



**Australian Government**

**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1353.1 – Measurement of Calprotectin as a marker of Bowel Inflammation - Resubmission***

**Applicant: Gastroenterological Society of Australia (GESA)**

**Date of MSAC consideration: MSAC 77<sup>th</sup> Meeting, 28-29 November 2019**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

A resubmission requesting Medicare Benefits Schedule (MBS) listing of measurement of faecal calprotectin (FC) in patients suspected of inflammatory bowel disease (IBD) was received from GESA by the Department of Health.

The resubmission focused solely on FC tests for the differential diagnosis of IBD from irritable bowel syndrome [IBS] in adults and IBD from non-IBD in children, and focuses on evidence from a primary care setting (instead of tertiary care).

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding of FC testing for the differential diagnosis of IBS from IBD in the adult population, and for differential diagnosis of IBD from non-IBD in the paediatric population.

MSAC considered that FC testing had acceptable diagnostic performance (sensitivity and specificity), evidence for comparative effectiveness and clinical utility, while being safer and significantly cheaper than endoscopy/biopsy with specialist referral.

MSAC advised that there was considerable uncertainty that FC testing outcomes would reduce specialist referrals and avoid unnecessary colonoscopies. MSAC therefore recommended that the Department monitor the utilisation and outcomes of FC testing, in particular the impact on the utilisation of colonoscopies.

### **Consumer summary**

The Gastroenterological Society of Australia applied for public funding through the Medicare Benefits Schedule (MBS) for faecal calprotectin (FC) testing to help diagnose different types of bowel disease. FC testing is used in Australia now, but patients have to pay for the test themselves.

FC testing is done on a faeces (poo) sample. FC testing is used to tell the difference between irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) in adults. It is also used to tell the difference between IBD and other types of bowel disease in children.

IBS and IBD have many symptoms in common, but it is important to tell them apart because they are treated differently. IBS can be managed by a General Practitioner (GP). But people with IBD need to see a specialist and have a colonoscopy (where a flexible tube containing a camera is inserted into the bowel).

MSAC agreed that FC testing is safe and effective, and much cheaper than colonoscopy, which has some risks as it is an invasive procedure.

MSAC also agreed that there is enough evidence that FC testing can tell the difference between IBS and IBD. If the FC test is negative, it is unlikely that the person has IBD so they will not need to have a colonoscopy.

MSAC had some concern that if GPs continue to refer people to specialists after a negative FC test, then the number of people having colonoscopies will not reduce. MSAC recommended that an education program for doctors will be needed to make sure this does not happen. MSAC also recommended that, if FC testing is approved for public funding, the number of colonoscopies is monitored to see if the anticipated reduction in the use of colonoscopies happens.

### **MSAC's advice to the Commonwealth Minister for Health**

MSAC recommended that FC testing be publicly funded because it is safe and effective, it will lead to fewer people needing a colonoscopy and it is much cheaper and less invasive for patients than a colonoscopy. MSAC further recommended that, if FC is funded, the frequency of colonoscopy testing is monitored to see if fewer tests are ordered as anticipated.

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

MSAC noted that the application requests funding of FC testing to differentiate between “functional” bowel disease (e.g. IBS) and “inflammatory” bowel disease (IBD; e.g. ulcerative colitis and Crohn’s disease). MSAC acknowledged that FC testing is a clinically relevant medical service, and has become a relatively widespread patient-funded test for this purpose.

MSAC noted the following changes made to the application since its previous consideration:

- limitation to diagnostic use only (use for monitoring has been removed)
- introduction of repeat testing under specialist supervision only if the initial result is inconclusive (i.e. in the intermediate range 50–100 µg/g)
- limitation to laboratory-based enzyme-linked immunosorbent assay (ELISA) testing (excluding point-of-care testing)
- more clearly defined target population (under 50 years of age, without alarm symptoms)

- inclusion of data on use in a lower prevalence setting (i.e. primary care); and
- clearer estimates of effects on downstream colonoscopy usage.

