# Medical Services Advisory Committee (MSAC) Public Summary Document

## Application No. 1761 – Faecal calprotectin for the monitoring of disease activity in patients with inflammatory bowel disease

**Applicant:**          Gastroenterological Society of Australia

**Date of MSAC consideration:**          29 November 2024

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

## 1.     Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of faecal calprotectin (FC) testing for the monitoring of inflammatory bowel disease (IBD) was received from the Gastroenterological Society of Australia by the Department of Health and Aged Care.

## 2.     MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for faecal calprotectin (FC) testing for the management of symptomatic patients with inflammatory bowel disease (IBD). MSAC did not support public funding of FC testing for the monitoring of asymptomatic patients with IBD. MSAC considered general practitioners (GPs) should be able to request FC testing on behalf of a specialist or consultant physician.

MSAC considered that FC testing for patients with symptomatic IBD has non-inferior clinical effectiveness and non-inferior safety compared with colonoscopy (the comparator). MSAC considered FC testing has clinical utility for symptomatic patients as it can help detect whether symptoms are due to increased IBD activity and monitor healing after an IBD flare. MSAC considered the clinical utility of FC testing for asymptomatic patients was highly uncertain due to limited evidence that using the test would change management and improve health outcomes in this subpopulation. MSAC considered that the claim of non-inferior comparative safety of FC testing was not supported for asymptomatic patients given the high rate of false positive FC results, which may lead to unnecessary escalation of therapy or additional colonoscopy and potentially expose this group to the adverse effects of these interventions.

MSAC noted that while the economic and financial models estimated cost savings from adoption of FC testing due to reductions in colonoscopies, MSAC considered this was unlikely even for the symptomatic population. MSAC considered that some of the estimated reductions in colonoscopies may have already occurred in clinical practice due to current usage of FC testing through private funding, public hospitals or use of existing MBS items for IBD diagnosis.

MSAC considered that there is a risk that the MBS item for symptomatic patients would be inappropriately used for asymptomatic IBD patients. MSAC advised that the utilisation of the MBS

items for FC testing should be reviewed 2 years after the new item for symptomatic patients is implemented.

MSAC's supported MBS item descriptor is provided below in Table 1.

**Table 1: MSAC's supported MBS item descriptor**

| Category 6 – Pathology Services |
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| MBS item *XXXX<br>Faecal Calprotectin test for the management of a symptomatic patient with diagnosed inflammatory bowel disease, requested by, or on behalf of, a specialist or consultant physician. |
| Fee: $75.00 Benefit: 75% = $56.25 85% = $63.75 |

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## Consumer summary

This is an application from the Gastroenterological Society of Australia requesting Medicare Benefits Schedule (MBS) listing of faecal calprotectin testing for the monitoring of people with inflammatory bowel disease (IBD).

IBD is not one disease but a group of conditions that are characterised by recurring inflammation of the gastrointestinal (GI) tract. These conditions include Crohn disease and ulcerative colitis. People with active IBD can have symptoms such as diarrhoea, stomach pain, weight loss and fatigue. If left untreated, IBD can lead to hospital admission, anaemia (when there are not enough red blood cells to carry oxygen around the body) and surgery, among other things. IBD can also greatly affect the person's emotional and social wellbeing. To avoid these outcomes, guidelines recommend that IBD be regularly monitored as a part of standard management and treatment.

Inflammation in the GI tract, specifically the intestines, causes the immune system to send white blood cells (neutrophils) to the inflamed area. The neutrophils release a protein called calprotectin into the intestines, where it mixes with faeces/stools. This protein is called faecal calprotectin (FC). A high level of FC can be a sign that the intestines are inflamed. Therefore, measuring FC using an FC test can be a way to determine intestinal inflammation in people with IBD. This is a non-invasive test and is done by taking a sample of the stool, which is then sent to a laboratory for testing. Alternatives to FC testing include current standard medical management (e.g. examining the patient's clinical history and other blood tests to check for inflammation in the body) and/or a colonoscopy (which involves putting a camera into the bowel to look at the insides of the intestines) to look for inflammation within the GI tract. A colonoscopy is a more invasive procedure that has risks such as perforation (small tearing) of the colon. FC testing may help some patients avoid having a colonoscopy.

MBS items already exist for FC testing to diagnose IBD in patients under 50 years of age. This application proposes a new MBS item for FC testing that can be used to monitor people with IBD, to check if they might be having a flare in their IBD, whether changes need to be made to a patient's treatment and whether the treatment a patient is using is working.

MSAC acknowledged that FC testing is already being widely used in Australia, and patients may currently have difficulty accessing the test because of out-of-pocket costs for the test. MSAC also recognised that FC testing would be particularly useful in children because it may help them to avoid more invasive procedures such as colonoscopy. However, based on the evidence, MSAC considered that the FC test was most beneficial for patients diagnosed with IBD who present with symptoms (symptomatic group), to help work out if those symptoms are due to a flare in their IBD. The benefits of FC testing were less clear for patients who are diagnosed with IBD but were currently not experiencing symptoms (asymptomatic group).

| Consumer summary |
| --- |
| There is better guidance backed up by research on how symptomatic patients should be managed following a FC test result, whereas it is unclear how the results of FC testing should be used to guide the management of asymptomatic patients. In addition, there is a risk that asymptomatic patients may be more likely to be inadvertently harmed from use of the test due to introduction of unnecessary invasive procedures, new treatments or escalation of their existing treatment that may result from uncertain/intermediate (neither positive or negative) or false positive test results (a test result that is incorrectly positive). Therefore, MSAC supported funding the test only for symptomatic patients (including children). To help patients access FC testing, MSAC also considered that general practitioners (GPs) should be able to request the test, in consultation with a specialist. |
| MSAC considered that GPs and specialists need further education about how to properly interpret the test results given that IBD is a complex condition. MSAC also advised that a review of the supported item should be performed after 24 months to ensure it is not being inappropriately used. |
| **MSAC's advice to the Commonwealth Minister for Health and Aged Care** |
| MSAC supported public funding of FC testing for the management of symptomatic people with IBD. MSAC considered that the test was safe and effective for symptomatic people, but there was not sufficient evidence to support the clinical utility of the test in asymptomatic people with IBD. MSAC advised that a review of the usage of FC testing should be performed after 24 months. |

# 3.    Summary of consideration and rationale for MSAC's advice

MSAC noted that this was an application from the Gastroenterological Society of Australia requesting Medicare Benefits Schedule (MBS) listing of faecal calprotectin (FC) testing for the monitoring of people with inflammatory bowel disease (IBD).

MSAC recalled that, in 2018, it had considered MBS listing of FC testing for the diagnosis and monitoring of IBD (MSAC Application 1353). MSAC did not support listing at the time, requesting further clarification on current Australian practice to monitor IBD, the clinical utility of the test, and the biological variability of inflammation among stable IBD patients (to understand when a change in clinical management would be initiated and for a better basis for the requested frequency of testing). In 2019, MSAC considered a resubmission (MSAC Application 1353.1) that requested MBS listing of FC testing for diagnosis of IBD only, which MSAC subsequently supported. MSAC noted FC testing is most useful in the diagnostic setting, due to its strong negative predictive value. In 2021, two items were introduced to the MBS for FC testing for the diagnosis of IBD in patients aged <50 years (item 66522 for general practitioners [GPs] and item 66523 for specialists). MSAC noted some repeat testing is occurring, meaning that some uses of the diagnostic test item could be for monitoring. MSAC noted that none of this usage was occurring in people aged >50 years, due to the age restrictions on this item.

MSAC noted that feedback from stakeholders was supportive of public funding. MSAC noted that the feedback had a strong view that overall, FC testing would reduce unnecessary colonoscopies and be useful for monitoring disease activity. MSAC noted that FC testing for monitoring patients with IBD is already being widely used in Australia and funded through various means including through public hospital settings, through private funding and the inappropriate use of the existing MBS items for diagnosis. MSAC considered that current arrangements for patients may result in access and equity issues as patients may need to pay out-of-pocket for the test.

MSAC noted that FC is a biomarker of gut inflammation. Raised levels in the stool reflect the migration of neutrophils into the gut lumen and may be indicative of IBD disease activity. MSAC noted the following thresholds for FC levels proposed in the clinical management algorithm, which align with some clinical guidelines including recommendations by the Gastroenterological Society of Australia:

- <100 µg/g: no inflammation
- 100–250 µg/g: intermediate
- >250 µg/g: active inflammation.

MSAC noted from the pre-MSAC response that there is a lack of consensus around FC thresholds in the literature and that there is no absolute level in which subsequent actions are mandated. MSAC also noted that the 'intermediate' range proposed in the clinical management algorithm of the current application covers a relatively wide range (100-250 µg/g) and noted that results within this range can be difficult to interpret. In their pre-MSAC response, the applicant proposed to work with pathology companies and other relevant/interested parties to standardise and clarify the wording of FC thresholds.

MSAC noted that interpreting FC results in isolation can be misleading, as FC values up to 600 µg/g can still be associated with minimal inflammation. MSAC also noted that there can be poor correlation between symptoms and inflammation at colonoscopy. Additionally, inter-patient and intra-patient variation is observed with FC test results. Therefore, MSAC considered that the FC trend over time is more meaningful than the absolute value of a single FC result. MSAC noted that the Royal College of Pathologists of Australasia (RCPA) and Public Pathology Australia both advised that the patient's clinical history, the trend in FC results and other diagnostic findings must be evaluated alongside an FC result. MSAC noted that an elevated FC result may be due to causes other than an IBD, and infection should be ruled out before any subsequent treatment decisions regarding IBD management are made. MSAC advised that if FC testing for IBD monitoring is funded, education measures are needed for GPs and specialists around the interpretation of results in a clinical context. MSAC noted that in their pre-MSAC response, the applicant proposed to implement an education program targeted to GPs and specialists on interpretation of FC results in a clinical context to encourage clinically appropriate decision making and reduce any risk of leakage and inappropriate referral for colonoscopy.

MSAC noted that the application presented two PICO sets. PICO set 1 included symptomatic patients with IBD, with FC testing used to assess disease activity and mucosal healing. PICO set 2 included asymptomatic patients, with FC testing used to predict IBD flares and relapses. The comparator for both PICO sets was colonoscopy + biopsy, with PICO set 2 having an additional comparator of standard medical management. MSAC noted that no evidence was presented for standard medical management as a comparator, so no additional evaluation was undertaken based on this second comparator.

MSAC noted that there was limited evidence available to inform safety of FC testing. MSAC considered that FC testing in the symptomatic group likely had non-inferior safety compared to colonoscopy, although raised concerns of the relatively high false positive rate of FC testing (~30%). MSAC considered that the comparative safety claim in the asymptomatic group was uncertain because the high false-positive rate meant that this group would be more likely to be harmed due to unnecessary treatment escalation or further investigation including colonoscopy. MSAC noted that in the pre-MSAC response, the applicant agreed that while in the asymptomatic group there was a potential for unnecessary colonoscopy referrals from FC testing, it was 'very unlikely to lead to additional colonoscopies because gastroenterologists are likely to retest in this circumstance'. However, MSAC considered that while not all patients with a high FC result will further proceed to a colonoscopy, they may require escalation in therapy. Thus, although an FC test may facilitate faster escalation in therapy, it could lead to unnecessary treatment escalation

in the case of false positive FC results. This was most concerning for the asymptomatic group because they would not otherwise receive an escalation in treatment, and this may unnecessarily expose them to the side effects of medication.

MSAC considered it appropriate that a linked evidence approach was used to determine clinical effectiveness. MSAC also considered it appropriate that clinical effectiveness was considered separately in both PICO sets, as utility of the test varied between the two populations. Based on a systematic review and meta-analysis of test accuracy studies (using a threshold of 100 µg/g), MSAC considered that FC testing had acceptable diagnostic accuracy in predicting disease activity and mucosal healing with a pooled sensitivity and specificity of 83% and 71% respectively. MSAC noted the meta-analysis for active disease monitoring had high heterogeneity.

MSAC noted that there was more evidence relating to the accuracy of FC testing in monitoring ulcerative colitis (UC) than for Crohn disease (CD). MSAC considered that, generally, patients with CD have more complications and more varied symptoms than those with UC. MSAC also considered that CD is typically more difficult to diagnose than UC.

MSAC noted that there was limited literature for the paediatric population but considered the available evidence to be acceptable. MSAC considered that colonoscopy should be avoided wherever possible in the paediatric population, due to the significant burden that undergoing colonoscopy presents to this patient group. As such, MSAC considered that there is a high clinical need for FC test within the paediatric population.

MSAC agreed with ESC and considered that the clinical utility in the asymptomatic group was highly uncertain. MSAC considered that although FC testing has acceptable sensitivity and specificity to predict relapse, it was uncertain how use of this test for monitoring affects clinical management and health outcomes in asymptomatic patients. There was moderate to high risk of bias in the retrospective evidence presented for clinical effectiveness in this group of patients. MSAC also noted that the recommended frequency of FC testing or colonoscopy in asymptomatic IBD patients is unclear. MSAC considered that most patients with IBD usually have regular planned colonoscopies regardless of symptoms, and the interval depends on severity, extent and type of disease. MSAC noted that many guidelines have included FC testing as a part of standard management of IBD without much supporting evidence.

Noting that FC results should be considered in context with clinical history and patient presentation, MSAC considered that the test is most useful when:

- a patient diagnosed with IBD has symptoms that may or may not be related to an IBD flare,
- a patient has had a recent flare and there is a need to monitor healing as a supplement to their recent symptoms,
- performed in children, who are likely the patient group with the highest clinical need.

Overall, MSAC accepted the clinical claim of non-inferior safety and effectiveness for FC testing in the symptomatic population. However, MSAC considered the claim of non-inferior safety in the asymptomatic population to be uncertain because the high false positive rate of testing posed a particularly high risk of inadvertent harm to this group due to the introduction of unnecessary invasive procedures or, the introduction of new therapy or escalation of their existing therapy, from a false positive result. The claim of non-inferior effectiveness for this group was also uncertain due to the lack of evidence that FC testing results in changes to patient management and health outcomes.

MSAC noted that the economic evaluation was a cost-minimisation analysis for the two PICO set populations, based on an assumption of non-inferior effectiveness and non-inferior safety. MSAC considered that inclusion of standard management as a comparator for asymptomatic patients

would require a cost-utility analysis rather than a cost minimisation analysis for this population. MSAC noted the model included biannual surveillance FC testing to detect either, disease activity and mucosal healing (for the symptomatic population; <100 µg/g), or relapse (for the asymptomatic population; >100 µg/g). The comparator for both populations in the economic model was colonoscopy + biopsy. Adherence to the surveillance testing was assumed to be 70% for symptomatic patients and 50% for asymptomatic patients.

MSAC noted that the updated base case (following advice from the applicant about the appropriate MBS item number for biopsy which is typically claimed with colonoscopy) was a cost saving of $17,951 per 100 patients with IBD, comprising cost savings for PICO set 1 (symptomatic group) of $34,031 per 100 patients and increased costs of $16,080 per 100 patients in PICO set 2 (asymptomatic group). MSAC noted that the key drivers of the model were the proportion of colonoscopies performed in public hospitals, adherence to and frequency of FC testing, and the reduction in the rate of colonoscopies.

MSAC considered that there were a number of issues with the model that contributed to its uncertainty. Firstly, the model assumed that 100% of symptomatic patients would receive the comparator (colonoscopy) in the absence of FC testing which MSAC considered to be unrealistic. This assumption was a key driver of the cost savings projected for FC testing. Secondly, the model did not account for escalated IBD treatment in the case of false-positive results, which would increase the cost and reduce savings estimated in the base case. Finally, the modelling inputs were based on a study of a single clinic in Melbourne and there were concerns with the translation and transferability of this study's inputs.

MSAC noted that ESC considered it unlikely that in clinical practice 100% of symptomatic patients would undergo a colonoscopy each year in the absence of FC testing given that colonoscopies are generally recommended 1-3 yearly but noted the applicant's pre-MSAC response clarifying that this proposed lower 1–3 yearly frequency was for dysplasia surveillance rather than for IBD disease monitoring. Nonetheless, MSAC considered that the assumption of a 100% colonoscopy rate was still unrealistic and that additional sensitivity analysis conducted post ESC with more realistic assumptions, such as reducing the proportion of patients who would receive a colonoscopy in the absence of FC testing to 70% or reduction in colonoscopy rates from 30% to 10% led to cost increases rather than cost savings from the use of FC testing.

MSAC noted that the revised base case net financial impact to the MBS was estimated as $32.9 million in year 1 to $37.2 million in year 6. MSAC noted that, when separated into the 2 PICO sets, the budget impacts were as follows:

- PICO set 1 (symptomatic patients): $9.73 million in year 1 to $11.00 million in year 6
- PICO set 2 (asymptomatic patients): $23.2 million in year 1 to $26.21 million in year 6.

Assuming a 30% reduction in public hospital colonoscopies, and no change in private colonoscopes, increased the net financial impact to the MBS to $40.1 million in year 1 to $45.4 million in year 6. MSAC noted that all estimates are highly variable because of the uncertainty of the assumptions informing them. MSAC considered the reduction in colonoscopies to be uncertain as there is already widespread use of the test and any effect on the number of colonoscopies has likely already been realised. MSAC considered that any potential reductions in total colonoscopy rates will likely only be seen in the symptomatic group in public hospitals and rural locations, given the abundant supply of colonoscopy services in most other areas.

Overall, MSAC was supportive of public funding for FC testing for the monitoring of people with IBD when limited to symptomatic patients (PICO set 1), including children. MSAC acknowledged that the proposed cost savings from funding FC testing were unlikely, however, the test has demonstrated clinical utility in the symptomatic population, acceptable diagnostic accuracy, and is already widely used for diagnosis and privately for monitoring. MSAC did not support funding

the service for asymptomatic patients due to the uncertain safety and effectiveness for this group of patients. Post-MSAC, Departmental advice was accepted that the specific MBS item should be for the 'management' of symptomatic patients with IBD (although the application was for use of the test for 'monitoring') because 'management' was more appropriate terminology for symptomatic patients.

MSAC considered there was no need to specify a frequency in the MBS item descriptor, so as to ensure access for patients who may need multiple tests. MSAC considered the MBS item descriptor should be age-agnostic. MSAC noted that the proposed fee ($75.00) is equivalent to that of the diagnosis items and considered this to be appropriate. MSAC also considered that GPs should be able to request FC testing on behalf of a specialist or consultant physician which will help address equity issues, particularly in rural and remote patients, by reducing the need to access a specialist. MSAC considered that an explanatory note should be accompanied to the MBS item ensuring infection has been excluded, and that this should be included on pathology reports to guide interpretation. In order to future proof the item descriptor, MSAC considered that relevant clinical guidelines (e.g. those developed by the Gastroenterological Society of Australia) should be referenced in the explanatory note rather than specifying currently used FC thresholds.

MSAC noted that there is possible leakage between current FC testing items available for diagnosis, which could be used for monitoring patients who have already been diagnosed with IBD. MSAC acknowledged that further leakage between symptomatic and asymptomatic IBD patients may occur with supported funding for a monitoring item for symptomatic patients. MSAC noted from the pre-MSAC response that the applicant may look to perform a post-implementation study at 12 months with guidance from the Department to understand the impact on healthcare resource use and health outcomes. MSAC advised that a post-implementation review at 24 months is appropriate to observe changes in FC testing for both monitoring and diagnosis, particularly concerning patients aged >50 years who currently do not have access to the MBS items for FC testing for IBD diagnosis, and it would be of clinical concern if this test was being used for diagnostic purposes in this age group MSAC advised that colonoscopy utilisation data as a part of this review is not required as colonoscopy is used for various other indications and therefore this data is unlikely to be informative.

# 4.  Background

In March 2018, MSAC considered but did not support MSAC application 1353, which requested public funding for FC testing for diagnosis and monitoring disease activity in patients with known IBD. Regarding the monitoring of disease, MSAC advised that further clarification should be provided on the matters of concern summarised in Table 2.

MBS items 66522 and 66523 corresponding to FC testing for the diagnosis of IBD, were introduced on the MBS from 1 November 2021 (MSAC application 1353.1).

