0.829 with estimated DOR of 11.20. UC: 35 studies with 5826 patients. FC had a diagnostic OR of 16 in detecting mucosal healing. Summary sensitivity was 80.4% (75.7 to 84.3), specificity was 81.7% (78.0 to 84.8). AUC was 0.858 with estimated DOR of 14.48.
(Mosli et al. 2015)	Patients with IBD and active disease as determined by endoscopy as gold standard. 19 studies included. Pooled sensitivity and specificity estimates of FC were 0.88 (0.84 – 0.90) and 0.73 (0.66-0.79). FC was more sensitive in UC than CD.
(Li et al. 2019)	The study conducted a meta-analysis: to assess FC as a surrogate marker for predicting relapse in adults with UC. 14 studies of 1110 patients with UC calculated pooled sensitivity and specificity to be 75% and 77% (cut-offs 55–341 µg/g).

AUC = area under the curve; CD = Crohn’s Disease; CI = confidence interval; DOR = diagnostic odds ratio; FC = faecal calprotectin; IBD = inflammatory bowel disease; OR = odds ratio; UC = Ulcerative Colitis

Based on the applicant's clinical claim of non-inferior safety and effectiveness of FC testing to monitor IBD compared to endoscopy/colonoscopy (± biopsy), a cost-minimisation analysis (CMA) would be appropriate. If the clinical claim during the assessment is found to differ from that proposed, Table 4 provides a guide for determining which type of economic evaluation is appropriate.

Table 4 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

a ‘Uncertainty’ covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

b An adequate assessment of ‘noninferiority’ is the preferred basis for demonstrating equivalence

PASC considered that if colonoscopy were adopted as the sole comparator then a cost-minimisation approach is appropriate insofar as a claim of clinical non-inferiority is being made. However, PASC considered that if FC testing led to tighter control of IBD and therefore better clinical outcomes and reductions in disease sequelae then a cost utility analysis might be more appropriate. PASC also considered that the approach could vary depending on the population and that potentially a cost minimisation approach may be more appropriate for the symptomatic population and a cost utility approach may be more appropriate for the asymptomatic population.

Cost reductions due to FC testing

FC testing is a less costly procedure compared to colonoscopy. Further, the rate of colonoscopies per patient is expected to decrease following the listing of FC testing. The applicant proposed two estimates for the cost of one colonoscopy to the healthcare system. One, based on MSAC application 1353.1, estimated the cost of colonoscopy to the healthcare system to be \$3,146 (including the cost of endoscopic complications) using MBS fee (2019) and National Hospitals Cost Data Collection (NHCDC) report. The other estimate of the cost of colonoscopy is \$6,735 from the NSW Health Activity Based Management casemix database (Badgery-Parker et al. 2019). Based on this, the applicant estimated a cost reduction of \$1,195.48 to \$2,559.30 per FC test due to the reduction in the number of colonoscopies alone assuming reduction in colonoscopies of up to 38%. This resulted in an overall net savings ranging from \$74 million to \$164 million in Year 1. The frequency of both colonoscopy and FC testing is uncertain and will vary between symptomatic and asymptomatic phases resulting in different cost offsets. Other cost implications due to change in management of disease following the incorporation of FC testing need to be considered to assess the magnitude of cost savings due to FC testing.

PASC noted that as biopsies are also taken with colonoscopies and there are complications associated with some colonoscopies, the costs associated with biopsies and complications which accompany a share of colonoscopies should also be taken into account in the economic evaluation (e.g these would be treated as additional comparator cost offsets assuming that FC testing led to a net reduction in colonoscopies).

PASC noted the concern that the introduction of FC testing may not reduce colonoscopies as much as suggested in the submission and in particular that the projected reduction of colonoscopy required for monitoring IBD patients by 50% could be unlikely. However, the applicant contended that the projection was a credible one as it was based on the results of an Australian clinical study.

As per PASC advice that false positive FC results be considered as part of the outcomes, PASC noted that the economic evaluation should take into account the costs of additional colonoscopies due to false positive/intermediate FC results.

Proposal for public funding

Currently there are existing MBS items (Item numbers 66522, 66523) for FC testing for the diagnosis of IBD. The applicant's proposal to list FC testing is for the management of IBD after the diagnosis and severity of disease is established. The applicant has requested that the service can only be requested by a specialist or a consultant physician practicing as a specialist gastroenterologist and proposed a maximum of 4 tests per year. However, as discussed in the 'Intervention' section above, some patients might require more than 4 FC tests per year, depending on their number of relapses and results of the FC monitoring tests.