MSAC confirmed that the words ‘on the basis of time’ should be excluded from the item descriptor. The descriptor already requires that patients have had symptoms for six weeks, which would exclude acute gastroenteritis; MSAC considered it is not necessary to stipulate pre-testing to exclude infection. MSAC also considered that specifying the need for previous tests was not required (as suggested by ESC). In addition, MSAC confirmed that it is not necessary to specify a lower age limit for FC testing.

MSAC also confirmed that ‘General Practitioner or Specialist’ in the item for testing in primary care (MBS item YYYYY) could be changed to ‘Medical Practitioner’ or removed. MSAC reiterated that restricting repeat testing after an inconclusive FC test to a specialist gastroenterologist is appropriate (MBS item ZZZZ).

MSAC agreed with the following amendments to the proposed item descriptors (in red), included lowering the fee to \$75, aligning with current fees charged by some major private pathology providers.

<p>Category 6 – PATHOLOGY SERVICES</p>
<p>Proposed MBS item YYYYY</p> <p>Faecal Calprotectin testing of patients aged ≤ 50 years with gastrointestinal symptoms suggestive of inflammatory or functional bowel disease of more than 6 weeks’ duration who are presenting to a <del>General Medical Practitioner, General Physician or Specialist</del>; where infectious causes have been excluded <del>on the basis of time</del> and the likelihood of malignancy has been assessed as low, and where no clinical alarms are present.</p> <p>A maximum of 1 test may be performed in any 12-month period.</p> <p>Fee: <del>\$80.00</del> \$75.00 Benefit: 75% = <del>\$60.00</del> \$56.25 85% = <del>\$68.00</del> \$63.75 (see para ... of exploratory notes to this item)</p>
<p>Proposed MBS item ZZZZ</p> <p>Faecal Calprotectin testing of patients aged ≤ 50 years with gastrointestinal symptoms suggestive of inflammatory or functional bowel disease and where no clinical alarms are present, presenting to a Specialist <del>Gastroenterologist</del>, in whom an initial faecal calprotectin test (MBS YYYYY) was inconclusive (50-100 µg/g), and where the Specialist feels an endoscopic examination is not initially warranted.</p> <p>A maximum of 1 test may be performed in any 12-month period.</p> <p>Fee: <del>\$80.00</del> \$75.00 Benefit: 75% = <del>\$60.00</del> \$56.25 85% = <del>\$68.00</del> \$63.75 (see para ... of exploratory notes to this item)</p>
<p>Explanatory note:</p> <p>Clinical alarms</p> <p>Unexplained weight loss (&gt; 3 kg or 5% bodyweight), iron deficiency ± anaemia, melaena, overt rectal bleeding, positive faecal human haemoglobin, abdominal pain awaking patient from sleep, diarrhoea, disturbing sleep or faecal incontinence, documented unexplained fever, family history of colon cancer, family history of inflammatory bowel disease (IBD) in symptomatic patients, or a family history of coeliac disease in symptomatic patients</p>

MSAC confirmed that there are no major safety issues with the test itself. However, MSAC noted that potential safety issues relate to cut-off values for sensitivity and specificity (with subsequent negative and positive predictive values), and associated risks of either delayed diagnosis (false negative) or ‘over-investigation’ (false positive). However, MSAC acknowledged that, without the FC test, patients would probably be investigated anyway. MSAC considered that there is benefit in avoiding harm associated with unnecessary colonoscopy (risk of perforation/bleeding estimated at 0.12–0.15%), and benefit in avoiding harm associated with delayed diagnosis of IBD.

MSAC noted that only 3–6% of adult patients (and an estimated 2–3% of children) with a negative FC test result in primary care would actually have an organic gastrointestinal disease (OGID), and only 1% of adult or child patients in primary care with a negative FC test result would actually have IBD (assuming prevalence of 3%). Therefore, MSAC considered that only a small proportion of patients would receive a delayed diagnosis.