**Table 2   Summary of key matters of concern**

| Component | Matter of concern (MSAC 1353) | How the current assessment report addresses it |
|---|---|---|
| Clinical claim | MSAC noted that no direct evidence had been presented to support use of the FC test for monitoring of patients already diagnosed with IBD (MSAC PSD 1353, page 4). | Clinical claim of diagnostic accuracy addressed<br><br>SLR and meta-analysis was conducted to assess the use of FC testing for monitoring purposes. |
| Clinical utility and management | Unclear definition of current Australian practice to monitor IBD. Lack of supportive data on the clinical utility to establish any clinical need for FC monitoring and better identification of the downstream management practices and health outcomes which might be improved by introducing FC monitoring (MSAC PSD 1353, page 2).<br>MSAC suggested that more information on the biological variability of inflammation in the stable IBD patients (FC test result <200 µg/g) would be helpful to provide a better basis for when to initiate a change in clinical management and frequency of FC testing (MSAC PSD 1353, page 2).<br>MSAC suggested that expert opinion would be helpful to define the current approach to monitoring of IBD in Australia (e.g. frequency of colonoscopies) and that data were needed to determine the frequency and clinical utility of the FC test for monitoring (MSAC PSD 1353, page 5). | "Partially" addressed<br><br>Review of clinical guidelines on the use of FC testing for monitoring purposes. Targeted literature search to assess the potential for colonoscopy replacement (Section 2.B3).<br><br>Australian data from Monash Health was analysed for a better proxy regarding frequency of testing and use of health resources. Some limitations were identified in this data set (Section 2B.3). |
| Economic evaluation | The economic model assumed that there was a 1:1 relationship between test performance and subsequent management. MSAC considered that this was an oversimplification which resulted in unreliable estimates of the comparative consequences of the changes in management in terms of subsequent healthcare resource use and health outcomes.<br>For example, the model underestimated the subsequent use of medicines to treat IBD (MSAC PSD 1353, page 5).<br>Need to appropriately amend the economic model structure (e.g. accurately capture the downstream changes in healthcare resource use and health outcomes of the claimed earlier detection of worsening IBD) and inputs (e.g. the frequency of monitoring) (MSAC PSD 1353, page 6). | Addressed<br><br>Section 3 includes an updated economic model (cost-minimisation) with sensitivity analysis that account for the uncertainty on the frequency of use of FC testing and reduction in the colonoscopy use. |

FC = faecal calprotectin; IBD, inflammatory bowel disease; MSAC = Medical Services Advisory Committee; PSD = Public Summary Document; SLR = systematic literature review.

# 5.   Prerequisites to implementation of any funding advice

Laboratory-based testing will be carried out in National Association of Testing Authorities (NATA)-accredited pathology laboratories.

# 6. Proposal for public funding

The new MBS item descriptor as proposed in the ratified PICO for the current application is summarised in Table 3. The proposed fee is equivalent to the fee for FC testing for diagnostic purposes (MBS items 66522 and 66523). The descriptor allows general practitioners (GPs) to order the test on behalf of a specialist gastroenterologist. 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 be improved if GPs could order it. This view is aligned with the consultation feedback and the Royal Australian College of General Practitioners (RACGP) that advised that allowing this test to be provided in primary care by GPs improves equity of access and better assessment of regional patients.

PASC noted that the PICO proposed item descriptor for FC testing should be reviewed by the RACGP for feedback regarding how ordering of FC tests for monitoring IBD patients by GPs should be addressed in the item descriptor. Following this advice, the department sought advice from RACGP on the PICO proposed item descriptor and 3 alternative department proposed item descriptors:

1. Alternative item descriptor 1: with GPs allowed to request the test by remaining silent on requestor type (Table 4).
2. Alternative item descriptor 2: with GPs allowed to request the test but to ensure that a specialist is involved in the patient's care, the descriptor also specified that the IBD must be confirmed by a specialist/consultant physician.
3. Alternative descriptor 3: with GPs allowed to request the test in the same manner as that proposed in Table 3 but without specifying gastroenterologist as the specialist type in 'b)' (i.e. stating that 'b) the service is requested by or on behalf of a specialist or consultant physician').

RACGP preference was to allow GPs to order the test by remaining silent on requestor type (i.e. specialists and non-specialist medical practitioners can request the test; alternative item descriptor 1, Table 4). The RACGP stated that this item supported a shared care model for IBD monitoring in asymptomatic patients with established IBD diagnoses where the GP can monitor for symptoms and perform investigations as required (eg. C-reactive protein (CRP) and FC) while the endoscopist can identify histological healing. RACGP noted that in symptomatic patients, the GP is well positioned to initially collate symptoms, signs and test results to establish if the symptoms represent an IBD flare.

The RACGP further noted that as IBD can only be diagnosed with gastroscopy/colonoscopy, all cases will have an initial diagnosis by a gastroenterologist. A requirement for IBD to be confirmed by a gastroenterologist on each request for FC as described in alternative descriptor 2 is unnecessary and may impose a barrier to patient care. In addition, public gastroenterology appointments and affordable private gastroenterology appointments are only available in select locations across Australia. Therefore, requiring gastroenterologist confirmation of an IBD diagnosis may limit access to monitoring FC testing and may be a barrier to effective patient care.

**Table 3  Proposed MBS item descriptor as per the ratified PICO of MSAC application 1761**

| Category 6 – Pathology Services |
| --- |
| MBS item *XXXX<br><br>Faecal Calprotectin test for assessment of disease activity if all the following apply:<br><br>    a)  the patient has diagnosed inflammatory bowel disease;<br>    b)  the service is requested by or on behalf of a specialist or consultant physician practising as a specialist gastroenterologist.<br><br>  A maximum of 10 tests per year may be performed. |
| Fee: $75.00 Benefit: 75% = $56.25 85% = $63.75 |

**Table 4 MBS item descriptor recommended by the Royal College of General Practitioners for faecal calprotectin testing**

| Category 6 – Pathology Services |
| --- |
| MBS item *XXXX<br>Faecal Calprotectin test for assessment of disease activity a patient with diagnosed inflammatory bowel disease:<br><br>A maximum of 10 tests per year may be performed. |
| Fee: $75.00 Benefit: 75% = $56.25 85% = $63.75 |

# 7.    Population

The application is for the use of FC testing in monitoring of disease activity in patients with known IBD. IBD is comprised of two chronic inflammatory conditions of the gastrointestinal (GI) tract: (1) ulcerative colitis (UC) where the disease is limited to the colon and; (2) Crohn disease (CD), which can affect any part of the GI tract, from the mouth to the anus.

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.

In Australia, a cross-sectional study performed on a national database of general practice electronic health records (MedicineInsight) estimated a crude prevalence of IBD as 653 per 100,000 people (CD: 306 per 100,000 and UC: 334 per 100,000) (Busingye et al. 2021). This means that prevalence may be as high as 181,000 people in Australia[1] (. Approximately 10–20% of IBD cases are diagnosed during childhood, with peak age of onset at 15–29 years[2].

IBD presents in a variable manner with a single patient possibly relapsing/remitting and therefore potentially transitioning between the four below health states in a given year:

- Asymptomatic, no biochemical evidence (e.g., elevated FC levels) of impending IBD relapse.

- Asymptomatic, with biochemical evidence of impending IBD relapse.

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[1] Australian Bureau of Statistics 2023. *Population clock and pyramid*.

[2] https://www.racgp.org.au/afp/2017/august/inflammatory-bowel-disease-in-adolescents

- 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.

While asymptomatic patients are at risk of IBD relapse (e.g., patients with recent flare or surgery but currently asymptomatic), symptomatic patients may present within a range of clinical severity (mild, moderate and severe), although this has poor correlation with mucosal disease activity[3] [4] . Different disease indexes are used for CD and UC which use clinically evaluable symptoms and the history of the disease to categorise patients as having mild, moderate or severe disease (Table 5).

**Table 5 Classification of disease based on IBD severity**

|  | Crohn disease | Ulcerative colitis |
|---|---|---|
| Mild | Outpatient management. Patient tolerates oral diet, have <10% weight loss and no symptoms of systemic disease (i.e., fever, tachycardia, abdominal tenderness) and no signs or symptoms of intestinal obstruction. They may have mild symptoms such as some soft stools, abdominal pain, or modest declines in their general wellbeing | 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 ESR. Mild crampy abdominal pain, tenesmus, and periods of constipation are also common. |
| Moderate | Prominent symptoms such as fever, weight loss, abdominal pain and tenderness, intermittent nausea or vomiting, or anaemia. Includes patients who have failed treatment for mild to moderate disease. | Frequent, loose, bloody stools (4-6 per day), mild anaemia not requiring blood transfusions, and abdominal pain that is not severe. Patients have no or minimal signs of systemic toxicity. Adequate nutrition is usually maintained. |
| Severe | Persistent symptoms despite glucocorticoids or biologic agents as outpatients, or individuals presenting with high fever, persistent vomiting, intestinal obstruction, peritoneal signs, cachexia, or evidence of an abscess. | Frequent, loose, bloody stools (≥6 per day) with severe cramps and evidence of systemic toxicity (i.e., fever, tachycardia, anaemia, and/or an elevated CRP or ESR. Patients may have weight loss |

CRP= C-reactive protein; ESR = erythrocyte sedimentation rate; IBD= inflammatory bowel disease

Most patients with IBD are managed by a gastroenterologist, with a minimum of one annual appointment[5]. However, access to gastroenterologists is limited in remote areas where patients are more likely to be monitored by GPs.

The diagnosis of a disease flare in symptomatic and asymptomatic patients may trigger treatment initiation with various types of medical therapies that control disease flare (e.g. anti-tumour necrosis factor (TNF) therapies, antiinterleukin (IL)-12/23 agents, sphingosine-1-phosphate (S1P) receptor inhibitors and small molecule therapies). The use of these therapies

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[3] Cellier C, Sahmoud T, Froguel E, 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)231-2

[4] Walsh A, Bryant R, Travis S. 2016. Current best practice for disease activity assessment in IBD. *Nat Rev Gastroenterol Hepatol* 13, 567–579.

[5] Australia, G. S. o. (2018). Clinical update for general practitioners and physicians: Inflammatory bowel disease. Melbourne: GESA, 2018. https://www.gesa.org.au/public/13/files/Education%20%26%20Resources/Clinical%20 Practice%20Resources/IBD/2018_IBD_Clinical_Update_May_update.pdf

may lead to prolonged periods of immunosuppression[6][7] which increase the risk of infections. There is substantial data suggesting that tumour necrosis factor (TNF) alpha antagonists (i.e. infliximab) and other targeted small molecules (i.e., tofacitinib) are associated with a 1.5 to 2 times higher risk of serious infections some of which may lead to hospitalisations, compared to non-biologic immunosuppressive agents (i.e., thiopurines). Furthermore, repeated mucosal inflammation causing cellular/DNA damage, combined with the use of certain medications has also shown to increase the risk of cancer. Among currently approved biologic therapies, TNF α antagonists may be linked to an increased risk of lymphoma, especially when used in combination with thiopurines[8] (Holmer el al, 2019). In Australia, 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. Endoscopy results demonstrating the severity of disease may expedite access to these treatments during acute relapses.

Two PICO sets were deemed necessary by the PICO Advisory Sub-committee (PASC) because the proposed intervention is applied to two distinct populations—symptomatic and asymptomatic patients—each for different purposes: monitoring disease activity/mucosal healing and predicting relapse, respectively. In both symptomatic and asymptomatic settings, FC monitoring may be requested by either a gastroenterologist or a GP. It is likely that more symptomatic patients will be evaluated by a gastroenterologist. Before considering making any changes to the management of symptomatic patients, it is proposed that a FC test will be conducted to determine whether the symptoms are due to an IBD flare or not. Table 6 and Table 7 summarise the PICO criteria for each relevant population.

**Table 6 PICO criteria for assessing FC test for IBD in symptomatic patients (linked evidence for test accuracy and change in management)**

| Component | Description |
|---|---|
| Population | Symptomatic patients with known IBD managed by a gastroenterologist. |
| Prior tests | None |
| Intervention | Quantitative enzyme-linked immunosorbent assay (ELISA) of FC |
| Comparator | Colonoscopy and biopsy |
| Reference standard (for test accuracy) | Colonoscopy |
| Outcomes | Test accuracy: sensitivity, specificity, positive predictive value, with 2x2 table (TP, TN, FP, FN) |
| | Change in management: non-invasive monitoring, early detection of flares, reduced need for colonoscopies, tailored treatment decisions, patient compliance and cost-effectiveness. |
| Systematic review questions: What is the diagnostic accuracy of FC testing for assessment of disease activity as reported by endoscopic and/or histological findings, in terms of sensitivity/specificity and positive/negative predictive value? | |

FC= faecal calprotectin; FN= false negative; FP= false positive; IBD= inflammatory bowel disease; N/A= not applicable; TN= true negative; TP= true positive.

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[6] McDowell C, Farooq U, Haseeb M. 2023. 'Inflammatory Bowel Disease.' in, StatPearls (StatPearls Publishing, StatPearls Publishing LLC.: Treasure Island (FL)).

[7] Axelrad JE, Lichtiger S, Yajnik V. 2016. 'Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment', *World J Gastroenterol*, 22: 4794-801.

[8] Holmer A, Singh, S. 2019. 'Overall and comparative safety of biologic and immunosuppressive therapy in inflammatory bowel diseases'. *Expert Review of Clinical Immunology*, 15(9), 969-979.

**Table 7 PICO criteria for assessing FC test for IBD in asymptomatic patients (linked evidence for test accuracy and change in management)**

| Component | Description |
|---|---|
| Population | Asymptomatic patients with known IBD managed by a gastroenterologist. |
| Prior tests | None |
| Intervention | Quantitative enzyme-linked immunosorbent assay (ELISA) of FC |
| Comparator | Colonoscopy and biopsy<br>Standard medical management |
| Reference standard (for test accuracy) | Colonoscopy |
| Outcomes | Test accuracy: Sensitivity, specificity, positive predictive value, with 2x2 table (TP, TN, FP, FN)<br>Change in management: non-invasive monitoring, early detection of flares, reduced need for colonoscopies, tailored treatment decisions, patient compliance and cost-effectiveness. |
| Systematic review questions:<br>What is the diagnostic accuracy of FC testing for predicting IBD flares/relapses compared to colonoscopy and standard medical management, and will it allow for early treatment prior to the development of symptomatic disease relapse? | |

FC: faecal calprotectin; FN: false negative; FP: false positive; IBD: inflammatory bowel disease; N/A: not applicable; TN: true negative; TP: true positive.

# 8. Comparator

Given the poor correlation between disease activity and clinical assessment (including currently available inflammatory biomarkers, such as CRP alone), the main relevant comparator for FC testing is colonoscopy. In both symptomatic and asymptomatic patients, FC testing will replace some (not all) of the colonoscopies currently conducted for monitoring purposes of IBD. In asymptomatic patients, standard medical management was proposed as a secondary comparator as these patients are less likely to undergo a colonoscopy for monitoring purposes due to the less favourable safety profile, invasiveness, practicality, and costs. In this setting, FC testing would be provided in addition to the current set of tests used to monitor the disease and hence would be more costly as it is an add-on test and superior to standard management.

The DCAR addresses most of the PICO elements that were prespecified in the PICO confirmation that was ratified by PASC. However, while the DCAR acknowledges standard medical management as the secondary comparator in the asymptomatic population, there is no evidence available to inform this comparison.

# 9. Summary of public consultation input

The MSAC welcomed consultation input received for this application and noted the period for public consultation closed on 11 October 2024. Consultation input was welcomed from ten (10) professional or non-consumer organisations and one (1) consumer organisation. Two (2) organisations provided input collected from individuals. 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 organisations that submitted input were:

- Therapeutic Goods Administration
- The Royal College of Pathologists of Australasia (RCPA)
- Australian Pathology
- Gastroenterological Nurses College of Australia
- Crohn's and Colitis Australia
- Public Pathology Australia (PPA)
- National Pathology Accreditation Advisory Council (NPAAC)
- Gastroenterological Society of Australia
- The Royal College of General Practitioners
- DiaSorin Australia
- Crohn's Colitis Cure

The consultation feedback received was strongly supportive of public funding for faecal calprotectin (FC) testing for the monitoring of patients with inflammatory bowel disease (IBD). There were however concerns raised from two organisations over standardisation of FC test reference ranges and test variation.

## Benefits

Consultation input identified benefits including:

- The FC test overall has good sensitivity and accurately reflects disease activity. RCPA indicated that FC testing is currently regarded as a gold standard of care in the management of IBD and Australian Pathology stated that FC testing is currently used and accepted as best clinical practice to monitor patients with IBD.
- The FC test is a non-invasive test. Use of FC testing for monitoring IBD may reduce the need for invasive practices (e.g. colonoscopy, surgery), which can carry significant risks. FC testing may also provide access for those who cannot undergo current invasive monitoring practices.
- Enabling General Practitioners to order FC tests reduces the barriers to access for patients, particularly those living in regional and rural areas who may have difficulty accessing gastroenterologists.
- Reduced costs to patients who are currently accessing FC testing privately.
- Early intervention due to closer monitoring with FC testing may decrease overall disease burden on the patient and reduce demand on the health system (e.g. fewer hospitalisations and presentations to specialists).

## Disadvantages/Implementation issues

While consultation input was supportive of the proposal, the input identified some potential disadvantages or issues related to implementation:

- Currently available FC assays are not well harmonised, with different cut off thresholds used by different commercial assays. Sensitivity and specificity of the assay varies with the set cut off threshold. RCPA input indicated that harmonisation between different kits is challenging and that steps need to be taken towards standardisation to improve agreement between currently available assays.
- Sample to sample variation may be large. It was noted that samples may have an intra-stool variation of 10-20%, as well as diurnal variation of 20%.
- There is potential for overuse of testing. Testing would need to be restricted to the target population.

## Additional Comments

RCPA stated that FC values within the normal reference range can vary by 20%. 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 a rise of >50% within normal range might prompt concern and lead to retesting of FC to determine the trend.

PPA stated that due to potential variations between assays, the testing should be performed with the same assay. PPA further stated that the exact cut-off value of the FC test is of lesser importance clinically than the serial results of a patient. PPA suggest that when reporting results, laboratories should state whether the result was above or below the cut-off value recommended by the reporting laboratory.

RCPA and PPA also noted that the patient's clinical history, trend in FC results and other diagnostic findings must be evaluated alongside a FC result, as abnormal FC levels may be due to causes other than IBD (e.g. infection).

NPAAC stated that an external quality assurance program for the test is available from the RCPA.

### Feedback following ESC consideration

ESC requested the department seek further clarification from RCPA regarding:

1) *Discordance between FC thresholds published in pathology reports and FC thresholds used in clinical practice. ESC acknowledged the manufacturer's cut-off values and agreed that in clinical practice, the FC cut-off threshold used is usually 100 µg/g. ESC queried:*
   a) *Whether it is possible for pathology reports to publish the FC threshold that is clinically relevant (ie. < 100 µg/g)?*
   b) *If not, what are the barriers to implementing this change and how can these be managed?*

The RCPA noted there is a lack of agreement on the best cut-off levels of FC for differentiating IBD from IBS and for predicting endoscopic activity, remission, and relapse. RCPA advised that Pathology laboratories have adopted 0-50 µg/g as a faecal calprotectin (FC) cut-off value indicating unlikely IBD; however, the low false negative rate of this cut-off value doesn't exclude the condition. RCPA also noted FC concentrations will be affected by miscellaneous factors such as age. Based on the expected values from the literature and the manufacturer's recommendations, RCPA advised that pathology laboratories have adopted the following reference intervals for FC concentration in adult patients with clinically suspected IBD:

| | |
|---|---|
| **0-50 µg/g** | IBD unlikely but not excluded. |
| **50-100 µg/g** | IBD likely; other inflammatory conditions, including but not limited to infection, coeliac disease and diverticular disease, cannot be excluded. |
| **100 µg/g** | Almost exclusively IBD. Other severe inflammatory diseases not excluded. |

2) *Harmonisation of FC thresholds. We understand from your response that harmonisation of different FC test kits will be challenging:*
   a) *Has there been any further progress towards harmonisation of FC test kits?*
   b) *If FC testing for monitoring of IBD is publicly funded, does RCPA (or other organisation) intend to harmonise FC thresholds?*
   c) *For MSAC's information, what are the challenges involved with harmonisation of FC thresholds? How are these best managed?*

RCPA responded saying a harmonisation group would be able to run this study and provide evidence behind the chosen low cut-off by the labs. The RCPA was willing to convene a working group of Fellows to standardise faecal calprotectin reporting and cut-off values as needed.