The proposed item descriptor requires the specialist gastroenterologist to make a separate pathology service request for each FC test. The applicant advised that patients with IBD are reviewed by their gastroenterologist at least once per year, depending on the complexity of their IBD.

The applicant acknowledged that there may be benefits to providing FC testing for the monitoring of established disease in primary care, but noted that since telehealth has improved access to gastroenterologists this would reduce equity issues associated with access to gastroenterologists in remote and rural areas; and therefore not allowing access to testing via primary care was less of a concern than the risk of leakage.

However, the applicant also acknowledged that some patients with very mild disease without major exacerbations may have a shared care arrangement with their GP. Moreover, Departmental medical advisors were of the view that a significant proportion of IBD patients relied on their GPs for day-to-day management of their disease and given the existence of a diagnostic item for FC in primary care, the risk of use outside of the proposed restriction for monitoring of established disease is low. The Department also noted that while telehealth had improved accessibility to gastroenterologists in terms of reducing the need for frequency of travel to see a gastroenterologist, the issue of financial accessibility remained and therefore the financial accessibility implications of restricting FC testing to gastroenterologists remained unaddressed by the availability of telehealth.

PASC may wish to consider in light of the above whether GPs should also be able to request FC testing.

PASC considered whether GPs should be able to request FC testing in addition to specialists to enable access to the test to a wider population, particularly for patients in rural and remote areas where specialist access is limited. PASC noted that some patients with IBD, particularly those who are in remission or with less severe disease, are in regular contact with their GP and access to the test would improve if GPs could order it. PASC and the applicant agreed that allowing GPs to order FC tests in consultation with a specialist would be appropriate. The Department advised that as long as the patient has an ongoing relationship with a gastroenterologist, then this would enable their GP to order FC tests while remaining compliant with MBS rules that the test had been ordered "in consultation with a specialist". PASC considered that a GP education program, implemented in consultation with GESA, would be helpful to assist GPs in understanding when to order FC tests and in interpreting FC test results. The applicant considered this would be appropriate and were happy to assist in developing the education program.

Patients requiring more than the number of tests covered under the MBS would face additional out-of-pocket expenses.

PASC and the applicant agreed that the upper limit of the frequency of FC testing should be increased to 10 FC tests per patient per year. PASC noted that very few patients (if any) would require the full 10 tests in the one year (and as such, this should be taken into consideration in the economic analysis), but this would enable patients who are experiencing a flare in symptoms to receive adequate FC monitoring. PASC considered the risk of leakage to be low given that the proposed IBD monitoring item is restricted to individuals already with an IBD diagnosis and because FC testing requires active participation by the patient (eg. the patient is required to collect the faecal sample for testing).

Based on the existing MBS items for FC testing (Item numbers 66522, 66523), the proposed MBS fee is assumed to be \$75.00. PASC noted that the existing MBS items for FC testing for diagnosis of IBD (items 66522 and 66523) were restricted to patients aged less than 50 years. PASC confirmed that the proposed FC test for monitoring should not be restricted by age.

Category 6 – Pathology Services
MBS item XXXX
Faecal Calprotectin test for assessment of disease activity if all the following apply: <ul style="list-style-type: none"> a. the patient has diagnosed inflammatory bowel disease; b. the service is requested by or on behalf of a specialist or consultant physician practising as a specialist gastroenterologist <p>A maximum of 10 tests per year may be performed.</p>
Fee: \$75.00 Benefit: 75% = \$56.25 85% = \$63.75

Summary of public consultation input

PASC noted and welcomed consultation input from 7 organisations. The individual input received was provided by two organisations. Crohn's and Colitis Australia submitted responses from 47 individual consumers. Gastroenterological Society of Australia provided feedback responses from 16 specialists and one consumer individual. In total, 64 individuals' consultation responses were received, 48 of whom were consumers and 16 health professionals. The 7 organisations that submitted input were:

- Therapeutic Goods Administration (TGA)
- Royal College of Pathologists of Australasia (RCPA)
- Australian Pathology
- Gastroenterological Nurses College of Australia (GENCA)
- Crohn's and Colitis Australia (CCA)
- Public Pathology Australia (PPA)
- Gastroenterological Society of Australia (GESA)

The consultation feedback received was all supportive of public funding for faecal calprotectin for monitoring of disease activity in patients with inflammatory bowel disease (IBD). In summary, faecal calprotectin (FC) for monitoring disease in IBD was seen as providing significant physical, mental health and financial benefits through an accessible, less invasive, and reliable test.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback included a decrease in expensive speciality care including magnetic resonance imaging and colonoscopy and lower out-of-pocket costs for consumers self-funding FC testing. FC for monitoring IBD was stated to be cost effective and able to detect early inflammation leading to earlier treatment changes, better clinical management, improved quality of life and alleviating patient and carer anxiety.