MSAC noted data from a recent systematic review and meta-analysis by An et al. (*Med J Aust* 2019) that examined the clinical effectiveness of diagnostic FC testing compared with a reference test, in primary care and outpatient hospital settings, with cut-offs of 50 or 100 µg/g faeces. For distinguishing patients with OGID (including IBD) from those with functional gastrointestinal disorders (FGIDs), the estimated sensitivity of FC testing was 81%, the specificity 81%, and area under the curve (AUC) was 0.87 (from 16 studies). For distinguishing IBD from FGIDs, sensitivity was 88%, specificity 72% and AUC 0.89 (from 10 studies). Assuming a population prevalence of OGID of 1%, the positive predictive value was 4.2% and the negative predictive value was 100%. The difference in sensitivity and specificity between FC testing cut-offs of 50 and 100 µg/g was not statistically significant. MSAC noted that these results are similar to those presented in the Contracted Assessment (CA). MSAC noted that the accuracy of ELISA FC to detect OGID vs. FGID against the reference standard did not differ significantly between adults and children, or between primary and specialist care settings.

MSAC noted that the results of the economic evaluation showed the proposed FC test would be dominant (have cost-savings and more effectiveness) compared with current practice across all clinical outcomes assessed. However, MSAC also noted that the model results were sensitive to the specialist referral rate and percentage of endoscopies performed in both adults and children. In addition, MSAC noted that repeat testing by a specialist was not included in the economic modelling. MSAC observed there were no data on the diagnostic accuracy or yield of sequential repeat FC testing in patients with intermediate results. The impact of repeat testing is therefore uncertain.

MSAC noted that the financial estimates suggest introduction of the test could result in substantial cost savings to the MBS of ~\$4-7 million per year and government health budgets of ~\$11-20 million per year. MSAC also noted the estimated saving to the private sector (private health insurers and patients) of ~\$32-73 million per year. Similar to the conclusions in the economic analyses, MSAC noted the financial estimates were sensitive to the number of referrals and endoscopies avoided due to the listing of FC test. In addition, MSAC noted that there is considerable uncertainty regarding the uptake rate of FC test and alteration in general practitioner (GP) referral habits.

MSAC noted that there is an established clinical pathway into which FC testing will fit; however, because the incidence of IBD in primary care is relatively low, it cannot be assumed that GPs will act in accordance with FC test results. MSAC acknowledged that there is a risk that patients with bad symptoms and a negative FC test may still go on to have a colonoscopy.

MSAC acknowledged that FC testing is currently being used in patients with IBD for assessing disease flares. MSAC therefore considered there is some potential for leakage, although this will be constrained by the restrictions in the descriptor.

MSAC considered it necessary to monitor the utilisation and outcomes of FC testing, in particular its impact to changes in the colonoscopy MBS item usage. However, MSAC noted that MBS items for colonoscopy are currently in transition and FC testing is already being used, so changes based on current usage may not give an accurate picture of the impact of

funding FC testing. Regardless, MSAC considered it important to monitor the proportion of patients proceeding to colonoscopy after FC testing, especially those with a negative or intermediate result. Linking FC item numbers to colonoscopy item numbers at an individual level may provide some data but results would need to be carefully interpreted. Thus, MSAC suggested that a research project funded through the Medical Research Future Fund, or establishing a registry may be appropriate mechanisms for gathering data.

MSAC noted advice from the National Pathology Accreditation Advisory Council (NPAAC) that FC testing is currently provided at a number of laboratories in both the private and public sector in Australia, using a range of different assays, on a fee for service basis. MSAC noted that the proposed fee for the test (\$80) has not previously been justified, but is in line with the fee advertised by some pathology providers. However, it may be possible to reduce the fee slightly, in line with that charged by some private providers (\$75).

MSAC also noted NPAAC advice that the results of the various assays are not comparable, but are consistent within the test methodology. NPAAC advised that an external quality assurance program (QAP) is available for FC testing. MSAC considered that the QAP testing is likely to be around the threshold where clinical decisions are made so will ensure that tests are accurate around the specified cut-off levels.

MSAC noted that there is currently large geographic variation in access to colonoscopy as well as overuse of colonoscopy where it is available. MSAC noted that a reduction in unnecessary colonoscopies should reduce waiting times for those who genuinely need them, and thus reduce time to diagnosis of OGID. Patient out-of-pocket costs for specialist referral and investigations would also be reduced, and travel costs and inconvenience would be reduced for rural/remote patients.

MSAC queried whether there would be any time- or temperature-critical issues with the test that would need to be considered with respect to postage or transport, especially in rural/remote areas.