# 10. Characteristics of the evidence base

A total of 46 and 34 studies met the inclusion criteria for assessing the test accuracy of FC compared to colonoscopy in symptomatic and asymptomatic patients that are in remission, respectively. A linked evidence approach was used to determine FC test accuracy in predicting endoscopic findings of mucosal healing or active disease, and the FC test's ability to predict relapse in IBD patients who are in remission. No studies were identified on the safety of FC testing.

The main inclusion criteria incorporated studies that had:

- currently diagnosed (symptomatic or asymptomatic) IBD patients (including UC and CD);
- an FC test compared to colonoscopy or colonoscopy/biopsy;
- reported outcomes for test accuracy (sensitivity, specificity, with a 2x2 tables (true positive, true negative, false positive and false negative);
- an enzyme-linked immunosorbent assay (ELISA) FC test only (POCT or enzyme-labelled antibodies against human calprotectin (EliA Calprotectin Conjugate) tests were excluded);
- no documented use of non-steroidal anti-inflammatory drugs in the study population;
- a maximum of 14 days between the collection of the FC sample and the colonoscopy; and
- A low risk of bias as determined by the QUADAS-2 tool.

The inclusion of ELISA FC test only was to limit the potential for confounding the results. There are a range of alternative FC testing methods such as such as Fluoro-enzyme immunoassay for calprotectin (EliA) and a range of rapid home testing kits (POCTs). However, there is substantial variability between the quantitative results of these different approaches. The ELISA FC test is considered the gold standard[9]. This decision also aligns with the PICO Confirmation that specified ELISA as the intervention FC test.

For linked evidence on FC test impact on change in management and on health outcomes a separate (non-systematic) targeted search was conducted.

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[9] Labaere D, Smismans A, Van Olmen A, et al. 2014. 'Comparison of six different calprotectin assays for the assessment of inflammatory bowel disease'. *United European Gastroenterology Journal*, 2(1), 30-37

**Table 8    Features of the key included evidence**

| Criterion | Type of evidence supplied | Extent of evidence supplied | Overall risk of bias in evidence base (QUADAS-II) |
|---|---|---|---|
| **Adult patients** | | | |
| **Mucosal healing** | Prospective and retrospective studies. Using a variety of endoscopic activity indices (MES, UCEIS, SES-CD) and histological indices (Geboes score) | n = 2,161 k = 19 | Low |
| | Assessment of accuracy to detect MH in CD threshold at <100 µg/g Prospective studies | n= 139 k=2 | Low |
| | Assessment of accuracy to detect MH in UC threshold at <100 µg/g 5 prospective, 1 retrospective 1 post-hoc study | n= 1,271 k=9[a] (7 individual studies) | Low |
| **Active disease** | Prospective and retrospective studies. Aim: test validity Using a variety of endoscopic activity indices (MES, UCEIS, Rachmilewitz Index, SES-CD) and histological indices (Geboes score) | n = 1,682 k = 18 | Medium |
| | Accuracy to detect active disease in CD at ≥100 µg/g. 4 Prospective and 1 retrospective study | n= 415 k=6[a] (5 individual studies) | Low |
| | Accuracy of to detect active disease in UC: ≥100 µg/g) 8 prospective and 3 retrospective studies | n= 883 k=11 | Medium |
| **Predicting relapse** | Prospective and retrospective studies detecting relapse in IBD patients – all follow-up periods | n = 2,319 k=27 | Low |
| | Accuracy to predict relapse in IBD (>100 µg/g) at 12-month follow-up in CD 5 prospective and 1 retrospective study | n = 408 k=6 | Medium |
| | Accuracy to predict relapse in IBD (>100 µg/g) at 12-month follow-up in UC Prospective studies | n = 1,267 k=14 | Low |
| | Accuracy to predict relapse in IBD (>100 µg/g) at 12-month follow-up in IBD Prospective studies | n = 264 k=2 | Low |
| **Paediatric patients** | | | |
| **Mucosal healing** | Accuracy to detect MH in CD in paediatric population: all cut-offs 2 Prospective and retrospective studies | n = 192 k = 4 | Low |
| **Predicting relapse** | Prospective and retrospective studies on predicting relapse for IBD (k=5) and CD (k=1) – all follow-up periods (3 – 36 months) | n= 416 k=6 (IBD= 5 – CD=1) | Medium |

CD = Crohn Disease; IBD = Inflammatory Bowel Disease; SES-CD = Simple Endoscopic Score for Crohn's Disease; k = number of studies; n = Number of participants; MES = Mayo Endoscopic Subscore; MH = mucosal healing; n = number of participants; QUADAS-II = Quality Assessment of Diagnostic Accuracy Studies-2; UC = Ulcerative Colitis; UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

[a] studies that reported on endoscopic and histological outcomes, had both outcomes included.

## Cut-off thresholds

Feedback was sought from relevant stakeholders regarding two issues identified by PASC regarding FC reference ranges/test thresholds as summarised below:

- PASC noted that reference ranges can vary between different brands of FC test kits, raising issues for standardisation/comparability between assays.
- PASC noted that there is discordance between the clinically accepted test thresholds compared to that which is published by manufacturers. For example, while an FC result of <50 µg/g is considered negative according to many published test thresholds, in clinical practice FC results <100 µg/g would generally be considered negative. This could be a source of confusion for clinicians and make test interpretation difficult.

Inputs were received from Public Pathology Australia, RACGP and the Royal College of Pathologists of Australia (RCPA) as summarised in Table 9.

**Table 9. Summary of stakeholder feedback on reference ranges/test thresholds**

|  | **Variability of reference ranges across FC test kits** | **Variability of thresholds to establish disease activity** |
|---|---|---|
| RACGP | This information should be based on best available evidence from published literature or broadly accepted contemporary Australian clinical practice guidelines. | Not addressed |
| Public Pathology Australia | The following statement should be used: `above [or below] the cut-off recommended by the reporting laboratory'. | One can expect variation among assays, but the sample-to-sample variation is also quite large. While a single cut-off value is used (positive vs negative), the probability of disease and the severity of disease are correlated with the concentration on a continuous scale. Thus, the exact cut-off value chosen is probably of lesser importance. What is important is when comparing serial results in a patient, the testing should be performed using the same assay with as consistent a sampling procedure as possible. |
| RCPA | Different cut points are needed for different commercial assays. There are currently no reference extraction, preparation, or measurement procedures for FC, which has contributed to the lack of agreement between assays. Harmonisation between different kits is challenging and steps need to be taken towards standardisation of currently available assays to improve agreement between assays. In the meantime, the addition of qualitative results in the form of positive, borderline, low or high, which indicate the significance of quantitative results to the treating clinician, may be of benefit. | FC concentrations correlate highly with intestinal inflammation, and any changes in levels are a surrogate marker of mucosal healing or recurrence of inflammation. As FC is not specific for IBD, it must be interpreted with appropriate consideration of a patient's clinical history, examination, and other diagnostic findings. A limitation of the use of a single cut-off value is that this diagnostic information is lost when results are interpreted as positive/negative only. While a result of 0-50 µg/g would indicate that IBD is unlikely, 50-100 µg/g is an intermediate result that should be interpreted within the clinical context. This interpretative ambiguity, together with the fact that there is a need to standardise methods for FC measurement, indicates that recommended cut-off values would have to be determined depending on the clinical setting in which they are used. |

FC = faecal calprotectin, IBD = inflammatory bowel disease; PASC = PICO Advisory Sub-committee; RACGP = Royal Australian College of General Practitioners; RCPA = Royal College of Pathologists of Australia.

Studies in the DCAR evidence base reported results based on a range of pre-specified cut-off threshold or estimated the optimal cut-off where sensitivity and specificity was maximised. The optimal sensitivity and specificity of FC testing are only truly useful if there is certainty that a patient will relapse, which is inherently uncertain.

The cut-off thresholds reported in the studies do not imply that all patients had the same results; instead, they indicate that most patients had results above the specified threshold. For example, a cut-off threshold of 100 μg/g does not mean all results were exactly 100 μg/g —they could be much higher. Restricting the cut-off thresholds to a range of 100 μg/g to 250 μg/g may be clinically relevant when monitoring asymptomatic patients that are in remission for relapse, as higher thresholds may indicate severe cases where intervention will be required. For FC results between 100 and 250 μg/g (the intermediate range), a clinician might repeat the test and monitor the patient or perform a colonoscopy. Capturing intermediate results (100 μg/g - 250 μg/g) is justifiable and useful for understanding the potential for relapse and determining appropriate interventions for intermediate outcomes.

Overall, the key strengths of this analysis were that the primary studies used were assessed as being high or moderate quality and only used the ELISA FC test. Key limitations of the analysis are that limited number of studies for CD assessing mucosal healing were identified, there is limited evidence in paediatric patients, and that the comparator for CD included a variety of endoscopic procedures (i.e., capsule endoscopy or ileocolonoscopy). Additionally, since the indicated comparator was colonoscopy/biopsy, histological indices were included in the analysis, wherever available.

# 11. Comparative safety

No comparative studies on the safety of FC testing compared to colonoscopy/biopsy were identified.

As the FC test is performed on a faecal sample taken after defecation, the testing procedure poses no safety concerns for the patient, as long as the sample is collected, labelled and stored as per instructions, and patients comply with appropriate hand hygiene principles.

The FC test result may pose additional safety concerns due to its influence on clinical management for example:

- some cases of false positive/negative results may result in over/under-treatment or investigation of IBD related disease activity.
- In rare circumstances, the FC results may also prompt clinicians to perform a colonoscopy in patients who would not have otherwise had a colonoscopy; for example, false positive results or patients with an FC result that falls within the intermediate range (between 100 and 250 μg/g). These patients will be exposed to the risks of colonoscopy due to the FC test result. However, overall, the FC test is expected to reduce the number of colonoscopies in the target population and reduce over/undertreatment of IBD flares.

Taking into account the instances of false positive and negative results, it remains reasonable to assume that patients treated in the setting where FC testing is available would have at least a non-inferior safety profile compared to patients treated in a setting where FC testing is not available. Moreover, since FC testing has a potential to reduce the need for colonoscopies, the overall safety risk associated with false positive or intermediate results are likely mitigated by the decreased exposure to the more invasive procedures.

The reference standard, colonoscopy/biopsy, is generally considered a safe procedure with a low risk of complications. However, factors such as age and IBD diagnosis can increase the risk of severe adverse events, including post-polypectomy syndrome, bleeding, and perforation.

# 12. Comparative effectiveness

**Effectiveness from linked evidence**

Overall, the results show a trend for better performance of FC testing in patients with UC compared to CD. This is likely due to the fact that in patients with UC, the inflammation is continuous and is confined to the colon/rectum, where there is little degradation of the calprotectin protein prior to excretion. In contrast, the inflammation observed in CD may be patchy (e.g. skip lesions) rather than continuous and can involve other parts of the gastrointestinal tract above the colon in addition to the colonic inflammation. As a result, in patients with CD, the calprotectin protein may have degraded as it travels through the gut, leading to unreliable and variable levels in stool samples, which may not accurately reflect the extent of inflammation present throughout the GI tract. Therefore, if the CD is located primarily or exclusively in the upper gut, FC may not be a reliable indicator of inflammation, noting that FC trends may still provide clinically relevant information.

## *FC test accuracy*

This section reports the results from a systematic review conducted for the DCAR to assess the accuracy of the FC test to detect active disease and predict mucosal healing in IBD patients compared to colonoscopy. Disease activity is an endoscopic finding which confirms an IBD flare, and may necessitate an escalation in treatment; further, the change in FC trend can be used to titrate treatment(s) to patients' needs, which colonoscopy cannot facilitate easily. Mucosal healing is a STRIDE-II treatment target for patients with an IBD flare who are being monitored for treatment response and remission, all of whom should be asymptomatic by the time they demonstrate mucosal healing. Finally, results are reported on the accuracy of the FC test to predict relapse in asymptomatic IBD patients who are in remission. The aim of the test in this population is to detect active disease before it becomes symptomatic.

### Detecting active disease and predicting mucosal healing in symptomatic patients

#### Adults

Studies included in the analyses employed a wide range of FC cut-off values to calculate sensitivity/specificity. For studies measuring active disease, it was observed that low FC cut-offs (e.g. >76 µg/g) provided high sensitivity/specificity, though this traversed 'normal' FC levels. A similar but opposite trend was observed for mucosal healing, where high FC cut-off values (e.g. <250 µg/g) generally provided the best sensitivity/specificity, but these cut-off values had limited clinical utility, as the 'normal' range for FC is 50-100 µg/g. To address these concerns, results were limited to cut-offs which correspond with the proposed treatment algorithm which aligns with some clinical guidelines, where an FC < 100 µg/g may be considered 'normal' or 'negative' for inflammation, and FC >100 µg/g may be considered 'positive' for inflammation.

There were eight studies that reported on the ability to detect active disease in CD with cut-off values ranging from 76 – 273 µg/g. Additionally, the histological disease activity result (Global histologic disease activity score) was also included in the estimates. At the threshold of FC ≥100 µg/g, the median sensitivity and specificity (k=6) for detecting active disease were 81% (95% CI; 71-88) and 64% (95% CI; 44-79), respectively.

A total of fourteen studies were included in UC population with FC cut-off values ranging from 60 – 800 µg/g. At the threshold of FC ≥100 µg/g, the median sensitivity and specificity (k=11) for detecting active disease were 85% (95% CI; 76-90) and 76% (95% CI; 62-86), respectively.

Three studies reported on the accuracy of FC testing against the reference standard (colonoscopy/ biopsy), in detecting mucosal healing in patients with CD. These studies had cut-off threshold values ranging from 71 to 180 µg/g. At the threshold of FC < 100 µg/g, the median sensitivity and specificity (k=2) for detecting mucosal healing were 87% (range 79-93) and 67% (range 57-77), respectively.

In the UC population, a total of sixteen studies were included with cut-off values ranging from 70 to 250 ug/g. At the threshold of FC <100 µg/g, the median sensitivity and specificity (k=7) for detecting mucosal healing were 82% (range 75-88) and 76% (range 67-83), respectively.

The area under the curve (AUC) estimate for CD and UC patients, provides a comprehensive measure of the test's accuracy across different FC thresholds. Overall, the results show:

- The AUC for CD in relation to detecting active disease for a FC cut-off of ≥100 µg/g is estimated at 0.784. This means that FC testing has the ability to detect disease activity in symptomatic CD patients 78.4% of the time.
- Similarly for UC patients the AUC estimate was 0.859. Indicating that FC testing has the ability to detect disease activity in symptomatic UC patients 85.9% of the time.
- The AUC estimate for predicting mucosal healing in CD at an FC cut-off of <100 µg/g showed a high AUC 0.840, indicating that FC testing can correctly detect mucosal healing in 84% of cases in symptomatic CD patients. However, due to a small sample size (k=3) this estimate may lack statistical power and could be subject to variability.
- In UC, considering an FC cut-off of <100 ug/g, AUC was estimated at 0.821, indicating the test's ability to detect mucosal healing in symptomatic UC patients in 82.1% of the time.

A summary of the results is presented in Table 10.

**Table 10 Summary of accuracy results for mucosal healing and active disease and mucosal healing at different cut-off thresholds**

| FC threshold | Number of studies | Number of patients | Sensitivity: Pooled estimate [95%CI] | Specificity: Pooled estimate [95%CI] | NPV, % PPV, % | AUC | CoE (GRADE) |
|---|---|---|---|---|---|---|---|
| **Adult CD population** | | | | | | | |
| Active disease: All FC cut-offs | k=9 | N=551 | 84% [76; 90] | 73% [54; 87] | 67 81 | 0.838 | ⊕⊕⊕⊙ |
| MH: All FC cut-offs | k=3 | N=210 | 87% [79; 93] | 67% [57; 77] | 95 49 | 0.848 | ⊕⊕⊕⊙ |
| Active disease: FC ≥100 µg/g | k=6 | N=415 | 81% [71: 88] | 64% [44; 79] | 65 76 | 0.784 | ⊕⊕⊕⊙ |
| MH: FC< 100 µg/g | k=2 | N=139 | 87% [77: 94] | 66% [50; 78] | 95 46 | 0.840 | ⊕⊕⊕⊙ |
| **Adult UC population** | | | | | | | |
| Active disease: All FC cut-offs | k=15 | N=1,244 | 86% [79; 91] | 77% [66; 86] | 76 80 | 0.867 | ⊕⊕⊙⊙ |
| MH: All FC cut-offs | k=19 | N=2,526 | 76% [71; 81] | 77% [73; 80] | 77 74 | 0.829 | ⊕⊕⊕⊙ |
| Active disease: FC≥ 100 µg/g | k=11 | N=883 | 85% [76: 90] | 76% [62; 86] | 79 77 | 0.859 | ⊕⊕⊙⊙ |
| MH: FC < 100 µg/g | k=9 | N=1,271 | 82% [75; 88] | 76% [67; 83] | 64 83 | 0.821 | ⊕⊕⊕⊙ |

AUC = area under the curve; CD = Crohn disease; CoE = certainty of evidence; DOR = diagnostic adds, ratio; FC = faecal calprotectin; k= number of studies; MH = mucosal healing; N = number of patients; N/A = not applicable; NPV= negative predictive value; PPV= positive predictive value; UC = ulcerative colitis.

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*Pooled results of mucosal healing/disease activity in CD and UC adult populations*

The combined results for UC and CD (Table 11) provide higher statistical power and the inclusion of a larger and broader population. These results show that the FC test performs consistently in both CD and UC populations, with an evident pattern of high reliability of the results.

The AUCs suggest excellent discrimination of the FC test to predict endoscopically-assessed active disease and mucosal healing, with an AUC of 0.834 and 0.825 respectively. This means that in approximately 83.4% of cases, the FC test correctly detects patients with active inflammation. Similarly, an AUC of 0.825 suggests that in about 82.5% of cases, the FC test accurately identifies patients with mucosal healing. The diagnostic odds ratio (DOR) show that a statistically significant difference was found in the performance of the FC test in identifying active disease between the CD and UC subgroups with a combined random effects DOR of 7.4 and 15.7 respectively (p < 0.01).

**Table 11. Summary of the diagnostic accuracy of FC compared with the colonoscopy (UC & CD, symptomatic)**

| FC threshold | Number of studies | Number of patients | Sensitivity [95% CI] Specificity [95% CI] | AUC | DOR [95% CI] | I² |
|---|---|---|---|---|---|---|
| FC ≥ 100 µg/g cut-off, active disease | k=17 | N =1,298 | Sensitivity: 0.814 [0.754, 0.862] Specificity: 0.699 [0.588, 0.790] | 0.834 | 11.9 [6.0; 23.4, p<0.01] CD: 7.4 [2.9; 18.5, p<0.01] UC: 15.7 [6.3; 39.2, p<0.01] | 75% |
| FC < 100 µg/g cut-off, MH | k=11 | N=1,552 | Sensitivity: 0.829 [0.757, 0.884] Specificity: 0.714 [0.649, 0.771] | 0.825 | 12.5 [8.9; 17.7, p=0.21] CD: 15.3 [6.8; 34.3, p=0.65] UC: 12.7 [8.3; 19.3, p=0.13] | 24% |

AUC=Area under curve; CI= confidence interval; DOR= diagnostics odds ratio; FC= faecal calprotectin; I² = heterogeneity test; k = number studies; MH =mucosal healing; N = number of patients; UC= ulcerative colitis.

## Key results and considerations of the evidence informing active disease and mucosal healing

The FC test shows 'excellent' predictive power compared to colonoscopy (i.e. AUC > 0.8), except for CD adult patients where the predictive power for active disease with the ≥100 µg/g threshold, may be considered 'acceptable' (i.e. 0.7 to 0.8) (Table 10)

Key aspects to consider when interpreting the evidence are:

- FC testing showed acceptable performance in detecting mucosal healing or active disease in patients with UC or CD. The pooled estimates for sensitivity and specificity of FC testing were similar in both diseases (UC and CD) in adults, with a trend for better performance in patients with UC.
- For patients with an IBD flare, the trend in FC values over time represents the most valuable clinical information to evaluate response to treatment. The proposed treatment algorithm describes a range of FC implementation options allowing for treatment monitoring and repeat FC tests every 2-12 weeks until FC stabilisation/normalisation, at which time clinicians may proceed to the long-term treat-to-target goals, as described by the STRIDE-II guidelines.