Most of the individual specialists noted that it had proven to be far more sensitive than other pathology testing and accurately reflected disease activity. RCPA indicated that FC testing is regarded as gold standard of care for the management of IBD and Australian Pathology stated that monitoring FC is the current and best clinical practice for IBD patients.

The main disadvantages of public funding received in the consultation feedback was the limitation on who can order FC testing, as the application specifies testing can only be ordered by a specialist gastroenterologist. Consultation feedback advocated the need to be able to provide this test in primary care by GPs to allow equity of access and better assessment of regional patients and GENCA advocated

that nurse practitioners should also be able to order FC testing as they are often the port of call for patients experiencing symptoms.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included further follow up if faecal calprotectin level is high including investigation by colonoscopy or scans and review by specialist nurse or gastroenterologist and potentially a dietitian.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback ranged from agreeing to strongly agreeing with the proposed population. Existing FC testing for diagnosis of IBD is restricted to patients less than 50 years of age and one individual highlighted the importance of including all patients with IBD for FC testing to monitor the disease.

The consultation feedback ranged from agreeing to strongly agreeing with the proposed comparator. Input indicated that colonoscopy has been used to assess disease severity and that less invasive FC testing would be used if supported by public funding.

The consultation feedback ranged from agreeing to strongly agreeing with the proposed clinical claim. RCPA stated that changes within the normal reference range are not of value to look at as values can vary at 20% and there is also diurnal variation. RCPA indicated there is no absolute level where actions are mandated, but a rise to 1000 would certainly trigger clinical assessment even if the patient is asymptomatic. PPA indicated that it is rare for biological fluctuation to rise above top of normal range (150) but also suggested that rise of >50% within normal range might prompt concern for retesting, but not invasive testing. Furthermore, low FC results with symptoms has prompted investigations for other causes of symptoms (e.g., infection, irritable bowel syndrome).

Cost information for the proposed medical service

The consultation feedback ranged from disagreeing to strongly agreeing with the proposed service descriptor. The input that disagreed with the proposed service descriptor advocated to include the option to order the test in primary care, indicating that the value of less costly monitoring and early intervention is lost if requesting FC testing is restricted to gastroenterologists. Australian Pathology indicated a preference not to restrict testing frequency and to allow the treating clinicians to determine when FC testing was appropriate.

The consultation feedback ranged from disagreeing to strongly agreeing with the proposed service fee. One individual noted that savings from better disease control will be greater than the cost of the test. Input noted that some patients are charged more than the proposed fee and that there is potential for out-of-pocket costs.

Consumer Feedback

Consumer feedback highlighted a preference to avoid colonoscopy as it is invasive and interrupted their life (including school and work), may require overnight hospitalisation and may have high out-of-pocket costs. Consumer feedback also highlighted adverse events associated with colonoscopy. This included uncontrollable bowel motions and bowel bleeding requiring admission to hospital and required a blood transfusion. Consumers reported that when their symptoms are stable, they need to go for FC testing 3-4 times in a year. One individual indicated that colonoscopy was limited due to strictures and that MRI was contraindicated due to staples. Consumers also provided detailed information about they manage their IBD.

PASC acknowledged the consultation input from The Royal College of Pathologists of Australasia (RCPA), Australian Pathology, Public Pathology Australia (PPA), Gastroenterological Society of Australia (GESA), Gastroenterological Nurses College of Australia (GENCA) and Crohn's & Colitis Australia (CCA).

PASC noted the consultation feedback that limiting access to the FC test through gastroenterologists raises a cost issue for people on low incomes, and it also potentially limits access to the test for people living in rural/regional areas.

Next steps

PASC noted that additional advice should be sought from pathology organisations regarding appropriate FC result test thresholds/reference ranges, and how these should be communicated to the clinician.