MSAC advised that a GP education program would be important, especially related to:

- the benefits of FC testing
- alarm symptoms that would invalidate the FC test (detailed in the proposed MBS item descriptor)
- inappropriateness of FC testing if alarm features are present; Gastroenterological Society of Australia guidelines do not make it clear that FC testing is not appropriate in this situation; and
- inability of FC testing to identify patients with non-neutrophilic OGID (e.g. lymphocytic colitis, collagenous colitis); this would need to be identified on colonoscopy/biopsy, and requires active treatment.

MSAC advised that consumer education would also be important to increase understanding and uptake of the test. However, MSAC agreed with the applicant's pre-MSAC response that patient compliance and acceptability of FC testing is unlikely to be a significant problem for implementation. Many patients: i) will have had stool tests for microscopy, culture and sensitivity (M, C and S) already and so will be familiar with sample collection; ii) would be keen for a diagnosis given chronicity of their symptoms, and iii) may be keen to avoid colonoscopy (and bowel preparation). MSAC acknowledged that there may be some risk of GPs co-claiming M, C and S items with FC, which would need to be monitored.

## 4. Background

At the March 2018 meeting, MSAC considered Application 1353 and did not support public funding of FC testing for the differential diagnosis of IBS from IBD in the adult population, for differential diagnosis of IBD from non-IBD in the paediatric population, or for monitoring disease activity in patients with known IBD.

MSAC acknowledged that there was a clinical need for a diagnostic triage test to differentiate IBD from IBS in adults and thus to avoid some of the more invasive subsequent investigations such as colonoscopies, but advised that clinical benefit for monitoring IBD with FC had not been established. MSAC therefore advised that any resubmission should focus on the use of the test for diagnostic rather than monitoring purposes.

A resubmission for diagnostic testing should provide:

- a clearer definition of the appropriate target population;
- more relevant and robust test performance data in a lower prevalence setting similar to that of the proposed target population, or more appropriate modelling of the likely operating point with its prediction area in summary receiver operating characteristic (SROC) curves;
- more realistic assumptions for the downstream consequences of FC testing versus no FC testing (such as for the estimated reduction in the extent of use of subsequent colonoscopy); and
- appropriately amended economic model structure and inputs, which may simplify (if changes in health outcomes are estimated to be small) to a cost-minimisation analysis where the extra costs of add-on FC testing are equally offset by the estimated reduction in the proportion of patients undergoing colonoscopy (Public Summary Document [PSD] Application 1353, March 2018, pp1-2).

## 5. Prerequisites to implementation of any funding advice

Refer to Application 1353 PSD 2018, p7 for details of one FC item listed on the Australian Register of Therapeutic Goods (ARTG entry 223904).

## 6. Proposal for public funding

The MBS item descriptor as proposed by the applicant is summarised in Table 1. The resubmission stated that the proposed item (XXXXX) differs from the previous application by limiting the population to those up to or including 50 years of age, and excluding those with any clinical alarm features. No point of care or monitoring tests were proposed.

**Table 1 Proposed MBS item descriptor by applicant**

Category 6 – PATHOLOGY SERVICES
Proposed MBS item XXXXX Faecal Calprotectin testing of patients aged ≤50 years with gastrointestinal symptoms suggestive of functional bowel disease of more than 6 weeks' duration who are presenting to a General Practitioner, General Physician or Specialist Gastroenterologist; where infectious causes and clinical alarm features have been excluded.
A maximum of 1 test may be performed in any 1-year period.
A second test in any 1-year period may be ordered by a Specialist Gastroenterologist when the results of the first test are within 50-100 µg/g, and the Specialist Gastroenterologist feels endoscopic examination is not initially warranted Fee: \$80

The Critique proposed the following changes to the proposed item descriptor (Table 2), to further clarify the target population (YYYYY), and allow Specialists to order a second test if the first was inconclusive (within the intermediate range of 50 to 100 µg/g) [ZZZZZ].