## Predicting relapse in asymptomatic patients who are in remission

Predicting relapse in IBD asymptomatic patients involves the ability to monitor patients for future flares, or worsening of IBD in patients who are currently in remission or have low disease activity. Elevated FC levels in patients who are in remission can indicate subclinical inflammation, which may precede a clinical relapse. Predicting relapse with FC test may lead to early changes in management to prevent a more severe flare of disease activity. For asymptomatic IBD patients in remission, a moderate FC elevation (e.g. above 150 µg/g) predicts a likely relapse within 12 months. In patients with active disease, the FC level and trend correlate with severity of inflammation.

Adults

Overall, the FC test demonstrated good sensitivity/specificity for predicting IBD relapse in asymptomatic IBD patients in remission (Table 12). However, sensitivity was lower than specificity noting overlapping 95% CIs. This means that the FC test was better at ruling in true positive patients who will experience relapse in the next 6-12 months than ruling out true negative patients. In clinical practice, this means that some IBD patients in remission who have a 'negative' FC result may still experience a symptomatic IBD flare in the next 6-12 months, however the patients who have a 'positive' FC result are highly likely to experience a flare within the next 6-12 months. The AUC was either acceptable (0.7 to 0.8) or excellent (0.8 to 0.9).

The results were split over two cut-offs to reflect clinical utility; first, all FC cut-offs ≥100 ug/g were included. Then, studies with FC cut-offs >250 were excluded from the results, to reflect likely clinical practice where an FC result >250 µg/g may be considered high and indicative of active disease, which may warrant additional FC testing ± further investigation (e.g. colonoscopy), and/or treatment. The AUC of the pooled studies with a 12-month follow-up and FC cut-off threshold of ≥100 µg/g was 0.813. This indicates that the FC test has excellent discrimination to predict patients who will relapse within 12 months (sensitivity of 71% and a specificity of 81%). Restricting the cut-off thresholds to a range of 100-250 µg/g may be clinically relevant when monitoring asymptomatic patients for relapse, as higher FC results are likely to indicate currently active disease, which indicates a need for treatment and/or further investigations (e.g. colonoscopy or imaging). For FC results between 100 to 250 µg/g (the intermediate range), a clinician might repeat the test and monitor the asymptomatic patient; if the repeat FC is rising, this may indicate the need to initiate/escalate treatment. Capturing intermediate results is important and useful for understanding the potential for relapse and determining appropriate interventions for intermediate outcomes. The sensitivity and specificity for detecting relapse were 70.4% and 77% (k= 16), respectively with an AUC of 0.792.

Table 12 summarizes the performance measures of the test in predicting relapse. Heterogeneity based on the $I^2$ was considered low for the sensitivity and high for specificity in both, CD and UC patients.

**Table 12 Summary of accuracy evidence included in the meta-analysis for predicting relapse**

| Outcome, FC threshold | Condition Number of studies (k) patients (n) | Sensitivity Pooled [95%CI] | Specificity Pooled [95%CI] | Heterogeneity $I^2$ | AUC | CoE (GRADE) |
|---|---|---|---|---|---|---|
| Relapse, cut-off >100 µg/g at 12-months follow-up. | CD, k =6, n = 408 | 75% [64: 83] | 70% [57; 81] | Sensitivity = 0% Specificity = 73% | 0.751 | ⊕⊕⊙⊙ |
| | UC k = 13, n = 1,110 | 73% [67; 79] | 83% [77; 88] | Sensitivity = 38% Specificity = 69% | 0.813 | ⊕⊕⊕⊙ |
| | IBD k=2, n=264 | NE | NE | NE | NE | ⊕⊕⊕⊙ |
| Relapse cut-off between 100-250 µg/g at 12-month follow-up | CD, k = 5, n =355 | 74% [63; 83] | 66% [56; 75] | Sensitivity = 0% Specificity = 63% | 0.764 | ⊕⊕⊕⊙ |
| | UC, k = 10, n = 799 | 73% [65; 80] | 80% [73; 86] | Sensitivity = 21% Specificity = 61% | 0.813 | ⊕⊕⊕⊙ |
| | IBD, k=2, n=264 | NE | NE | NE | NE | ⊕⊕⊕⊙ |
| **aCombined analysis: CD, UC, IBD** | | | | | | |
| > 100 µg/g at 12-month follow-up | Combined UC, CD, IBD k = 21, n = 1,782 | 71% [65; 77] | 80% [75; 85] | 46.6 – 58% | 0.813 | ⊕⊕⊕⊙ |
| 100-250 µg/g at 12-month follow-up | Combined UC, CD, IBD k = 16, n = 1,418 | 70% [64; 76] | 77% [71; 82] | 14.8 - 21.2% | 0.792 | ⊕⊕⊕⊙ |

CD= Crohn disease; CI= confidence interval; IBD= inflammatory bowel disease; NE= not estimable; UC= ulcerative colitis.
aResults reflect the combined analysis reported in the ROC with the corresponding unadjusted Holling statistic.

There is currently no guideline consensus on the optimum testing regime to predict IBD flares in a timely manner in asymptomatic IBD patients that are in remission. A recently published meta-analysis on this topic found an FC cut-off of 152 µg/g was optimal for predicting risk of relapse[10]. Other studies have shown that FC levels may begin to rise approximately 3 months before the manifestation of a symptomatic flare[11]. Considering the available evidence in the literature and the meta-analysis results presented above, one potential clinical application of available evidence is as follows:

- All asymptomatic, eligible Australian IBD patients receive one surveillance FC test per year. If the result of this test is ≥150 µg/g, then these patients are considered to be at a significantly increased risk of relapse within the next 12 months, and serial FC tests every 3-4 months are recommended; if FC levels have normalised by the end of the 12 months with no relapse/flare, then patients may be able to return to the baseline 1x FC test per year.

## Key considerations of the evidence informing the accuracy of relapse

- Most studies look at the predictive power of a single FC measurement taken at baseline, and FC levels were correlated with relapse rates within a pre-specified timeframe (e.g. 12 months) to calculate how the baseline FC level relates to a risk of relapse within the next 12 months. However, while a single FC result may predict the likelihood of a relapse within the next 12 to 24 months, this does not give clinicians enough information to determine when the optimum time might be to commence therapy prior to symptomatic presentation.
- Studies reported results on the test accuracy to predict relapse on a range of pre-specified FC cut-off thresholds or estimated the optimal cut-off where sensitivity and specificity was maximised. However, if clinicians would like to commence treatment for a flare before it becomes clinically apparent, there is an additional requirement for regular FC monitoring (ie. repeated FC tests within a specified time period) in patients determined to be at a high risk of relapse.

### Paediatric population

The evidence for paediatric patient population is presented in this subsection. The results of the FC testing ability to detect active disease and predict mucosal healing in symptomatic patients, as well as the ability to predict relapse in asymptomatic paediatric patients is presented below.

The evidence for FC test accuracy in paediatric patients was limited, with three studies reporting on CD (mucosal healing and active disease) and one study reporting on UC (active disease) with a combined N = 290 patients (Table 13). The AUC of combined CD and UC paediatric population for both mucosal healing and active disease estimates an AUC of 0.839 (indicating excellent FC test accuracy) with similar sensitivity and specificity values, noting that the wide confidence intervals and paucity of data make this result uncertain. In paediatric patients, maintaining disease control is crucial as it directly impacts their development and growth. Additionally, colonoscopies in this population are technically challenging, as bowel preparation and fasting are difficult for children to endure, and the procedure requires general anaesthetic (which has associated risks); therefore, colonoscopies are performed judiciously in this population. As such,

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[10] Shi T, Chen N, Xu ., et al. 2023. 'Diagnostic Accuracy of Fecal Calprotectin for Predicting Relapse in Inflammatory Bowel Disease: A Meta-Analysis', *Journal of Clinical Medicine*, 12(3), 18.

[11] Maaser C, Sturm A, Vavricka S. R. et al. 2019. 'ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications', *Journal of Crohn's and Colitis*, 13(2), 144-164K.

there is a high need in the paediatric population for a non-invasive and effective method to monitor disease.

**Table 13 Summary of accuracy results for mucosal healing and active disease at different cut-off thresholds in paediatric patients with IBD**

| FC threshold | Number of studies | Number of patients | Sensitivity: Pooled estimate [95%CI] | Specificity: Pooled estimate [95%CI] | NPV, % PPV, % | AUC | CoE (GRADE) |
|---|---|---|---|---|---|---|---|
| Pooled UC and CD, MH and active disease, all FC cut-offs | k=4 | N = 290 | 75% [66; 83] | 70% [34; 92] | 89 61 | 0.839 | ⊕⊕⊙⊙ |
| Pooled IBD and CD, predicting relapse, all FC cut-offs | k=6 | N = 416 | 80% [63; 91] | 71% [51; 85] | 89 57 | 0.826 | ⊕⊕⊙⊙ |

AUC = area under the curve; CD = Crohn disease; CoE = certainty of evidence; FC = faecal calprotectin; IBD = irritable bowel disease; k= number of studies; I² : quantifies the proportion of total variation across studies that is due to heterogeneity; MH = mucosal healing; N = number of patients; N/A = not applicable; NPV= negative predictive value; PPV= positive predictive value; UC = ulcerative colitis.

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

FC testing in paediatric patients demonstrated good predictive value for relapse, despite limited data and high heterogeneity. In total, six studies involving a total of 416 paediatric patients met the inclusion criteria. Of these, one study focused specifically on CD, while the other five reported on IBD (UC and CD combined). Follow-up periods varied across studies, ranging from 3 to 36 months.

Compared to studies on adult patients, the cut-off thresholds in these paediatric studies were higher, consistent with the anticipated elevated baseline FC levels observed in children with values ranging from 100-500 µg/g. The pooled sensitivity and specificity for detecting relapse were 80% (95% CI: 63 - 91) and 71% (95% CI: 51 - 85), respectively. The estimated AUC of 0.826 (Table 13) indicates that the test is excellent at distinguishing between who are going to experience relapse and those who will not, noting the wide confidence intervals and spread of included studies, making this result uncertain.

### *Linked evidence of change in management*

Symptomatic and asymptomatic IBD patients may benefit from tailored management strategies that incorporate FC testing into clinical guidelines. Based on FC test results, treatment decisions, such as initiation, escalation, or de-escalation of therapy, can be made. FC testing enables regular, non-invasive monitoring which may subsequently lead to early intervention and tighter disease management.

To identify the changes in clinical management from the introduction of FC testing, a review of the current guidelines for the use of FC tests in treatment of symptomatic IBD patients and a targeted literature search of published studies was conducted. Acknowledging that variations in

individual clinicians' behaviour cannot be fully accounted for, the guidelines provide the most robust interpretation of available evidence, produced and agreed upon by groups of prominent gastroenterologists. Therefore, the guidelines are considered the best proxy to predict mainstream clinician behaviour and are a more robust predictor of clinical practice than individual studies. In their application for the PICO Confirmation, the Gastroenterological Society of Australia (GESA) cited multiple guidelines and the treat-to-target approach to IBD management. The search results identified several studies to support the guidelines, some of which reviewed these guidelines and provided additional evidence and interpretation.

The STRIDE-II guidelines[12] endorse the use of FC testing to monitor for treatment response, and the normalisation of FC levels are an intermediate treat-to-target goal in patients with an active IBD flare. The treat-to-target approach is considered to produce optimum patient outcomes, primarily informed by two studies (REACT and CALM)[13]. However, the treat-to-target approach requires adoption by clinicians, and patient adherence; some Australian clinicians have listed a range of concerns with this approach, suggesting more evidence/clarity is required before they may adopt it. The concerns included the increased burden of additional endoscopies which may impact accessibility and increase the exposure of patients to the risks associated with endoscopy. Other concerns included the lack of standardised and validated definitions of mucosal healing and concern whether patients would be able to comply with monitoring strategies (eg. regular clinical follow-up, endoscopy and regular CRP and faecal calprotectin testing) [14].

Clinical evidence is increasingly supporting the use of FC testing as a key component of IBD management strategies, demonstrating its impact on improving patient outcomes through early detection and timely therapeutic interventions. Colombel et al.[15] and Cortesi et al. (2023)[16] have demonstrated that integrating FC testing into treatment protocols can reduce relapse rates (20.9% reduction in relapses per patient), particularly when used to guide active dose escalation based on predefined thresholds. Taking this approach aligns with the principles of "tight control" and "treat-to-target" strategies, where close monitoring of biomarkers, such as FC, is utilised to make proactive treatment adjustments before clinical symptoms reappear (West et al. 2023). The STRIDE-II guidelines further emphasise the clinical value of FC, advocating for its routine use to support ongoing disease management [17].

Despite its growing utility, the use of FC testing in IBD management presents certain challenges. In particular, abnormal FC results can result in unnecessarily escalating to more potent therapies, which carries increased risks of side effects and adverse events. Additionally, the therapeutic thresholds for FC are not yet precisely defined, which could lead to variability in clinical decision-making and the potential for unnecessary treatment adjustments. A careful

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[12] Turner D, Ricciuto A, Lewis A, et al. 2021. 'STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organisation for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD', *Gastroenterology*, 160(5), 1570-1583.

[13] Seow, C. 2023. 'Using a Treat-to-Target Approach to Manage Patients With Inflammatory Bowel Disease', *Gastroenterology & Hepatology*, 19(7), 415

[14] West, J., Tan, K., Devi, J., Macrae, F., Christensen, B., & Segal, J. P. (2023). Benefits and challenges of treat-to-target in inflammatory bowel disease. Journal of Clinical Medicine, 12(19), 6292.

[15] Colombel JF, D'haens G, Lee, WJ et al. 2020. 'Outcomes and strategies to support a treat-to-target approach in inflammatory bowel disease: a systematic review', *Journal of Crohn's and Colitis*, 14(2), 254-266.

[16] Cortesi PA, Fiorino G, Peyrin-Biroulet L, et al. 2023. 'Non-invasive monitoring and treat-to-target approach are cost-effective in patients with mild-moderate ulcerative colitis', *Alimentary Pharmacology and Therapeutics*, 57(5)(5), 486-495.

[17] Srinivasan, A. R. 2024. 'Treat to target in Crohn's disease: A practical guide for clinicians', *World Journal of Gastroenterology*, 30(1), 21.

interpretation of FC results within the broader clinical context is essential to avoid excess treatment risks while still maximising the benefits of early intervention and disease control.

A summary of the anticipated impact of FC testing in terms of change in patient management is presented in Table 14.

**Table 14 Summary of the impact of FC testing in the change on patient management of IBD patients**

| Aspect | Impact of FC test |
|---|---|
| Early detection of relapse or flare-ups | Predictive Value: Allows early intervention by predicting relapse or flare-ups in asymptomatic patients. Plevris & Lees (2022)[18], emphasised proactive longitudinal monitoring using FC testing to detect early disease flare-up in asymptomatic patients, with data showing FC predicting relapse within 2-3 months with 78% sensitivity and 73% specificity. |
|  | Treatment Adjustment: Elevated FC levels prompt treatment adjustments before clinical symptoms appear, preventing or limiting severe flare-ups. Lasson et al (2015)[19] showed that active dose escalation triggered by FC results significantly reduced the relapse rate compared to control group (28.6% vs 57.1%, respectively; $p < 0.05$). |
| Monitoring disease activity | Regular Monitoring: Provides a non-invasive means for regularly monitoring disease activity in symptomatic patients, tracking response to treatment[13]. |
|  | Guiding Treatment Decisions: Changes in FC levels guide decisions on escalating, maintaining, or de-escalating therapy, ensuring appropriate care ([19]. |
| Reducing need for invasive and expensive procedures | Replacement for Colonoscopy: In certain cases, FC testing can replace colonoscopy for monitoring disease activity, reducing the need for invasive procedures. The 'Motaganhalli et al 2019[20] study conducted in Australia, estimated that the use of FC testing resulted in approximately 18% reduction in colonoscopies with 51% apparent cost reduction and another study from Scotland [18] showed an approximately 40% reduction' in colonoscopies |
| Tailored treatment plans | Individualised Care: Enables a more personalised approach to treatment by frequently monitoring FC levels, adjusting plans based on real-time disease activity rather than waiting for symptomatic changes or scheduled colonoscopies. |

FC= faecal calprotectin; IBD= inflammatory bowel disease.

Frequency of FC testing is a critical component in the management of IBD, however, the interpretation of FC results is nuanced and must be integrated with other clinical parameters including patient symptoms, duration of clinical remission, concurrent medications, and additional biomarkers. In addition, FC trends overtime are considered more valuable than a single FC result[5]. The proposed treatment algorithm stratifies patients into three FC thresholds (<100 µg/g, 100-250 µg/g, and >250 µg/g). For patients with FC levels consistently below 100 µg/g, conservative management with baseline FC monitoring is advised (see Figure 4). Conversely, an FC level exceeding 250 µg/g typically warrants more immediate intervention, such as treatment escalation, to mitigate the risk of disease progression. Patients with intermediate FC levels (100-250 µg/g) may require closer monitoring, potentially involving repeat FC testing or colonoscopy before any changes in management are considered. FC results should be

[18] Plevris N, Lees CW 2022. 'Disease monitoring in inflammatory bowel disease: evolving principles and possibilities', *Gastroenterology*, 162(5), 1456-1475.

[19] Lasson A, Öhman L, Stotzer PO, et al. 2015. 'Pharmacological intervention based on fecal calprotectin levels in patients with ulcerative colitis at high risk of a relapse: A prospective, randomized, controlled study', *United European Gastroenterology Journal*, 3(1), 72-79.

[20] Motaganahalli S, Beswick L, Con D, et al. 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(1), 94-100.

interpreted within the clinical context, and situations where the FC results do not correspond to the clinical presentation will likely require additional investigations (e.g. imaging/colonoscopy).

The current clinical guidelines vary in the recommended frequency for FC testing, generally recommending intervals ranging from 3 to 12 months based on factors such as recent disease activity, time since diagnosis, recent therapeutic modifications, and patient preference.

### *Linked evidence of health outcomes*

Based on the evidence presented in Section 2B.2, FC test offers significant clinical benefits as a non-invasive tool for identifying disease activity, confirming remission and predicting potential flares in IBD. With or without changes in treatment, its use can contribute in preventing morbidities, avoiding complications, and improving health-related quality of life. The FC test is associated with no known adverse effects, and its ability to potentially replace the colonoscopies in symptomatic patients could reduce the number of colonoscopy-related adverse events[18][20]. Moreover, trends in FC results can provide valuable insights for long-term management, particularly in predicting disease recurrence during the post-treatment maintenance phase[5].

Overall, the health benefits of FC testing for the assessment and monitoring of disease activity in IBD patients may lead to improved health outcomes due to :(1) improved safety due to reduction in colonoscopies [21] and (2) a tighter disease control[15]. Colonoscopies are associated with risks such as post-colonoscopy bleeding, bowel perforation, and infection, with perforation rates as high as 1% in IBD patients[22]. By reducing colonoscopy frequency, FC testing can mitigate these risks, offering a safer monitoring alternative.

Regular FC testing may improve disease management by predicting relapses early and optimising treatment response, thereby reducing disease progression and complications[16]. In this regard, the CALM study was the first randomised controlled trial that showed that patients with early CD who had their treatment monitored using biochemical targets (tight control arm) achieved higher rates of endoscopic remission at 1 year compared to those whose treatment was guided by clinical targets alone[15]. A significantly higher proportion of patients achieved mucosal healing at 48 weeks (46% vs. 30%; adjusted risk difference 16.1%, 95% CI: 3.9–28.3; p = 0.010) with a tight control strategy compared to symptom-driven clinical management. Additionally, the tight control arm experienced fewer Crohn disease-related hospitalisations (13.2 vs. 28.0 events per 100 patient-years; p = 0.021). Follow-up data for an additional three years from the CALM study on 122 patients showed that achieving endoscopic remission (adjusted hazard ratio = 0.44, 95% CI: 0.20–0.96) and combined endoscopic and clinical (deep) remission (HR = 0.25, 95% CI: 0.09–0.72) at 1 year was associated with a significantly lower risk of adverse outcomes. These outcomes included new internal fistulas or abscesses, strictures, perianal fistulas or abscesses, hospitalisations, or surgeries during long-term follow-up[23].