PASC noted that the proposed item descriptor for FC testing should be reviewed by the Royal Australian College of General Practitioners (RACGP) for feedback regarding how ordering of FC tests for monitoring IBD patients by GPs should be addressed in the item descriptor.

PASC noted the applicant has elected to progress its application as a DCAR (Department Contracted Assessment Report).

Applicant Comments on Ratified PICO

The Applicant had no comment.

References

- Al Hashash, J, Regueiro, M. 2023. "Medical management of low-risk adult patients with mild to moderate ulcerative colitis." In. UpToDate: Wolters Kluwer.
- Australian Bureau of Statistics. 2023. "Population clock and pyramid." In, edited by Australian Bureau of Statistics. Australian Government.
- Axelrad, J. E., S. Lichtiger, and V. Yajnik. 2016. 'Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment', *World J Gastroenterol*, 22: 4794-801 doi: 10.3748/wjg.v22.i20.4794.
- Badgery-Parker, Tim, Sallie-Anne Pearson, Kelsey Chalmers, Jonathan Brett, Ian A Scott, Susan Dunn, Neville Onley, and Adam G Elshaug. 2019. 'Low-value care in Australian public hospitals: prevalence and trends over time', *BMJ Quality & Safety*, 28: 205-14 doi: 10.1136/bmjqs-2018-008338.
- Bohra, A., G. Mohamed, A. Vasudevan, D. Lewis, D. R. Van Langenberg, and J. P. Segal. 2023. 'The Utility of Faecal Calprotectin, Lactoferrin and Other Faecal Biomarkers in Discriminating Endoscopic Activity in Crohn's Disease: A Systematic Review and Meta-Analysis', *Biomedicines*, 11 doi: 10.3390/biomedicines11051408.
- Bromke, M. A., K. Neubauer, R. Kempirski, and M. Krzystek-Korpacka. 2021. 'Faecal Calprotectin in Assessment of Mucosal Healing in Adults with Inflammatory Bowel Disease: A Meta-Analysis', *J Clin Med*, 10 doi: 10.3390/jcm10102203.
- Busingye, D., A. Pollack, and K. Chidwick. 2021. 'Prevalence of inflammatory bowel disease in the Australian general practice population: A cross-sectional study', *PLoS One*, 16: e0252458 doi: 10.1371/journal.pone.0252458.
- Cellier C, Sahnoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, et al. 1994. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gut*. 35(2)231-235.
- Central Adelaide Local Health Network. 2023. 'Using ultrasound to monitor inflammatory bowel disease'. https://centraladelaide.health.sa.gov.au/ultrasound_for_ibd/.
- Corewell Health. 2023. "Calprotectin, Feces." In.: Mayo Foundation for Medical Education and Research.
- Costa, F., M. G. Mumolo, L. Ceccarelli, M. Bellini, M. R. Romano, C. Sterpi, A. Ricchiuti, S. Marchi, and M. Bottai. 2005. 'Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease', *Gut*, 54: 364-8 doi: 10.1136/gut.2004.043406.
- Dunn, R., D. Kejarawal, I. Malik, O. Ogunrinde, A. Kannan, and S. Farook. 2017. 'PTU-061 Determining a value of faecal calprotectin above which colonoscopy is indicated in the county durham and darlington population', *Gut, suppl. Supplement 2*, 66 doi: <https://doi.org/10.1136/gutjnl-2017-314472.156>.
- Flanagan, A., S. M. Allsopp, S. A. O'Connor, J. Tobin, C. Pretorius, I. S. Brown, S. Bell, and A. J. M. Daveson. 2023. 'High incidence of inflammatory bowel disease in Northern Australia: a prospective community population-based Australian incidence study in the Mackay-Isaac-Whitsunday region', *Intern Med J*, 53: 1602-09 doi: 10.1111/imj.15941.
- Gisbert, J. P., A. C. Marín, and M. Chaparro. 2015. 'Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy', *Alimentary Pharmacology & Therapeutics*, 42: 391-405 doi: <https://doi.org/10.1111/apt.13276>.
- Kucharzik, Torsten, Bianca M. Wittig, Ulf Helwig, Norbert Börner, Alexander Rössler, Stefan Rath, Christian Maaser, Axel Naumann, Gregor Pelster, Jörg Spengler, Carsten Büning, Enno Gentz, Harald Matthes, Dieter Nürnberg, Adelheid Jung, Jochen Maul, Daniel C. Baumgart, Deike Strobel, Gabriele Manok, Matthias Breidert, Michael Scheurlen, Andreas Stallmach, Uwe Will, Thomas Krause, Rolf-Achim Krüger, Niels Teich, Ingolf Schiefke, Annette Krummenerl, Klaus Fellermann, Rüdiger Kilian, Torsten Kucharzik, Christian Maaser, Ulf Helwig, Volker Meister, Stefan Mielck, Diether Ludwig, Norbert Börner, Stefan Schanz, Robert Kihn, Robert Manfred Hoffmann, Barbara