If tight control of IBD improves mucosal healing it will reduce inflammation which consequently may reduce the damage caused by inflammation at a cellular/DNA level. Chronic intestinal inflammation is the primary risk factor for the development of gastrointestinal malignancy (including colorectal cancer, small bowel adenocarcinoma, intestinal lymphoma, anal cancer, and

[21] Waddingham W, Kamran U, Kumar B, et al. 2023. 'Complications of colonoscopy: common and rare—recognition, assessment and management', *BMJ Open Gastroenterology*, 10(1), e001193

[22] Navaneethan U, Parasa S, Venkatesh PG, et al. 2011. 'Prevalence and risk factors for colonic perforation during colonoscopy in hospitalized inflammatory bowel disease patients', *Journal of Crohn's and Colitis*, 5(3), 189-195.

[23] Ungaro RC, Yzet C, Bossuyt P,et al. 2020. 'Deep Remission at 1 Year Prevents Progression of Early Crohn's Disease', *Gastroenterology*, 159(1):139-147.

cholangiocarcinoma)[24]. This underlying inflammatory state together with the medical therapies that control disease flare (e.g. anti-tumour necrosis factor (TNF) therapies, antiinterleukin (IL)-12/23 agents, sphingosine-1-phosphate (S1P) receptor inhibitors and small molecule therapies) increase the risk of developing extra-intestinal malignancies[6][7][25] . There is substantial data suggesting that the immunosuppression caused by TNF alpha antagonists (i.e. infliximab) and other targeted small molecules (i.e., tofacitinib) lead to a 1.5 to 2 times higher risk of serious infections leading to hospitalisations compared to non-biologic immunosuppressive agents (i.e., thiopurines). Among currently approved biologic therapies, TNF alpha antagonists may be linked to an increased risk of lymphoma, especially when used in combination with thiopurines[8]. Reducing IBD patients' immunosuppressive status by reducing the exposure to these medications may also improve health outcomes. Potentially, FC testing may help in this regard.

However, the success of this approach depends on patient adherence to FC testing among other tests, which may be challenged due to the need for repeated stool sample collection.

The potential benefits of FC testing can be summarised as follows:

- Potentially reduced burden of colonoscopy due to the replacement for FC: colonoscopy is invasive, resource-intensive, and is associated with patient discomfort mainly from bowel preparation. Integrating FC testing into clinical practice can reduce the number of these procedures, thus optimising patient care[26].
- Improved safety due to avoidance of colonoscopy: While colonoscopy has significant diagnostic value, it carries inherent risks such as bowel perforation, bleeding, and sedation-related complications[21]. FC testing offers a non-invasive alternative to monitor disease activity, potentially preventing some of these risks.
- Earlier treatment decisions: FC testing can guide earlier treatment interventions including initiation, dose escalation/de-escalation or maintenance therapy[20]. Personalised treatment ensures appropriate care while minimising unnecessary interventions. This may lead to benefits in terms of reduced hospitalisations, particularly if relapses can be identified before they become symptomatic [15][23]. Potentially this may also reduce the time off work and provide psychological benefits due to avoided colonoscopies [27].
- Mitigation of complications related to treatment therapies: FC-guided therapy decisions may lead to safer treatment profiles by optimising the length, duration and intensity of escalated therapies (e.g. immunomodulators, biologics) [7][8][16].

The economic evaluation section based the rates of colonoscopy-related perforation rates on two large US cohort studies, that were previously presented in the MSAC application 1353.1[28][29].

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[24] Beaugerie L, Itzkowitz SH. 2015. 'Cancers complicating inflammatory bowel disease', *New England Journal of Medicine*, 372(15), 1441-1452.

[25] Pedersen N, Duricova D, Elkjaer M, et al. 2010. 'Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies', *Official journal of the American College of Gastroenterology*| ACG, 105(7), 1480-1487

[26] Gonczi L, Bessissow T, Lakatos PL. Disease monitoring strategies in inflammatory bowel diseases: What do we mean by "tight control"? *World J Gastroenterol*. 2019 Nov 7;25(41):6172-6189.

[27] Jain A, Jain R, Nugent Z, et al. 2022.' Improving colonoscopy bowel preparation and reducing patient anxiety through recently developed online information resource: a cross-sectional study', *Journal of the Canadian Association of Gastroenterology*, 5(4), 161-168

[28] Arora G, Gaurav A, et al. 2009. "Risk of perforation from a colonoscopy in adults: a large population-based study", *Gastrointestinal endoscopy*, 69(3), 654-664.

[29] Mukewar S, Costedio M, Wu X, et al. 2014. 'Severe adverse outcomes of endoscopic perforations in patients with and without IBD', *Inflammatory Bowel Diseases*, 20(11), 2056-2066

Clinical claim

On the basis of collective evidence profile relative to colonoscopy and biopsy, FC testing has non-inferior effectiveness and at least non-inferior safety.

The FC test can play an important role in the monitoring of IBD flares, whilst acknowledging it is not a perfect surrogate for endoscopy. The evidence showed that:

- The use of FC test results in at least non-inferior safety compared with colonoscopy/biopsy, based on its non-invasive nature.
- The FC test accurately detects mucosal healing or active disease in patients with diagnosed UC or CD,
- FC testing of asymptomatic patients with IBD, particularly in 3-4 months intervals, demonstrated a good ability to predict disease relapse.
- The FC test may be used to guide therapeutic intervention in IBD patients with an active flare, facilitating judicious use of escalated therapies.

The results in the pooled analyses were largely driven by the UC studies, but individual accuracy estimates showed consistent accuracy in sensitivity and specificity across pooled UC and CD patient groups.

When the FC test is used, with the option for follow-up colonoscopy if needed, IBD patients are likely to receive a superior model of care compared to when colonoscopy alone is available. Further, the FC test may predict the earlier onset of a future flare in asymptomatic patients.

The benefit of the FC test compared to colonoscopy/biopsy lies in the ease-of-use and timing of information provided for the monitoring of IBD patients.

For the majority of symptomatic and some asymptomatic patients, FC testing may preclude the need for an endoscopy.

# 13.   Economic evaluation

The clinical assessment of the evidence suggested that relative to colonoscopy/biopsy, FC testing has non-inferior effectiveness in predicting mucosal healing, active disease or relapse in symptomatic and asymptomatic patients. However, because of at least non-inferior safety and potential indirect health outcomes, it may be plausible that inclusion of FC testing is overall a superior model of care compared to when colonoscopy/biopsy alone is available. Given that the number of adverse events associated with colonoscopies is likely small and that improved health outcomes from a tighter disease management with the availability of FC testing is theoretical, a conservative approach was adopted of assuming non-inferiority of FC testing. Therefore, a cost-minimisation analysis (CMA) was considered appropriate for both symptomatic and asymptomatic patients. A summary of the key characteristics of the CMA is presented in Table 15.

While the safety argument applies to both, symptomatic and asymptomatic patients, currently asymptomatic patients are likely to be monitored less frequently through colonoscopy due to factors like the need for anaesthesia, bowel preparation, and safety concerns. In these patients, standard medical management was proposed as a secondary comparator, noting that FC testing would not replace but rather take place in addition to standard medical management. However, there is no evidence available to inform this comparison.

**Table 15 Summary of the economic evaluation**

| Component | Description |
|---|---|
| Therapeutic claim: effectiveness | Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior. |
| Therapeutic claim: safety | Based on evidence presented in Section 2, safety is assumed at least non-inferior. |
| Evidence base | Linked evidence to test accuracy to health outcomes |
| Time horizon | One year |
| Computational method | Decision tree |
| Direct health technology costs | Lower; FC test cost[1] = $75 vs colonoscopy+biopsy cost[2] = $3,070.93 |
| Other costs or cost offsets | Yes. <br><br> Cost of additional colonoscopies/biopsies and associated complications due to incorrect FC result. Cost of colonoscopies/biopsies which would not otherwise be performed in asymptomatic patients in the absence of FC testing and associated complications. Costs resulting due to additional GP and specialist consults. <br><br> FC testing reduces the number of colonoscopies thus offsetting the cost due to FC testing. |

FC= faecal calprotectin
[1] This cost is based on MBS item 66522 and 66523 corresponding to FC testing for the diagnosis of IBD.
[2] This cost corresponds to the weighted average across different types of colonoscopies and potential for complications, including the cost of biopsy (MBS Item 72824 = $141.35).

The CMA estimated the cost differences arising from the introduction of FC testing for the monitoring of IBD using a decision-analytic model (Figure 1). Patients with IBD can be monitored through colonoscopy/biopsy or FC testing. Patients entering the model are categorised based on symptoms (symptomatic or asymptomatic) and further based on endoscopic activity, which can be either moderate/severe (mucosal healing negative, MH–) or mild/remission (mucosal healing positive, MH+). Therefore, symptomatic patients are considered diagnosis positive if they are positive for mucosal healing (MH+ or no IBD) and diagnosis negative if they are mucosal healing negative (MH - or active IBD). FC testing of patients can result in positive or negative for IBD based on pre-defined cut-off threshold.

In the FC arm, upon FC testing, patients are categorised based on the FC result in true positive (TP), true negative (TN), false positive (FP) and false negative (FN) (Figure 1). In the symptomatic arm, FC testing is aimed to detect mucosal healing (<100 µg/g) and in the asymptomatic arm FC testing is aimed to detect relapse (>100 µg/g). Test positive (T+) in the symptomatic arm are those that achieved mucosal healing whilst T+ in the asymptomatic arm are those that have relapsed. These outcomes are based on the sensitivity and specificity of the test for detecting mucosal healing at a cut-off <100 µg/g (in the symptomatic arm) or predicting relapse at a cut-off >100 µg/g (in the asymptomatic arm). There is no sensitivity or specificity for moderate or intermediate results, as FC results can be considered ambiguous when results fall in this range (FC results between 100 and 250 ug/g).

Interpretation of the test outcomes in symptomatic and asymptomatic arms is as follows:

**Symptomatic arm:** The symptomatic arm reflects patients that are symptomatic at the time of disease assessment, with or without treatment.

- TP: Truly identified as mild/remission (mild on colonoscopy and tested mild on FC, <100 µg/g)
- FN: Falsely identified as moderate/severe disease (mild on colonoscopy but suspected to be moderate or severe based on FC result, >100 µg/g)

- TN: Truly identified as moderate/severe disease (moderate/severe on colonoscopy and FC, >100 µg/g)
- FP: Falsely identified as mild/remission (moderate/severe on colonoscopy but suspected to be mild based on FC result, <100 µg/g)

**Asymptomatic arm:** The asymptomatic arm reflects patients that at the time of disease assessment are in remission, therefore without treatment.

- TP: Truly identified as relapsed or moderate/severe disease (relapsed or moderate/severe on colonoscopy and FC, >100 µg/g)
- FN: Falsely identified as in mild/remission (relapsed or moderate/severe on colonoscopy but suspected to be in remission mild based on FC result, <100 µg/g)
- TN: Truly identified as in mild/remission (in remission or mild on colonoscopy and tested mild on FC, <100 µg/g)
- FP: Falsely identified as relapsed or moderate/severe disease (mild on colonoscopy but suspected to be relapsed or moderate/severe based on FC result, >100 µg/g)

In the No FC arm, symptomatic patients are categorised based on endoscopic severity of an IBD flare, which can be either mild, moderate or severe. As colonoscopy is considered the gold standard, testing through colonoscopy in the No FC arm would not result in any FP or FN cases.

The total cost of each monitoring pathway was estimated over the 1-year time horizon by multiplying the cost of each test by the frequency of testing required over the time horizon.

**Figure 1 Disease-based approach used to account for the accuracy of FC testing in the monitoring of IBD**
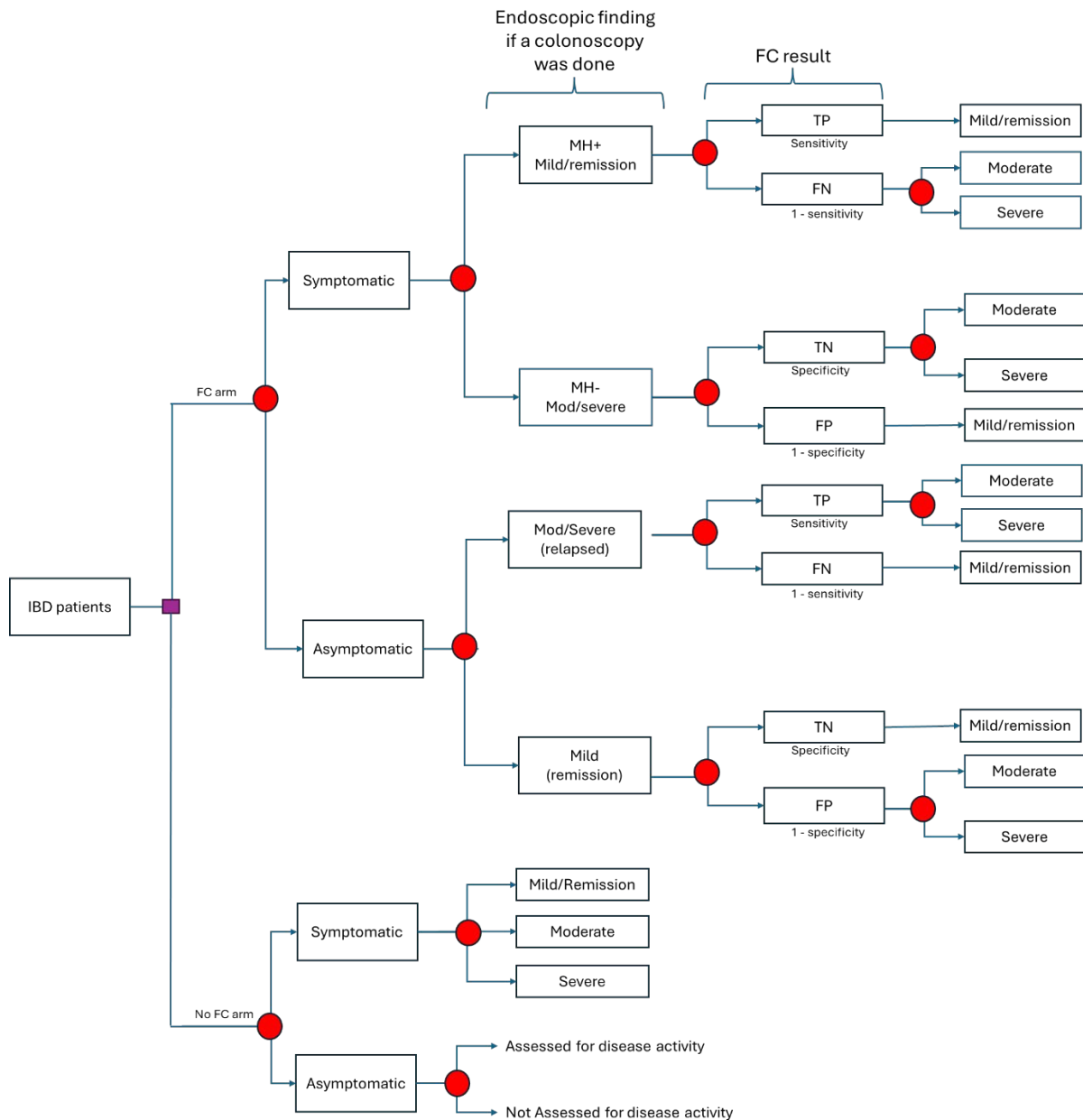


FC = faecal calprotectin; FN = false negative; FP = false positive; IBD = inflammatory bowel disease; MH+ = mucosal healing positive; MH- = mucosal healing negative; Mod = moderate; TN = true negative; TP = true positive.
Notes: purple square reflects a decision node and the red circles reflect a chance node.

The likelihood of being symptomatic and asymptomatic and further distribution by severity and remission status was based on a published Canadian study[30] and Monash data shared by the applicant. Distribution of patients based on their symptoms and their severity in the base case is presented in Table 16.

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[30] Melesse DY, Lix LM, Nugent Z, et al. 2016. 'Estimates of Disease Course in Inflammatory Bowel Disease Using Administrative Data: A Population-level Study', *Journal of Crohn's and Colitis*, 11(5), 562-570.

**Table 16 Distribution of IBD patients by severity**

| Severity | Proportion | Source |
|---|---|---|
| **Symptomatic (both arms)** | 40% | Canadian study* |
| Mild | 43.39% | Canadian study* |
| Moderate and severe | 56.61% | Canadian study* |
| **Asymptomatic** | 60% | Canadian study* |
| **FC arm** | | |
| Mild/Remission | 61.80% | Monash data** |
| Moderate and severe/Relapsed | 38.20% | Monash data** |
| **No FC arm** | | |
| Assessed with colonoscopy | 10% | Assumption |
| Not assessed with colonoscopy | 90% | Assumption |

FC= faecal calprotectin; IBD= inflammatory bowel disease.
* Melesse, D. Y., Lix, L. M., Nugent, Z., Targownik, L. E., Singh, H., Blanchard, J. F., & Bernstein, C. N. (2016). Estimates of Disease Course in Inflammatory Bowel Disease Using Administrative Data: A Population-level Study. *Journal of Crohn's and Colitis, 11*(5), 562-570.
**Data from Monash Health Pathology provided by the applicant during the DCAR development stage.

The FC test accuracy (sensitivity and specificity) for mucosal healing and relapse, were based on the results of the meta-analysis conducted during the assessment (Table 17). Given that the aim of the FC test is to discriminate between patients with and without active disease, all results >100 µg/g were considered to be indicative of relapse, and results <100 µg/g were indicative of mucosal healing. There is no sensitivity or specificity for moderate or intermediate results, as clinical decision-making becomes ambiguous when FC results fall in this range (100 - 250 µg/g).

**Table 17 Sensitivity and specificity to capture TP, FP, TN and FN cases.**

| Population | Outcome | FC cut-off (µg/g) | Sensitivity | Specificity |
|---|---|---|---|---|
| Symptomatic patients | Mucosal healing | <100 | 82.9% [75.7% – 88.4%] | 71.4% [64.9% – 77.1%] |
| Asymptomatic patients | Relapse | >100 | 71.4% [65.2% - 76.9%] | 80.3% [74.7% - 84.9%] |

FN= false negative; FP= false positive; TN= true negative; TP = true positive.

The model assumed that all patients in the FC arm would receive two FC tests per year, consistent with the applicant's proposed 6-monthly testing schedule. The base case scenario assumes that not all patients will adhere to the FC monitoring strategy, and it was assumed that symptomatic patients will adhere better to regular FC testing compared to asymptomatic patients, 70% and 50%, respectively. The number of colonoscopies in the FC arm depends on the FC results. Patients who have FC results in the equivocal range of 100 µg/g to 250 µg/g (both true and false positive results in this range) may be clinically ambiguous, and require additional monitoring and investigations (e.g. imaging, repeat FC, and/or colonoscopy) to determine if they have an IBD flare or not. In the rest of the cases (mild and severe), FC is expected to replace colonoscopy. For instance, symptomatic patients correctly identified as not having active disease may avoid a colonoscopy/biopsy. Conversely, if patients are incorrectly identified as having active disease (false positive), it was assumed that additional tests might be required to establish a trend, and further investigation via colonoscopy might be necessary. The other resource use included in the model are repeat FC testing, general practitioner, specialist and subsequent specialist consultations arising due to FC testing. Repeat FC testing is necessary to establish a trend especially if the FC results are in intermediate range. Adherence to repeat tests was assumed to be 100%. Each FC test also requires a GP consultation, and each colonoscopy would

require a specialist and subsequent specialist consultation. Patients with moderate/severe disease are also expected to visit a specialist more often compared to those with mild symptoms/remission.

In the No FC arm, patients could be assessed or not assessed with colonoscopy. The assessment report assumed all symptomatic patients (40% of total no FC arm) and 10% of asymptomatic patients (60% of total no FC arm) in the model would undergo one colonoscopy evaluation as part of their regular monitoring (periodic endoscopic examinations to assess mucosal healing) and treatment adjustment. Most asymptomatic patients (90%) would receive only standard medical management (not assessed for endoscopic activity), with no additional costs allocated, as colonoscopy/FC testing was assumed to be an add-on to the standard medical management. Resource use assumed in the analysis in the FC arm and No FC arm are presented in Table 18 and Table 19, respectively. The impact of a proportion of mild/moderate symptomatic patients accessing GP consults instead of specialist consultation was tested in a sensitivity analysis.

**Table 18 Frequency of annual resources in the FC arm**

| Distribution of patients | Routine FC | Repeat FC | Colonoscopy/ biopsy | GP | Specialist | Subsequent specialist consult |
|---|---|---|---|---|---|---|
| **Symptomatic – Mild/Remission** | | | | | | |
| TP[1] | 2 | 0 | 0 | 2 | 1 | 0 |
| FN | 2 | 2 | 1 | 2 | 1 | 1 |
| TN (moderate disease)[2] | 2 | 3 | 1 | 2 | 1 | 2 |
| TN (severe disease)[2] | 2 | 3 | 0 | 2 | 1 | 2 |
| FP | 2 | 3 | 1 | 2 | 1 | 2 |
| **Asymptomatic** | | | | | | |
| TP, moderate | 2 | 3 | 1 | 2 | 1 | 2 |
| TP, severe | 2 | 3 | 0 | 2 | 1 | 2 |
| FN | 2 | 2 | 0 | 2 | 1 | 1 |
| TN | 2 | 0 | 0 | 2 | 0 | 0 |
| FP | 2 | 2 | 1 | 2 | 1 | 2 |

FC= faecal calprotectin; FN= false negative; FP= false positive; GP= general practitioner; TN= true negative; TP = true positive.
[1] These patients are true positives for being in a state of remission.
[2] These patients are true negatives for being in a state of remission; i.e. they have either moderate or severe disease activity.

**Table 19 Frequency of resources in the No-FC arm**

| | Routine FC | Repeat FC | Colonoscopy / biopsy | GP | Specialist | Subsequent specialist consult |
|---|---|---|---|---|---|---|
| **Symptomatic** | | | | | | |
| Mild | 0 | 0 | 1 | 0 | 1 | 0 |
| Moderate | 0 | 0 | 1 | 0 | 1 | 1 |
| Severe | 0 | 0 | 1 | 0 | 1 | 1 |
| **Asymptomatic** | | | | | | |
| Assessed for disease activity | 0 | 0 | 1 | 0 | 1 | 1 |
| Not assessed | 0 | 0 | 0 | 0 | 0 | 0 |

FC= faecal calprotectin; GP = general practitioner

Only the costs associated with the monitoring of IBD were accounted for in this CMA (Table 20). These include the cost of the FC test, colonoscopy and biopsy, and GP and specialist visits. Cost data were obtained from MBS fee found on the MBS website[31], the Australian Refined Diagnosis Related Groups (AR-DRGs) and the National Hospital Cost Data Collection (NHCDC) data. All costs were reported in 2024 Australian Dollars.

**Table 20 Summary of the costs included in the cost-minimisation approach**

| Parameter | Value | Source |
|---|---|---|
| **Direct health technology costs** | | |
| Colonoscopy | $2,929.58 | AR-DRG (NHCDC 2021-22) |
| Biopsy | $141.35 | MBS Item 72824 |
| FC testing | $75 | MBS Item 66522 and 66523 |
| **Additional costs and/or cost offsets** | | |
| GP consultation | $42.85 | MBS Item 23 |
| Specialist consultation | $174.50 | MBS Item 110 |
| Specialist subsequent consultation | $87.30 | MBS Item 116 |

AR-DRG= Australian Refined Diagnosis Related Groups; FC = faecal calprotectin; GP= general practitioner; NHCDC= National Hospital Cost Data Collection.

Assuming 100 patients are being monitored through colonoscopy/biopsy (No FC arm) or through FC, the base case results show that fewer colonoscopies/biopsies (15 for every 100 patients) are undertaken in symptomatic cases. Conversely, given the high anticipated rate of asymptomatic patients not currently being assessed through colonoscopy, the introduction of FC testing may lead to additional colonoscopies being performed due to tighter monitoring. For every 100 asymptomatic patients monitored through colonoscopy/biopsy or FC, 0.87 additional procedures are expected. Overall, monitoring through FC testing resulted in a 30% reduction in colonoscopies/biopsies (a reduction of 14 colonoscopy/biopsies for every 100 IBD patients). An Australian study by Motaganahlli et al. 2019[20], estimated a 50% reduction in colonoscopies in a hospital-based setting. Monitoring through FC testing also translates into an increase in GP consultations and specialist consultations (Table 21).

It is estimated that every 100 IBD patients monitored through FC will require 206 FC tests including both routine and repeat testing (2.06 FC tests per patient per year). An increased number of subsequent specialist consultations are estimated in the FC arm compared to the initial specialist consultations as the CMA assumed that repeat FC tests and treatment monitoring occurs as a follow-up consultation (i.e., subsequent specialist consultation). As there is no repeat testing in the No FC arm, CMA estimated lower number of subsequent specialist consultations compared to initial specialist consultations.

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[31] https://www.mbsonline.gov.au/

**Table 21 Estimated resource use – Frequency of use per 100 IBD patients per year**

| Resource | FC Arm | No FC Arm | Difference |
|---|---|---|---|
| Surveillance FC | 116.00 | 0.00 | 116.00 |
| Repeat FC | 90.08 | 0.00 | 90.08 |
| Colonoscopy | 32.06 | 46.00 | -13.94 |
| Biopsy | 32.06 | 46.00 | -13.94 |
| GP consultation | 116.00 | 0.00 | 116.00 |
| Initial specialist consultation | 55.11 | 46.00 | 9.11 |
| Specialist subsequent consultation | 67.49 | 28.64 | 38.84 |

FC = Faecal calprotectin; GP= general practitioner; IBD= inflammatory bowel disease; ND = not defined

For every 100 patients monitored through FC testing an overall reduction in costs of $33,455 is anticipated in symptomatic patients and an overall increase in costs of $16,046 is anticipated in asymptomatic patients leading to an overall cost saving of $17,408 (Table 22).

**Table 22 Estimated cost of monitoring per 100 IBD patients (symptomatic and asymptomatic) per year**

| Resource | FC Arm | No FC Arm | Additional costs/cost offsets |
|---|---|---|---|
| Surveillance FC | $8,700 | $0 | $8,700 |
| Repeat FC | $6,756 | $0 | $6,756 |
| Colonoscopy | $93,916 | $134,761 | -$40,845 |
| Biopsy | $4,531 | $6,502 | -$1,971 |
| GP consultation | $4,971 | $0 | $4,971 |
| Initial specialist consultation | $9,617 | $8,027 | $1,590 |
| Specialist subsequent consultation | $5,891 | $2,501 | $3,391 |
| **Total Cost** | **$134,382** | **$151,790** | **-$17,408** |

FC = Faecal calprotectin; GP= general practitioner.

*In its pre-ESC response the applicant advised that the appropriate MBS item for biopsy should be 72825 (with a fee of $180.250 instead of 72824 (fee of $141.35). This further increased the base case cost savings to $17,951 for every 100 patients. Additional sensitivity analyses based on this revised base case are presented in the Addendum.*

The sensitivity analysis shows the results are robust as most of the changes led to a reduction in the overall cost from the introduction of FC testing for the monitoring of IBD (Table 23). The inputs that most significantly impacted the results were the proportion of colonoscopies conducted in public hospitals, estimated reduction in colonoscopies, proportion of asymptomatic patients assessed for disease activity in no FC arm, adherence to FC testing and frequency of routine FC testing.

The cost of colonoscopy estimated in the CMA was based on the weighted average of relevant AR-DRG costs plus MBS costs for biopsy ($3070.93), inclusive of all healthcare system costs including public hospitals and outpatient procedures. Assuming 27.9% of colonoscopies are conducted in public hospitals (as per Section 4.5) and 72.1[32]% are conducted in the private day patient setting (as per Section 4.3), the cost per colonoscopy drops to $1,862.47 ([27.9% * $3070.93] + [72.1% * ($488.34[33] + $906.51[34])]). A sensitivity analysis assuming this colonoscopy cost reduces the cost savings by 87% leading to an overall reduction of −$560 per 100 IBD.

The CMA estimated a 30% reduction in colonoscopies due to FC testing. Increasing the reduction in colonoscopies to 50% increases the cost savings by 160% (Table 23). An increase in the proportion of asymptomatic patients assessed for disease activity in no FC arm from 10% to 20% increased the cost savings by 115%. An increase of adherence to FC testing in symptomatic cases from 70% in the base case to 100% increased the cost savings by 82%. An increase in the adherence to FC testing in asymptomatic patients from 50% to 70% reduced the cost savings by 83%. The intervention is estimated to result in additional costs if the frequency of routine FC testing increases beyond 6 FC tests per year per patient. A reduction in the proportion of mild cases in no FC arm that are monitored through colonoscopy from 100% to 70% reduced the cost savings by 64%.

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[32] Worthington T, He E, Lew J, et al. 2023. 'Colonoscopies in Australia – how much does the National Bowel Cancer Screening Program contribute to colonoscopy use?', *Public Health Research & Practice.*

[33] Cost of colonoscopy to MBS including co-claimed services as estimated in Section 4.

[34] Cost of colonoscopy in private health system based on Private Hospital Data Bureau: Annual Report (2021-22) was estimated to be $765.16 (weighted average of hospital change per separation for AR-DRG G48A and G48B, after adjusting for inflation). Cost of colonoscopy plus biopsy ($141.35, MBS Item 72824) in private day care is $906.51.

**Table 23 One way sensitivity analysis: cost of FC testing per 100 patients**

| | Scenario | Base case | SA | FC Arm | No FC Arm | Additional costs/cost offsets | % Inc |
|---|---|---|---|---|---|---|---|
| | **Base case** | | | **$134,382** | **$151,790** | **-$17,408** | **$134,382** |
| SA 1 | Proportion of colonoscopies in public hospital[a] | 100% | 27.9% | $95,642 | $96,201 | -$560 | ↓ 96.8% |
| SA 2 | Estimated reduction in colonoscopies | 30% | 20% 40% 50% | $148,945 $120,693 $106,567 | $151,790 $151,709 $151,790 | -$2,845 -$31,098 -$45,224 | ↓ 84% ↑ 78.6% ↑ 160% |
| SA 3 | Assessed for disease activity: asymptomatic patients | 10% | 20% | $134,382 | $171,787 | -$37,405 | ↑ 115% |
| SA 4 | Adherence to FC testing symptomatic | 70% | 100% | $120,044 | $151,790 | -$31,746 | ↑ 82% |
| SA 5 | Adhere to FC testing asymptomatic | 50% | 70% | $148,799 | $151,790 | -$2,991 | ↓83% |
| SA 6 | Lower bound 95% CI FC accuracy in symptomatic (sensitivity/specificity) | 83% 71% | 75.7% 64.9% | $138,602 | $151,790 | -$13,188 | ↓ 27% |
| SA 7 | Lower bound 95% CI FC accuracy in asymptomatic: sensitivity/specificity | 71.4% 81.3% | 65.2% 74.7% | $137,158 | $151,790 | -$14,632 | ↓16% |
| SA 8 | Frequency of FC testing per year | 2 | 4 | $143,082 | $151,790 | -$8,708 | ↓50% |
| SA 9 | Frequency of FC testing per year | 2 | 6 | $151,782 | $151,790 | -$8 | ↓100% |
| SA10 | % of moderate cases in FC arm which may result in a colonoscopy and biopsy | 100% | 70% | $128,326 | $151,790 | -$23,464 | ↑ 35% |
| SA11 | % of mild cases in No FC arm monitored through colonoscopy | 100% | 70% | $129,585 | $135,801 | -$6,216 | ↓ 64% |
| SA12 | Proportion of specialist vs GP consults for mild/moderate cases in No FC arm | 100% vs 0% | 80% vs 20% | $134,063 | $150,987 | -$16,924 | ↓ 3% |
| SA13 | % of GP consultations in No FC arm[b] | 0% | 28% | $134,382 | $152,342 | -$17,960 | ↑ 3% |
| SA14 | SA12 + SA13 | | | $134,063 | $151,539 | -$17,476 | 0% |

CI= confidence interval; FC = Faecal calprotectin; Inc= incremental; SA= sensitivity analysis.

[a] This sensitivity analysis assumes the remaining colonoscopies are conducted privately. Cost per colonoscopy plus biopsy including the MBS service cost in private day care is $1,394.85 and cost per colonoscopy plus biopsy in public hospital is $3,070.93. The assumption is that 27.9% of the colonoscopies are done in public hospitals, the remaining 72.1% are conducted in the private day care.

[b] It was assumed that people living in rural/remote Australia (28%) may not have direct access to specialist. An additional GP consult was assumed in No FC arm for Symptomatic and Asymptomatic patients who are assessed for disease. Asymptomatic patients who are not assessed for disease were assumed to be in remission and not under medication and have no reason to see a GP/specialist.

# 14. Financial/budgetary impacts

An epidemiological approach is used to estimate the eligible population that uses FC testing for monitoring of IBD in Australia. The assessment considered the incidence and prevalence of IBD in Australia to estimate the burden of IBD in Australia i.e., the eligible population for monitoring of IBD. The prevalence was based on a cross-sectional study using data from a national database of general practice electronic health records from 1 July 2017 to 30 June 2019 conducted by Busingye et al. This study showed a prevalence of 653 per 100,000. Previous Australian studies had reported a lower prevalence, but those studies were conducted more than 10 years ago and evidence was limited by location (Victoria), sample size, and characteristics of the population studied. The assessment assumed an incidence of 19.8 per 100,000 based on a meta-analysis conducted by Forbes et al. 2024[35]. A summary of the epidemiological data used is presented in Table 24.

**Table 24 Epidemiological data sources and input values**

| Author | Title | Year Location | Prevalence | Incidence |
|---|---|---|---|---|
| Wilson J et al 2010[36] | High incidence of inflammatory bowel disease in Australia: a prospective population-based Australian incidence study | 2007 – 2008 Greater Geelong, Victoria | NR | 29.6 per 100,000 |
| Studd C et al 2015[37] | Never underestimate inflammatory bowel disease: High prevalence rates and confirmation of high incidence rates in Australia | 2011 Barwon, Victoria | Crude estimate: 344.6/100,000 | Crude estimate: 24.2/100,000 |
| Crohn's & Colitis Australia 2013[38] | Improving Inflammatory Bowel Disease care across Australia | 2012 | Estimated mean[1]: 74,955 | NR |
| Busingye D et al, 2021[39] | Prevalence of inflammatory bowel disease in the Australian general practice population: A cross-sectional study | 2017-2019 | 653 per 100,000 patients[2] | NR |
| Forbes et al., 2023[35] | The Epidemiology of Inflammatory Bowel Disease in Oceania: A Systematic Review and Meta-Analysis of Incidence and Prevalence | Australia, New Zealand and Pacific islands | Pooled estimate of 303 per 100,000 | 19.8 per 100,000[2] |

NR= not reported

[1] This number was estimated based on a triangulation method based on published Australian data. Two of the three sources used in this approach were identified during this DCAR.

[2] IBD prevalence and incidence inputs used in the current assessment.

[35] Forbes A J, Frampton C.MA, Day A.S, et al. 2024. 'The Epidemiology of Inflammatory Bowel Disease in Oceania: A Systematic Review and Meta-Analysis of Incidence and Prevalence.', *Inflammatory Bowel Diseases* 30(11):2076-2086.

[36] Wilson J, Hair C, Knight R, et al. 2010. 'High incidence of inflammatory bowel disease in Australia: A prospective population-based Australian incidence study', Inflammatory Bowel Diseases, 16(9), 1550-1556

[37] Studd C, Cameron G, Beswick L, et al. 2016. 'Never underestimate inflammatory bowel disease: High prevalence rates and confirmation of high incidence rates in Australia', *Journal of Gastroenterology & Hepatology*, 31(1), 81-86.

[38] https://crohnsandcolitis.org.au/advocacy/our-projects/improving-inflammatory-bowel-disease-care-across-australia/

[39] Busingye D, Pollack A, Chidwick K. 2021. 'Prevalence of inflammatory bowel disease in the Australian general practice population: A cross-sectional study', *PLoS ONE* [Electronic Resource], 16(5), e0252458. https://doi.org/10.1371/journal.pone.0252458

Table 25 presents the 6-year projected prevalence (2025-2030) which was estimated based on a prevalence of 653 per 100,000 population, an incidence of 19.8 per 100,000 population, a projected Australian population in 2024 of 27,824,827 and an annual population growth of 2.5%[1]

**Table 25 Estimated burden of IBD in Australia**

| Parameter | Calculation | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|---|
| Population | Annual population growing at a rate of 2.5% per year | 28,520,448 | 29,233,459 | 29,964,295 | 30,713,403 | 31,481,238 | 32,268,269 |
| Incidence | 19.8 per 100,000 | 5,647 | 5,788 | 5,933 | 6,081 | 6,233 | 6,389 |
| Prevalence | 653 per 100,000 | 186,239 | 190,894 | 195,667 | 200,559 | 205,572 | 210,712 |
| Total IBD population | Incidence + Prevalence | 191,886 | 196,683 | 201,600 | 206,640 | 211,806 | 217,101 |

IBD= inflammatory bowel disease.

The expected use of resources and the respective unit costs are the same as applied in the CMA except for the cost of colonoscopy/biopsy. Cost of colonoscopy in CMA was based on AR-DRGs and cost of biopsy was based on MBS Item 72824. For the purpose of financial analysis to measure the cost to MBS, cost of colonoscopy/biopsy was based on the communication received from the Department during the development of DCAR. Based on this, the most relevant MBS item identified for colonoscopy and biopsy in the context of IBD monitoring were items 32222 and 72824 (which accounts for 2 to 4 separately identified specimens), respectively. Each colonoscopy service will require other MBS services which are co-claimed with item 32222 but not exclusively in the context of IBD monitoring (e.g. colorectal cancer screening). The estimated MBS cost of each colonoscopy was $488.34. It should be noted that the colonoscopy cost estimated in the CMA ($3,070.93), was estimated based on the weighted average of relevant AR-DRGs for colonoscopy in public hospital and MBS cost for biopsy.

The Department sought the applicant's advice on the most relevant MBS item/s for biopsy which are typically co-claimed with colonoscopy, by gastroenterologists in this setting. *In its pre-ESC response the applicant advised that the appropriate MBS item for biopsy should be 72825 (with a fee of $180.250 instead of 72824 (fee of $141.35). Additional financial sensitivity analyses based on this revised base case are presented in the Addendum.*

The introduction of FC testing for the monitoring of IBD led to an overall average additional cost of over $35 million per year to the MBS mainly due to increase in GP, specialist and subsequent specialist visits. In total, a reduction of 170,893 colonoscopies and biopsies was estimated at a population level over a 6-year period (Table 26).

**Table 26 Net financial implications of FC testing for monitoring IBD to the MBS**

| Parameter | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|
| Estimated use and cost of the proposed health technology | | | | | | |
| Number of people eligible for FC testing | 191,886 | 196,683 | 201,600 | 206,640 | 211,806 | 217,101 |
| Number of FC tests[a] | 395,439 | 405,324 | 415,458 | 425,844 | 436,490 | 447,402 |
| Cost to the MBS[b] | $25,209,204 | $25,839,435 | $26,485,420 | $27,147,556 | $27,826,245 | $28,521,901 |
| Change in use and cost of other health technologies | | | | | | |
| Change in use of colonoscopies[c] | -26,753 | -27,422 | -28,108 | -28,810 | -29,531 | -30,269 |
| Change in GP visits[d] | 222,587 | 228,152 | 233,856 | 239,702 | 245,695 | 251,837 |
| Change in specialist visits[e] | 17,485 | 17,922 | 18,371 | 18,830 | 19,301 | 19,783 |
| Change in subsequent specialist visits[f] | 74,531 | 76,394 | 78,304 | 80,261 | 82,268 | 84,325 |
| Change in cost of colonoscopies[g] | -$9,419,661 | -$9,655,152 | -$9,896,531 | -$10,143,944 | -$10,397,543 | -$10,657,481 |
| Change in cost of GP visits[h] | $9,537,864 | $9,776,311 | $10,020,719 | $10,271,237 | $10,528,017 | $10,791,218 |
| Change in cost of specialist visits[i] | $2,593,513 | $2,658,351 | $2,724,810 | $2,792,930 | $2,862,754 | $2,934,322 |
| Change in cost of subsequent specialist visits[j] | $5,530,544 | $5,668,807 | $5,810,527 | $5,955,791 | $6,104,685 | $6,257,302 |
| **Net financial impact to the MBS (less copayments)** | **$33,451,465** | **$34,287,752** | **$35,144,946** | **$36,023,569** | **$36,924,158** | **$37,847,262** |

FC = Faecal calprotectin; GP= general practitioner.