- Lanyi, Robert Eehalt, Burghard Wilborn, Franz Ludwig Dumoulin, Wolfgang Mohl, Andreas Lügering, Thomas Krummenerl, Jan Heidemann, Matthias Pichler, Hans Allescher, Frank Meyer-Hilse, Gerd-Rüdiger Franke, Oliver Bachmann, and Martin Fährndrich. 2017. 'Use of Intestinal Ultrasound to Monitor Crohn's Disease Activity', *Clinical Gastroenterology and Hepatology*, 15: 535-42.e2 doi: <https://doi.org/10.1016/j.cgh.2016.10.040>.
- Labaere, D., A. Smismans, A. Van Olmen, P. Christiaens, G. D'Haens, V. Moons, P. J. Cuyle, J. Frans, and P. Bossuyt. 2014. 'Comparison of six different calprotectin assays for the assessment of inflammatory bowel disease', *United European Gastroenterol J*, 2: 30-7 doi: 10.1177/2050640613518201.
- Li, J., X. Zhao, X. Li, M. Lu, and H. Zhang. 2019. 'Systematic Review with Meta-Analysis: Fecal Calprotectin as a Surrogate Marker for Predicting Relapse in Adults with Ulcerative Colitis', *Mediators Inflamm*, 2019: 2136501 doi: 10.1155/2019/2136501.
- Lichtenstein, G. R., E. V. Loftus, K. L. Isaacs, M. D. Regueiro, L. B. Gerson, and B. E. Sands. 2018. 'ACG Clinical Guideline: Management of Crohn's Disease in Adults', *Am J Gastroenterol*, 113: 481-517 doi: 10.1038/ajg.2018.27.
- Maaser, C., A. Sturm, S. R. Vavricka, T. Kucharzik, G. Fiorino, V. Annese, E. Calabrese, D. C. Baumgart, D. Bettenworth, P. Borralho Nunes, J. Burisch, F. Castiglione, R. Eliakim, P. Ellul, Y. González-Lama, H. Gordon, S. Halligan, K. Katsanos, U. Kopylov, P. G. Kotze, E. Krustinš, A. Laghi, J. K. Limdi, F. Rieder, J. Rimola, S. A. Taylor, D. Tolan, P. van Rheenen, B. Verstockt, and J. Stoker. 2019. 'ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications', *J Crohns Colitis*, 13: 144-64 doi: 10.1093/ecco-jcc/jyy113.
- McDowell, C., U. Farooq, and M. Haseeb. 2023. 'Inflammatory Bowel Disease.' in, *StatPearls* (StatPearls Publishing, StatPearls Publishing LLC.: Treasure Island (FL)).
- MedicineWise, NPS. 2021. 'FAECAL CALPROTECTIN IN INFLAMMATORY BOWEL DISEASE (IBD)', NPS MedicineWise. https://www.nps.org.au/assets/NPS/pdf/NPSMW2394_Faecal_Calprotectin_Algorithm.pdf.
- Mosli, Mahmoud H, Guangyong Zou, Sushil K Garg, Sean G Feagan, John K MacDonald, Nilesh Chande, William J Sandborn, and Brian G Feagan. 2015. 'C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis', *Official journal of the American College of Gastroenterology | ACG*, 110: 802-19 doi: 10.1038/ajg.2015.120.
- Motaganahalli, Satwik, Lauren Beswick, Danny Con, and Daniel R. van Langenberg. 2019. 'Faecal calprotectin delivers on convenience, cost reduction and clinical decision-making in inflammatory bowel disease: a real-world cohort study', *Internal Medicine Journal*, 49: 94-100 doi: <https://doi.org/10.1111/imj.14027>.
- MSAC. 2017. "Protocol to guide the assessment of a faecal calprotectin test to help differentiate between functional and inflammatory bowel disorders, and for monitoring disease activity in people with known inflammatory bowel disease (IBD)." In, edited by Australian Government Department of Health and Aged Care.
- Neurath, M. and Vieth, M. 2023. 'Different levels of healing in inflammatory bowel diseases: mucosal, histological, transmural, barrier and complete healing', *Gut*, 72:2164-2183 doi: 10.1136/gutjnl-2023-329964
- Pathirana, W. G. W., S. P. Chubb, M. J. Gillett, and S. D. Vasikaran. 2018. 'Faecal Calprotectin', *Clin Biochem Rev*, 39: 77-90.
- Plevris, N., and C. W. Lees. 2022. 'Disease Monitoring in Inflammatory Bowel Disease: Evolving Principles and Possibilities', *Gastroenterology*, 162: 1456-75.e1 doi: 10.1053/j.gastro.2022.01.024.
- PwC. 2013. 'Improving Inflammatory Bowel Disease care across Australia'. <https://crohnsandcolitis.org.au/wp-content/uploads/2022/02/PwC-report-2013.pdf>.
- Roda, G., S. Chien Ng, P. G. Kotze, M. Argollo, R. Panaccione, A. Spinelli, A. Kaser, L. Peyrin-Biroulet, and S. Danese. 2020. 'Crohn's disease', *Nat Rev Dis Primers*, 6: 22 doi: 10.1038/s41572-020-0156-2.