[a] Number of FC tests per year per patient = 2.06

[b] One FC test cost= $63.75 (85% of full schedule fee based on MBS item 66522 and 66523)

[c] Change in number of colonoscopies per patient per year = -0.14

[d] Change in GP visits per patient per year = 1.16

[e] Change in specialist visits per patient per year = 0.09

[f] Change in subsequent specialist visits per patient per year = 0.39

[g] Cost per colonoscopy+biopsy including the co-claimed services to MBS= $488.34. Assuming 72.1% of colonoscopies are conducted in private day care.

[h] GP cost = $42.85 (100% of the full schedule fee based on MBS Item 23)

[i] Specialist visit cost = $148.33 (85% of the full schedule fee based on MBS item 110)

[j] Subsequent specialist consultation cost = $74.21 (85% of the full schedule fee based on MBS item 116)

The cost to public hospitals was estimated using the cost of colonoscopies based on AR-DRG as in CMA ($3,070.93, cost of colonoscopy plus biopsy) as estimated in Table 27. It was assumed

that 27.9%[32] of colonoscopies conducted for monitoring of IBD purposes are done in public hospitals. Overall, it is anticipated that there would be a reduction in the cost to public hospitals of $22,921,918 in 2025 which increases to $25,934,046 in 2030.

**Table 27 Net financial implications of FC testing in public hospitals**

| Parameter | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|
| **Cost to public hospitals** | | | | | | |
| Number of colonoscopies avoided | -26,753 | -27,422 | -28,108 | -28,810 | -29,531 | -30,269 |
| Colonoscopies avoided in public hospital[a] | -7,464 | -7,651 | -7,842 | -8,038 | -8,239 | -8,445 |
| Cost of Colonoscopy[b] | $3,070.93 | $3,070.93 | $23,070.93 | $3,070.93 | $3,070.93 | $3,070.93 |
| **Cost to public hospitals** | **-$22,921,918** | **-$23,494,966** | **-$24,082,340** | **-$24,684,398** | **-$25,301,508** | **-$25,934,046** |

AUD= Australian Dollar; FC = faecal calprotectin, GP= general practitioner; MBS = Medicare Benefits Schedule
[a] It was assumed that 27.9% of colonoscopies were conducted in public hospitals.
[b] Estimated cost of colonoscopy based on relevant AR-DRGs plus cost of biopsy $3,070.93.

The introduction of FC testing leads to additional cost to the MBS mostly driven by additional GP, specialist and subsequent specialist consultations. A sensitivity analysis was conducted assuming 100% adherence to the monitoring strategy in symptomatic patients, 70% adherence in asymptomatic patients, increased frequency of testing from 6-monthly to quarterly testing and assuming that FC testing occurs in an inpatient setting therefore the MBS rebate was reduced to 75%. The sensitivity analysis presented in Table 28 show that additional cost to MBS ranges from approximately $34 million to nearly $54 million in 2030.

**Table 28 Net financial implications of FC testing in the MBS: sensitivity analysis**

| Scenario | Base case | SA | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|---|---|
| **Base case** | | | $33,451,465 | $34,287,752 | $35,144,946 | $36,023,569 | $36,924,158 | $37,847,262 |
| Adherence to FC testing in symptomatic patients | 70% | 100% | $37,875,699 | $38,822,591 | $39,793,156 | $40,787,985 | $41,807,685 | $42,852,877 |
| Adherence to FC testing in asymptomatic patients | 50% | 70% | $45,349,055 | $46,482,782 | $47,644,851 | $48,835,972 | $50,056,872 | $51,308,293 |
| Increased frequency of routine FC testing | 2 | 4 | $47,641,403 | $48,832,438 | $50,053,249 | $51,304,580 | $52,587,195 | $53,901,875 |
| FC test provided inpatient (MBS rebate) | 85% | 75% | $30,485,676 | $31,247,818 | $32,029,014 | $32,829,739 | $33,650,483 | $34,491,745 |

FC = Faecal calprotectin; MBS = Medicare Benefits Schedule

# 15. Other relevant information

Nil.

# 16. Key issues from ESC to MSAC

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**Main issues for MSAC consideration**

**Clinical issues:**

- Faecal calprotectin (FC) thresholds included in pathology reports are different to what is included in the Department Commissioned Assessment Report (DCAR), which has implications for practice. The different FC thresholds may result in confusion for clinicians and are likely to result in repeat FC testing due to misinterpretation. Advice is needed from the Royal College of Pathologists of Australasia (RCPA) regarding clinical consequences, and whether a change in the way FC results are reported is needed.

- Comparative safety is uncertain. The safety of FC testing compared with colonoscopy (or medical management in asymptomatic patients) is unknown, because although colonoscopies avoided from using FC testing results in greater safety, false positive results of FC testing may lead to an increase in unwarranted colonoscopies and more aggressive IBD therapies which may be associated with reduced safety.

- FC testing appears to have good diagnostic accuracy, but the downstream changes are uncertain. The data presented to support change in management and change in clinical outcomes were low quality (mainly based on guidelines and narrative data) and only a targeted search was conducted to identify change in clinical decisions and health outcomes. Therefore clinical effectiveness is uncertain.

- In terms of predicting relapse, the clinical utility of FC testing is uncertain as there is currently no guideline consensus on the optimum testing regime to predict IBD flares in a timely manner in asymptomatic IBD patients who are in remission.

**Economic issues:**

- There is limited evidence on how much colonoscopy utilisation rates may be reduced by the introduction of FC testing. There are several uncertain assumptions that have been made that favour the cost offsets seen in the economic model, namely:

o The model assumed that 100% of symptomatic patients in the no FC arm receive colonoscopy.

o An assumed 100% adherence to repeat FC testing.

**Financial issues:**

- Cost offsets are likely overestimated. FC testing is currently widely used in clinical practice for monitoring patients with IBD via various funding mechanisms. Therefore, an observable significant reduction in colonoscopies is unlikely, particularly in the private sector.

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**ESC discussion**

ESC noted that this application was for Medicare Benefits Schedule (MBS) listing of faecal calprotectin (FC) testing for the monitoring of people with diagnosed inflammatory bowel disease (IBD). ESC noted that FC testing for monitoring of IBD is already widely performed in Australian clinical practice through various funding mechanisms.

ESC noted that in March 2018, MSAC considered but did not support MBS listing of FC testing for the diagnosis and monitoring of IBD (MSAC Application 1353). In its decision, MSAC advised that a resubmission for monitoring patients with IBD should provide:

- a definition of current Australian practice to monitor IBD (for example, 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 to better identify the downstream management practices and health outcomes that might be improved by introducing FC monitoring; ESC considered that this had been partially addressed by this current application.

- further information on the biological variability of inflammation in the stable IBD patient cohort to provide a better basis for when to initiate a change in clinical management and a better basis for the requested frequency of FC testing; ESC considered that this was still unknown.

In November 2019 MSAC considered a resubmission (MSAC Application 1353.1) which focused only on FC testing for diagnosis of IBD and which MSAC subsequently supported publicly funding. Two MBS items were introduced in November 2021 that focused on FC testing for diagnosis of IBD in patients aged <50 years: MBS items 66522 (for general practitioners [GPs]) and 66523 (for specialists). The current application is seeking FC test listing for disease monitoring in patients with IBD.

ESC noted that FC is a biomarker of gut inflammation. Raised levels in the stool reflect the migration of neutrophils into the gut lumen. ESC noted the following thresholds for FC levels proposed in the clinical algorithm which aligns with some clinical guidelines including recommendations by the Gastroenterological Society of Australia:

- <100 µg/g: no inflammation
- 100–250 µg/g: intermediate
- >250 µg/g: active inflammation.

ESC noted that false positive results may be caused by infection or nonsteroidal anti-inflammatory drugs (NSAIDs). ESC noted that an intermediate FC result, which has a very wide range, can be difficult for clinicians to interpret. Also, ESC noted feedback from the Royal College of Pathologists of Australasia (RCPA) that there is a 20% diurnal variation in FC levels. Therefore, it is recommended that the test is performed in the morning when FC levels are at their highest. ESC noted that this was not factored into the threshold levels or in any other part of the application.

ESC noted that this application received a strong response from health professionals, organisations and individual consumers from the PASC and MSAC consultation stages. The feedback highlighted the benefits of reduced colonoscopies/more-invasive testing and increased access for rural patients, especially if GPs are eligible to order the test. Further benefits also noted were IBD disease monitoring through FC testing could potentially lead to better treatment outcomes, and potential cost savings from avoiding unnecessary treatments. ESC noted from the feedback that, because the test is currently accessible through private patient payments, approving funding will reduce the costs for consumers. The only risks highlighted by the feedback were false positive results.

ESC noted that the proposed clinical management algorithm was missing the option for colonoscopy irrespective of FC result in symptomatic patients – instead, it assumed that 100% of patients would undergo FC testing prior to decision making regarding colonoscopy, but ESC considered that this would not be the case in clinical practice.

ESC noted that the application included two PICO sets:

- PICO set 1: symptomatic patients with known IBD; the comparator is colonoscopy and biopsy. FC testing will be used to predict disease activity or mucosal healing.
- PICO set 2: asymptomatic patients with known IBD; the comparators are colonoscopy and biopsy, and standard medical management. FC testing will be used to predict relapse.

ESC noted that for PICO set 2, PASC had proposed a secondary comparator of standard medical management. ESC noted that under this comparator FC testing would be an add-on test rather than a replacement and an overall claim of superiority rather than non-inferiority would have to be made to assess FC testing which would in turn have required a cost utility model rather than the cost minimisation model employed in the economic evaluation (see later discussion). However, ESC noted that the DCAR stated that there was no evidence available to inform the assessment against this secondary comparator.

ESC noted the heterogeneity of the patients in the target population. ESC noted that this application was generally targeted at IBD patients who are at the more severe end of the spectrum and are typically managed by specialists. ESC considered that FC testing would also be useful for triaging IBD patients at the less severe end of the spectrum who are mainly managed in primary care and may intermittently develop symptoms requiring specialist intervention.

ESC noted that the proposed item descriptor specifies that a maximum of 10 tests may be performed per year. ESC considered that this restriction was unnecessary as patients who are symptomatic may require more than 10 tests per year, although this was considered a rare scenario. ESC considered whether it would be helpful to look at the overall utilisation for MBS items 66522 and 66523, but noted that both these items are restricted to diagnosis. In addition, MBS item 66523 is not used regularly as this item is specifically for patients with inconclusive FC results or ongoing symptoms. These patients tend to proceed to colonoscopy rather than undergo repeat FC testing.

Regarding the proposed item restriction to specialist requestors only, ESC noted that the applicant in the pre-ESC response agreed to allow access to GPs but only in consultation with specialists. ESC considered this to be an acceptable approach. ESC considered that specialists may have more training and experience to interpret and act on FC results appropriately. However, allowing GPs to order FC tests may address access issues arising from both geographical location and financial barriers. ESC also noted that pathology reports currently use an incorrect FC threshold of 50 µg/g, which can lead to unnecessary repeat testing and unnecessary referrals for colonoscopies. ESC considered that provided there were clear standardised thresholds, clinicians would be able to interpret FC test results more easily. ESC considered that advice is needed from the RCPA regarding clinical consequences, and whether a change in the way FC results are reported is needed. ESC noted from the pre-ESC response that the applicant would be pleased to work with pathology companies to help with standardisation of thresholds. ESC considered whether IBD nurse practitioners should also be allowed to order FC tests.

Regarding whether this should be a new item, or the proposed service should be subsumed into the current MBS items 66522/66523, ESC preferred this to be a new item. MBS items 66522 and 66523 for IBD diagnosis are currently restricted to individuals under 50 years of age, and ESC considered that this age restrictor should not be removed as FC testing for the initial diagnosis of gut symptoms in older patients (>50 years) is not clinically indicated as other pathologies take precedence in this age group.

ESC considered that the MBS item descriptor should include an explanatory note to exclude infection first as infections can be a cause of false positive results. Additionally, ESC considered

that the item descriptor should specify that this test be performed in a NATA accredited laboratory in order to exclude point of care testing.

ESC noted that the clinical claim was that FC testing has non-inferior effectiveness and at least non-inferior safety relative to colonoscopy and/or biopsy. A linked evidence approach was used for both comparative safety and effectiveness.

ESC considered that, overall, the claim of comparative safety is uncertain. Although there were negligible safety issues with the test itself, safety issues may arise from false positive results which may cause unnecessary escalation in therapy and an increase in the number of unwarranted colonoscopies, with higher costs and increased risk of adverse effects from testing and treatment. Given the specificity of FC is approximately 70%, ESC considered that there may be appreciable impact from false positive results. This also depends on how the intermediate test results are handled in practice (for example, how many FC tests are repeated, how many cases go on to colonoscopy). However, compared with colonoscopies and their associated risks, ESC considered that FC testing may have non-inferior safety due to an overall reduction in the number of colonoscopies (taking into account both the symptomatic and asymptomatic groups). However, ESC also noted that guidelines (STRIDE-II) suggest disease monitoring in asymptomatic patients, and in this patient group an intermediate or high FC result could lead to a colonoscopy. Therefore, FC testing could increase the number of colonoscopies performed in the asymptomatic group, given that few asymptomatic patients are currently undergoing colonoscopies, particularly in the public setting.

ESC noted that effectiveness of FC testing compared with colonoscopy was determined in terms of predicting disease activity, predicting mucosal healing and predicting relapse (with subsequent effects on health outcomes). ESC noted that while diagnostic accuracy of the test was adequately supported by multiple prospective studies, empirical data to inform change in clinical decisions (treatment management) and health outcomes were very limited and the literature to support this was mainly opinion based. ESC noted that a targeted search was conducted to identify change in clinical decisions and health outcomes and there were no safety studies identified at either step.

ESC noted that the evidence for diagnostic accuracy comprised a systematic review and meta-analysis of test accuracy studies comparing FC to colonoscopy. ESC considered it appropriate to use a threshold of 100 µg/g to assess test accuracy in line with clinical guidelines. The approach included studies of ulcerative colitis (UC) and Crohn disease (CD) both separately and combined and assessed diagnostic accuracy compared to colonoscopy. ESC noted that there were more studies to inform the use of the test in UC compared to CD. ESC considered the results of the UC and CD sub-populations to be comparable and therefore considered it appropriate to combine the results to increase the statistical power of the analyses.

In the combined analysis, ESC considered that FC testing has acceptable diagnostic accuracy at a threshold of 100 µg/g in predicting active disease or in determining mucosal healing. ESC noted that in this context, FC testing has a lower specificity of ~70% (compared to sensitivity ~80%), suggesting that approximately one in three cases may be incorrectly assumed to have disease when they do not, potentially resulting in unnecessary colonoscopies. ESC noted that, although the results for area under the curve (AUC) were suggestive of discriminatory capability (AUC= 0.834) for a FC threshold of ≥100 µg/g to detect active disease, the $I^2$ for the meta-analysis (percentage of total variation across studies that is due to heterogeneity rather than chance) was 75%, suggesting that the studies were too different to be confidently combined. ESC noted that this has implications regarding certainty of the diagnostic accuracy data when using a FC threshold of ≥100 µg/g to detect active disease.

ESC noted that the evidence base regarding diagnostic accuracy of FC testing in predicting active disease for the paediatric population was limited to four studies (*N* = 209). The estimates regarding diagnostic accuracy in the studies were similar to each other but they had wide confidence intervals. Therefore, the appropriateness of generalisability of the adult studies to paediatric populations is uncertain. ESC acknowledged that although the data regarding diagnostic accuracy for the paediatric population was limited and less robust than that for the adult population, ESC considered that it would be appropriate to generalise the results of the adult population to the paediatric population. ESC considered that this could be accepted as there is a high clinical need to avoid colonoscopies in a paediatric population.

In terms of predicting relapse, ESC noted from the DCAR that the clinical utility of FC testing in the asymptomatic population is uncertain as there is currently no guideline consensus on the optimum testing regime to predict IBD flares in a timely manner in asymptomatic IBD patients who are in remission. ESC also noted that there is a lack of consensus on what threshold should constitute a change in treatment for this population and considered that further research is needed. The DCAR examined studies with a FC test cut-off of 100 µg/g and the ability of FC testing to predict relapse within 12 months of the initial test. Based on this evidence, ESC considered that FC testing exhibits an acceptable level of sensitivity and specificity in predicting relapse and found that the AUC was 0.81. ESC noted that the evidence reviewed comprised both prospective and retrospective studies but considered that retrospective studies did not provide compelling evidence as they are likely to be biased in terms of including selected, high-need populations. ESC considered that, if FC testing is approved for the prediction of disease activity or mucosal healing in symptomatic IBD patients, there would be no implementable way of excluding use of FC for predicting relapse in the asymptomatic population, despite the clinical claim for the latter being less supported.

ESC noted that the evidence included in the DCAR for change in clinical management mainly comprised guidelines (e.g. STRIDE-II[40]) and narrative studies. ESC noted that one of the studies (Motaganhalli et al. 2019)[41], which examined whether FC testing changes colonoscopy use, was a retrospective study conducted in Australia comparing two cohorts before and after FC test availability. It involved an observational review of hospital charts and examined whether people with FC testing went on to colonoscopy, but there was no evidence of FC directly impacting clinician choice of colonoscopy use. The study hypothesised that, in the absence of the FC test, a colonoscopy would have been performed for disease activity assessment/re-assessment in most patients. However, ESC considered that this study had multiple potential biases and was very low certainty evidence. Another study (Plevris and Lees 2022[42]) was a narrative review that proposed that FC testing would result in a 40% reduction in colonoscopies but presented no empirical data. ESC noted that the STRIDE-II guidelines endorse the use of FC, informed by two studies (REACT[43]

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[40] Turner D, Ricciuto A, Lewis A, et al. 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. 2021 Apr;160(5):1570-1583.

[41] Motaganahalli S, Beswick L, Con D, van Langenberg DR. Faecal calprotectin delivers on convenience, cost reduction and clinical decision-making in inflammatory bowel disease: a real-world cohort study. Intern Med J. 2019 Jan;49(1):94-100.

[42] Plevris N, Lees CW. Disease Monitoring in Inflammatory Bowel Disease: Evolving Principles and Possibilities. Gastroenterology. 2022 Apr;162(5):1456-1475.e1.

[43] Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet. 2015 Nov 7;386(10006):1825-34. doi: 10.1016/S0140-6736(15)00068-9.

and CALM[44]). However, ESC noted several issues with the applicability of the guidelines to Australian clinical practice:

- The evidence has limited generalisability, as the CALM study is a randomised clinical trial using a treat-to-target approach using FC testing in combination with other markers. Therefore, the contribution of FC testing alone to improvements in health outcomes is unclear.
- The FC threshold for disease remission was high at <250 µg/g.
- Clinician adoption of STRIDE-II is not widespread.

ESC considered where FC testing may sit in clinical practice and noted that guidelines appear to have introduced this test as part of routine clinical care. ESC considered that it is possible that a proportion of symptomatic patients may receive colonoscopies regardless of the FC result. In this scenario, FC testing would be an add on test rather than a replacement test for colonoscopy.

ESC also noted that the DCAR did not discuss the signal-to-noise ratio of the FC test (see Technical Guidance 15.4 Monitoring section of the 2021 MSAC Guidelines). A study identified in the European Federation of Clinical Chemistry and Laboratory Medicine Biological Variation Database[45] shows that, in healthy asymptomatic people, testing for circulating calprotectin (using blood tests) has high intra-person and inter-person variation. Among patients with IBD, FC levels are noted to have high intra-person variation (pre-analytical variation)[46]. As noted previously, the RCPA gave feedback that one of the contributors to this variation is the 20% diurnal variation in FC levels which had not been factored into threshold levels. These high levels of variation represent the "noise" against which a "signal" needs to be detected. ESC also noted that different assays are not comparable with each other, and the sensitivity across the FC tests to detect an FC level of 50 ug/g differs depending on the assay used. ESC considered it important to understand the background noise of the test if it is being used for monitoring, especially because a threshold of 50 µg/g is used in pathology reports. Additionally, ESC considered it would be important to harmonise the different assays to facilitate interpretation of results. The RCPA may be able to advise on the process for achieving this.