- Rokkas, T., P. Portincasa, and I. E. Koutroubakis. 2018. 'Fecal calprotectin in assessing inflammatory bowel disease endoscopic activity: a diagnostic accuracy meta-analysis', *J Gastrointest Liver Dis*, 27: 299-306 doi: 10.15403/jgld.2014.1121.273.pti.
- Sandborn, W. J. 2014. 'Crohn's disease evaluation and treatment: clinical decision tool', *Gastroenterology*, 147: 702-5 doi: 10.1053/j.gastro.2014.07.022.
- Studd, C., G. Cameron, L. Beswick, R. Knight, C. Hair, J. McNeil, P. Desmond, J. Wilson, W. Connell, and S. Bell. 2016. 'Never underestimate inflammatory bowel disease: High prevalence rates and confirmation of high incidence rates in Australia', *J Gastroenterol Hepatol*, 31: 81-6 doi: 10.1111/jgh.13050.
- Suárez Ferrer, C., J. Poza Cordón, O. Crivillén Anguita, P. Mayor Delgado, J. L. Rueda García, E. Martín Arranz, M. Sánchez Azofra, J. Noci Belda, L. García Ramírez, and M. D. Martín Arranz. 2021. 'Prognostic value of ultrasound activity and parietal healing in patients with Crohn's disease', *Rev Esp Enferm Dig*, 113: 494-99 doi: 10.17235/reed.2020.7347/2020.
- Turner, D., A. Ricciuto, A. Lewis, F. D'Amico, J. Dhaliwal, A. M. Griffiths, D. Bettenworth, W. J. Sandborn, B. E. Sands, W. Reinisch, J. Schölmerich, W. Bemelman, S. Danese, J. Y. Mary, D. Rubin, J. F. Colombel, L. Peyrin-Biroulet, I. Dotan, M. T. Abreu, and A. Dignass. 2021. 'STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD', *Gastroenterology*, 160: 1570-83 doi: 10.1053/j.gastro.2020.12.031.
- Villanacci, V., L. Reggiani-Bonetti, T. Salviato, G. Leoncini, M. Cadei, L. Albarello, A. Caputo, M. C. Aquilano, S. Battista, and P. Parente. 2021. 'Histopathology of IBD Colitis. A practical approach from the pathologists of the Italian Group for the study of the gastrointestinal tract (GIPAD)', *Pathologica*, 113: 39-53 doi: 10.32074/1591-951x-235.
- Waljee, Akbar K., Rachel Lipson, Wyndy L. Wiitala, Yiwei Zhang, Boang Liu, Ji Zhu, Beth Wallace, Shail M. Govani, Ryan W. Stidham, Rodney Hayward, and Peter D. R. Higgins. 2018. 'Predicting Hospitalization and Outpatient Corticosteroid Use in Inflammatory Bowel Disease Patients Using Machine Learning', *Inflammatory Bowel Diseases*, 24: 45-53 doi: 10.1093/ibd/izx007
- Walsh, A., Bryant, R. & Travis, S. 2016. Current best practice for disease activity assessment in IBD. *Nat Rev Gastroenterol Hepatol* 13, 567–579.