Regarding the evidence for health outcomes, ESC noted that the DCAR presented a narrative discussion of studies, some of which were used to support earlier steps in the linked evidence approach. Most of the studies were low quality (retrospective) and did not provide direct data for FC testing to outcomes. Additionally, FC testing was often done in association with other biomarkers, so the contribution of FC testing alone was unclear. Overall, there was no empirical evidence that FC testing changes health outcomes.

Overall, in assessing the safety and effectiveness data presented in the DCAR, ESC considered that:

- There was no data presented on comparative safety on which there was a high degree of uncertainty.

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[44] Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2017 Dec 23;390(10114):2779-2789.

[45] Briers M, Massa B, Vander Cruyssen B. et al. Discriminating signal from noise: the biological variation of circulating calprotectin in serum and plasma. Clin Chem Lab Med 2024; 62(5): e113–e115.

[46] D'Amico F, Rubin DT, Kotze PG, et al. International consensus on methodological issues in standardization of fecal calprotectin measurement in inflammatory bowel diseases. United European Gastroenterol J 2021, 9: 451-460. https://doi.org/10.1002/ueg2.12069

- The evidence base presented for comparative effectiveness for diagnostic accuracy was of moderate quality, the magnitude of impact (of increased diagnostic accuracy from use of FC testing) was acceptable and this claim had a low degree of uncertainty.
- The level of evidence presented for comparative effectiveness for change in treatment and outcomes was very low, the magnitude of impact (in terms of change in management and outcomes) was unknown and this claim had a high degree of uncertainty.

ESC noted that the economic evaluation was a cost-minimisation analysis using a simple decision tree for the two PICO populations (symptomatic and asymptomatic). It did not incorporate additional costs for escalated IBD treatment resulting from false positive results. Sensitivity and specificity were informed by meta-analyses and included biannual FC testing to detect either mucosal healing (for the symptomatic population; <100 µg/g) or relapse (for the asymptomatic population; >100 µg/g). The comparator was colonoscopy + biopsy.

The economic evaluation assumed that in the no FC arm 10% of the asymptomatic patients and 100% of the symptomatic patients would receive the comparator. ESC considered the latter assumption to be unrealistically high. ESC noted that the pre-ESC response argued that the percentage of asymptomatic patients receiving colonoscopies annually could be as high as 20% (compared to the estimate of 10% used in the economic model) and that therefore the economic cost savings from use of FC testing could be potentially higher than estimated. However, ESC considered that there is no empirical evidence to support this claim and in particular there is little capacity for public hospitals to perform colonoscopies in asymptomatic patients at the rates suggested in the pre-ESC response. ESC considered the DCAR estimate of 10% to be appropriate.

The model assumed symptomatic patients have 70% adherence to FC testing and 100% for repeat FC testing, while adherence was assumed to be 50% for asymptomatic patients.

ESC noted that the results of the economic evaluation showed that FC testing resulted in fewer colonoscopies (an estimated reduction of approximately 30%) and increased number of GP and specialist consultations, resulting in a total cost reduction of $17,408 per 100 IBD patients compared with no FC testing. The results were most sensitive to:

- the proportion of colonoscopies performed in public hospitals

- the estimated reduction in colonoscopies performed (a reduction of less than 20% may no longer be cost saving)

- adherence to and frequency of FC testing. For instance, a doubling in frequency of FC testing led to a 50% reduction in cost savings relative to the base case.

ESC noted that if this analysis is reported by patient group, cost offsets only apply to the symptomatic group (a cost saving of $33,455 per 100 IBD patients); the asymptomatic group incurs additional cost ($16,046 per 100 IBD patients).

ESC noted that the pre-ESC response recommended that the item number claimed for biopsy should be MBS item 72825 (fee of $180.25) instead of MBS item 72824 (fee of $141.35) which was used in the economic model. ESC noted that the rejoinder estimated that using the biopsy item number recommended in the pre-ESC response increased the cost savings from $17,408 to $17,951 per 100 IBD patients. ESC also noted a sensitivity analysis performed by the rejoinder – where 75% of the "no FC" arm would also have a 6-monthly GP visit (when assumed to be part of standard medical management) – increased the cost savings to $24,378 for every 100 IBD patients (using the updated biopsy item).

ESC noted several issues with the economic evaluation:

- The distribution of IBD severity was based on a single outpatient clinic in Melbourne ($n$ = 240) and may not be nationally representative. It is also unclear if the results are generalisable to the paediatric population.

- As noted previously the model assumed that 100% of symptomatic patients in the no FC arm receive colonoscopy. This is likely to overestimate the number of colonoscopies replaced by FC testing.

- The model estimated 30% reduction in colonoscopies based on a number of assumptions regarding resource use including a 100% adherence to repeat FC testing. However, the DCAR did not include any sensitivity analysis testing for the impacts of lower adherence rates on the estimated reduction in colonoscopies and costs.

ESC noted that the cost to the MBS for FC testing alone was estimated as $25.2million in Year 1, increasing to $28.5 million in Year 6, or approximately $161 million over 6 years. Accounting for change in the use and cost of other medical services such as GP and specialist consultations raised the net financial impact to the MBS to $33.5 million in Year 1, to $37.8million in Year 6, or approximately $213.7 million over 6 years. However, ESC considered these to be highly variable based on the uncertainty of the assumptions.

ESC considered that the full reduction in colonoscopies estimated in the economic modelling of 30% which was then used as an input into the financial modelling is unlikely to be achieved as FC testing has been widely used in the proposed population for some years and is funded by multiple means including public hospitals, privately paid for by patients and some bulk billing (potentially incorrectly through MBS item 66523) especially in private settings. However, ESC noted that the extent to which FC testing is already being used in the proposed population is unknown. ESC considered it unlikely that FC testing will further offset colonoscopies performed in the private setting (as there are lesser barriers to access colonoscopies in this setting), however considered that offsets may be observed in the public setting. ESC therefore requested that a sensitivity analysis should be undertaken of the financial estimates assuming a 30% reduction in colonoscopies performed in public hospitals only and with no change in the number of private colonoscopies. Reductions in the number of colonoscopies performed in public hospitals has implications to non-MBS funding mechanisms such as state government funding.

ESC advised that before MSAC consideration of this application, the following sensitivity analyses should be undertaken in the economic modelling with the results of these sensitivity analyses (in terms of estimated reductions in colonoscopies achieved) to be then fed into sensitivity analyses of the financial estimates:

- A sensitivity analysis based on the assumption that only 50-70% of symptomatic patients receive colonoscopy in the no FC arm as the assumption of 100% symptomatic patients receiving a colonoscopy is not realistic.
- A sensitivity analysis assuming 70% of symptomatic patients and 50% of asymptomatic patients adhere to repeat FC testing
- A sensitivity analysis assuming the reduction in colonoscopies is reduced to 0-10%.
- A sensitivity analysis assuming the lower bounds of adherence to surveillance FC testing (50%) for symptomatic patients.

ESC also queried the assumption made in the economic model that patients in the FC arm are billed item 110 annually for the initial specialist consultation. This assumes that a patient has a referral that is valid for 12 months only and must obtain a new referral annually, allowing the specialist to bill item 110 on an annual basis. However, a proportion of patients may have an indefinite referral to a specialist and therefore would be billed item 110 only once, and all subsequent appointments would be billed the lower cost item 116. As such, ESC requested that

a sensitivity analysis be undertaken to account for this scenario. ESC considered that equity issues may arise if FC testing for IBD monitoring purposes were MBS listed due to out-of-pocket payments for FC tests and GP and specialist consultations.  The increase in GP and specialist consultations may also cause issues with access to GPs and specialists. However, ESC also considered that the test would be unlikely to result in an increase in the number of GP visits for patients whose IBD is already primarily managed by their GP.

# 17.  Applicant comments on MSAC's Public Summary Document

The applicant had no comments.

# 18.  Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

# Addendum: Post-ESC additional analyses

### 1. Net financial implications of FC testing for monitoring IBD to the MBS

In its pre-ESC response, the applicant advised that the appropriate MBS item for biopsy should be 72825 (with a fee of $180.250) instead of item 72824 (fee of $141.35). The net financial implications of FC testing for monitoring IBD in both the symptomatic and asymptomatic population based on the applicant proposed MBS item for biopsy (72825) is presented in Addendum Table 1. Addendum Table 2 presents the net financial implication in the symptomatic IBD population and Addendum Table 3 presents the net financial implication in the asymptomatic IBD population.

Addendum Table 1: Net financial implications of FC testing for monitoring IBD to the MBS (symptomatic and asymptomatic population)

| Parameter | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|
| Estimated use and cost of the proposed health technology | | | | | | |
| Number of people eligible for FC testing | 191,886 | 196,683 | 201,600 | 206,640 | 211,806 | 217,101 |
| Number of FC tests | 395,439 | 405,324 | 415,458 | 425,844 | 436,490 | 447,402 |
| Cost to the MBS | $25,209,204 | $25,839,435 | $26,485,420 | $27,147,556 | $27,826,245 | $28,521,901 |
| Change in use and cost of other health technologies | | | | | | |
| Change in use of colonoscopies | -26,753 | -27,422 | -28,108 | -28,810 | -29,531 | -30,269 |
| Change in GP visits | 222,587 | 228,152 | 233,856 | 239,702 | 245,695 | 251,837 |
| Change in specialist visits | 17,485 | 17,922 | 18,371 | 18,830 | 19,301 | 19,783 |
| Change in subsequent specialist visits | 74,531 | 76,394 | 78,304 | 80,261 | 82,268 | 84,325 |
| Change in cost of colonoscopies | -$9,981,697 | -$10,231,239 | -$10,487,020 | -$10,749,196 | -$11,017,926 | -$11,293,374 |
| Change in cost of GP visits | $9,537,864 | $9,776,311 | $10,020,719 | $10,271,237 | $10,528,017 | $10,791,218 |
| Change in cost of specialist visits | $2,593,513 | $2,658,351 | $2,724,810 | $2,792,930 | $2,862,754 | $2,934,322 |
| Change in cost of subsequent specialist visits | $5,530,544 | $5,668,807 | $5,810,527 | $5,955,791 | $6,104,685 | $6,257,302 |
| Net financial impact to the MBS (less copayments) | $32,889,429 | $33,711,665 | $34,554,456 | $35,418,318 | $36,303,776 | $37,211,370 |

The financial impact was calculated based on the MBS item 72825 for biopsy, as advised by the applicant. FC = faecal calprotectin; IBD = inflammatory bowel disease; MBS = Medicare Benefits Schedule; GP = general practitioner

**Addendum Table 2: Net financial implications of FC testing for monitoring IBD to the MBS (symptomatic population)**

| Parameter | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|
| **Estimated use and cost of the proposed health technology** | | | | | | |
| **Number of people eligible for FC testing** | 191,886 | 196,683 | 201,600 | 206,640 | 211,806 | 217,101 |
| **Number of FC tests** | 206,675 | 211,842 | 217,138 | 222,567 | 228,131 | 233,834 |
| **Cost to the MBS** | **$13,175,547** | **$13,504,936** | **$13,842,559** | **$14,188,623** | **$14,543,339** | **$14,906,923** |
| **Change in use and cost of other health technologies** | | | | | | |
| **Change in use of colonoscopies** | -28,429 | -29,140 | -29,868 | -30,615 | -31,380 | -32,165 |
| **Change in GP visits** | 107,456 | 110,142 | 112,896 | 115,718 | 118,611 | 121,577 |
| **Change in specialist visits** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Change in subsequent specialist visits** | 34,402 | 35,262 | 36,144 | 37,047 | 37,973 | 38,923 |
| **Change in cost of colonoscopies** | -$10,606,853 | -$10,872,024 | -$11,143,825 | -$11,422,421 | -$11,707,981 | -$12,000,681 |
| **Change in cost of GP visits** | $4,604,486 | $4,719,598 | $4,837,588 | $4,958,528 | $5,082,491 | $5,209,553 |
| **Change in cost of specialist visits** | $0 | $0 | $0 | $0 | $0 | $0 |
| **Change in cost of subsequent specialist visits** | $2,552,795 | $2,616,614 | $2,682,030 | $2,749,081 | $2,817,808 | $2,888,253 |
| **Net financial impact to the MBS (less copayments)** | **$9,725,975** | **$9,969,124** | **$10,218,353** | **$10,473,811** | **$10,735,657** | **$11,004,048** |

The financial impact was calculated based on the MBS item 72825 for biopsy, as advised by the applicant. FC = faecal calprotectin; IBD = inflammatory bowel disease; MBS = Medicare Benefits Schedule; GP = general practitioner.

**Addendum Table 3: Net financial implications of FC testing for monitoring IBD to the MBS (asymptomatic population)**

| Parameter | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|
| **Estimated use and cost of the proposed health technology** | | | | | | |
| **Number of people eligible for FC testing** | 191,886 | 196,683 | 201,600 | 206,640 | 211,806 | 217,101 |
| **Number of FC tests** | 188,763 | 193,482 | 198,319 | 203,277 | 208,359 | 213,568 |
| **Cost to the MBS** | $12,033,657 | $12,334,499 | $12,642,861 | $12,958,932 | $13,282,906 | $13,614,978 |
| **Change in use and cost of other health technologies** | | | | | | |
| **Change in use of colonoscopies** | 1,676 | 1,717 | 1,760 | 1,804 | 1,850 | 1,896 |
| **Change in GP visits** | 115,131 | 118,010 | 120,960 | 123,984 | 127,083 | 130,261 |
| **Change in specialist visits** | 17,485 | 17,922 | 18,371 | 18,830 | 19,301 | 19,783 |
| **Change in subsequent specialist visits** | 40,129 | 41,132 | 42,160 | 43,214 | 44,295 | 45,402 |
| **Change in cost of colonoscopies** | $625,156 | $640,785 | $656,805 | $673,225 | $690,056 | $707,307 |
| **Change in cost of GP visits** | $4,933,378 | $5,056,713 | $5,183,130 | $5,312,709 | $5,445,526 | $5,581,664 |
| **Change in cost of specialist visits** | $2,593,513 | $2,658,351 | $2,724,810 | $2,792,930 | $2,862,754 | $2,934,322 |
| **Change in cost of subsequent specialist visits** | $2,977,749 | $3,052,193 | $3,128,498 | $3,206,710 | $3,286,878 | $3,369,050 |
| **Net financial impact to the MBS (less copayments)** | **$23,163,454** | **$23,742,540** | **$24,336,104** | **$24,944,506** | **$25,568,119** | **$26,207,322** |

The financial impact was calculated based on the MBS item 72825 for biopsy, as advised by the applicant. FC = faecal calprotectin; IBD = inflammatory bowel disease; MBS = Medicare Benefits Schedule; GP = general practitioner

## 2. Additional economic and financial sensitivity analysis

Additional economic and financial sensitivity analyses were requested by ESC (SA1-SA5) and the Department (SA6). The results of the analysis are reported in Addendum Tables 4 and 5 below.

**Addendum Table 4: Additional sensitivity analysis: cost of FC testing per 100 patients (Symptomatic and Asymptomatic)**

| | Scenario | SA | FC Arm | No FC Arm | Additional costs/cost offsets | % Inc |
|---|---|---|---|---|---|---|
| | **Base case*** | | **$135,629** | **$153,580** | **-$17,951** | |
| SA1 | 100% of symptomatic patients receive colonoscopy in no FC arm | 50%<br>60%<br>70% | $116,970<br>$120,702<br>$124,434 | $91,383<br>$103,823<br>$116,262 | $25,587<br>$16,879<br>$8,172 | 242.50%<br>194.70%<br>145.50% |
| SA2 | 30.31% Reduction in colonoscopies | 0%<br>10% | $178,987<br>$164,682 | $153,580<br>$153,580 | $25,408<br>$11,102 | 241.50%<br>161.8% |
| SA3 | 70% Adherence to surveillance FC testing in symptomatic patients | 50% | $145,352 | $153,580 | -$8,228 | 54.20% |
| SA4 | 100% Adherence to repeat FC testing in symptomatic and asymptomatic patients | 70% in symptomatic patients<br><br>50% in asymptomatic patients | $133,027 | $153,580 | -$20,553 | -14.5% |
| SA5[a] | Ongoing patients are billed item 110 annually and all subsequent appointments in that year are billed item 116. | Ongoing patients are billed item 110 for their first appointment only and item 116 for all subsequent appointments | $130,823 | $149,569 | -$18,745 | -4.4% |
| SA6 | 0% of asymptomatic true positive severe patients undergo colonoscopy | 10%<br>20%<br>30% | $137,161<br>$138,694<br>$140,226 | $153,580<br>$153,580<br>$153,580 | -$16,418<br>-$14,886<br>-$13,354 | 8.50%<br>17.10%<br>25.60% |

* The base case was updated in the rejoinder by revising the cost of biopsy to $180.25 (MBS Item 72825) based on applicant's suggestion.
a This is meant to capture the scenario where the patient has an indefinite referral and only needs to incur the initial item once.

**Addendum Table 5: Net financial implications of requested sensitivity analyses**

|  | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|
| **Base case** * | **$32,889,429** | **$33,711,665** | **$34,554,456** | **$35,418,318** | **$36,303,776** | **$37,211,370** |
| SA1[a] 50% | $42,912,434 | $43,985,244 | $45,084,875 | $46,211,997 | $47,367,297 | $48,551,480 |
| 60% | $40,907,833 | $41,930,528 | $42,978,792 | $44,053,261 | $45,154,593 | $46,283,458 |
| 70% | $38,903,232 | $39,875,812 | $40,872,708 | $41,894,525 | $42,941,889 | $44,015,436 |
| SA2 0% | $42,871,126 | $43,942,904 | $45,041,477 | $46,167,513 | $47,321,701 | $48,504,744 |
| 10% | $39,577,853 | $40,567,299 | $41,581,482 | $42,621,019 | $43,686,544 | $44,778,708 |
| SA3 50% | $30,110,579 | $30,863,343 | $31,634,927 | $32,425,800 | $33,236,445 | $34,067,356 |
| SA4 | $28,644,842 | $29,360,963 | $30,094,987 | $30,847,362 | $31,618,546 | $32,409,010 |
| SA5 | $31,593,415 | $32,383,251 | $33,192,832 | $34,022,653 | $34,873,219 | $35,745,050 |
| SA6 10% | $33,242,184 | $34,073,238 | $34,925,069 | $35,798,196 | $36,693,151 | $37,610,479 |
| 20% | $33,594,938 | $34,434,812 | $35,295,682 | $36,178,074 | $37,082,526 | $38,009,589 |
| 30% | $33,947,693 | $34,796,385 | $35,666,295 | $36,557,952 | $37,471,901 | $38,408,698 |

\* The base case was updated in the rejoinder by revising the cost of biopsy to $180.25 (MBS Item 72825) based on applicant's suggestion.

3. **Financial sensitivity analysis assuming a 30% reduction in colonoscopy in public hospitals only and no change to private colonoscopies.**

ESC also requested a financial estimate of the cost to the MBS assuming a 30% reduction in public hospital colonoscopies and no further reduction in private colonoscopies. The results of this over a 6-year period are reported in Addendum Table 6 below.

**Addendum Table 6: Cost to MBS assuming a 30% reduction in public hospital colonoscopies and no further reduction in private colonoscopies**

|  | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 |
|---|---|---|---|---|---|---|
| **Cost** |  |  |  |  |  |  |
| **Base case** * | **$32,889,429** | **$33,711,665** | **$34,554,456** | **$35,418,318** | **$36,303,776** | **$37,211,370** |
| SA7[a] Cost to MBS assuming no change in private colonoscopies | $40,114,656 | $41,117,523 | $42,145,461 | $43,199,097 | $44,279,075 | $45,386,052 |

\* The base case was updated in the rejoinder by revising the cost of biopsy to $180.25 (MBS Item 72825) based on applicant's suggestion. This scenario assumes, as per base case, that 28% of colonoscopies are conducted in public hospitals and the remaining 72% in private hospitals.