**Table 2 Proposed MBS item descriptor by the Critique**

Category 6 – PATHOLOGY SERVICES
<p>Proposed MBS item YYYYY</p> <p>Faecal Calprotectin testing of patients aged ≤ 50 years with gastrointestinal symptoms suggestive of inflammatory or functional bowel disease of more than 6 weeks' duration who are presenting to a General Practitioner, General Physician or Specialist; where infectious causes have been excluded on the basis of time and the likelihood of malignancy has been assessed as low, and where no clinical alarms are present.</p> <p>A maximum of 1 test may be performed in any 12-month period.</p> <p>Fee: \$80.00 Benefit: 75% = \$60.00 85% = \$68.00 (see para ... of exploratory notes to this item)</p>
<p>Proposed MBS item ZZZZZ</p> <p>Faecal Calprotectin testing of patients aged ≤ 50 years with gastrointestinal symptoms suggestive of inflammatory or functional bowel disease and where no clinical alarms are present, presenting to a Specialist, in whom an initial faecal calprotectin test (MBS YYYYY) was inconclusive (50-100 µg/g), and where the Specialist feels an endoscopic examination is not initially warranted.</p> <p>A maximum of 1 test may be performed in any 12-month period.</p> <p>Fee: \$80.00 Benefit: 75% = \$60.00 85% = \$68.00 (see para ... of exploratory notes to this item)</p>
<p>Explanatory note:</p> <p>Clinical alarms</p> <p>Unexplained weight loss (&gt; 3 kg or 5% bodyweight), iron deficiency ± anaemia, melaena, overt rectal bleeding, positive faecal human haemoglobin, abdominal pain awaking patient from sleep, diarrhoea, disturbing sleep or faecal incontinence, documented unexplained fever, family history of colon cancer, family history of inflammatory bowel disease (IBD) in symptomatic patients, or a family history of coeliac disease in symptomatic patients</p>

## 7. Summary of public consultation feedback/consumer Issues

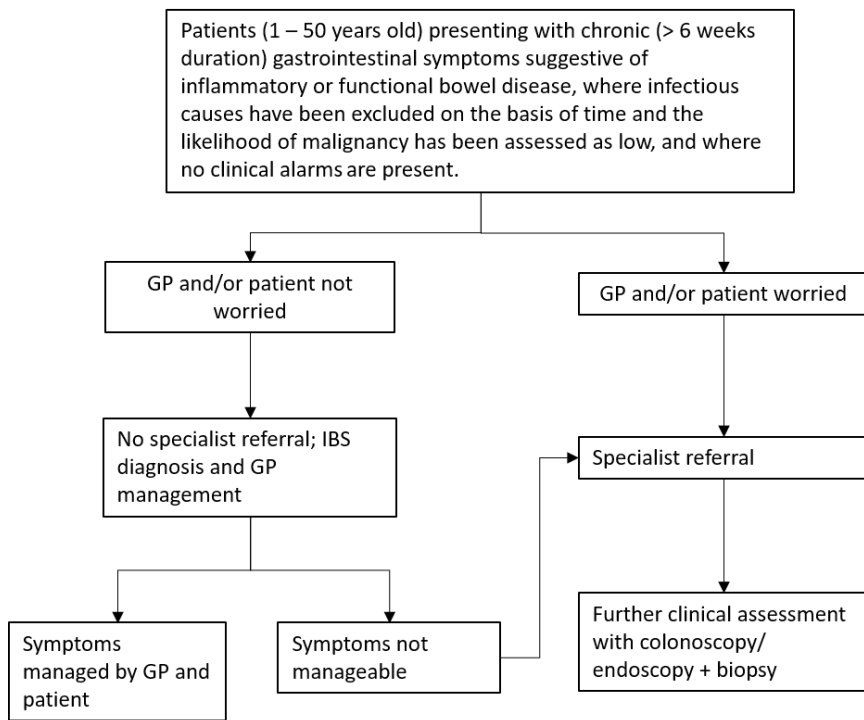
Refer Application 1353 PSD March 2018 on the MSAC website.

## 8. Proposed intervention's place in clinical management

The proposed MBS population is for patients aged ≤ 50 years with gastrointestinal symptoms suggestive of inflammatory or functional bowel disease of more than six weeks' duration who are presenting to a GP, General Physician or Specialist; where infectious causes have been excluded on the basis of time and the likelihood of malignancy has been assessed as low, and where no clinical alarms are present.

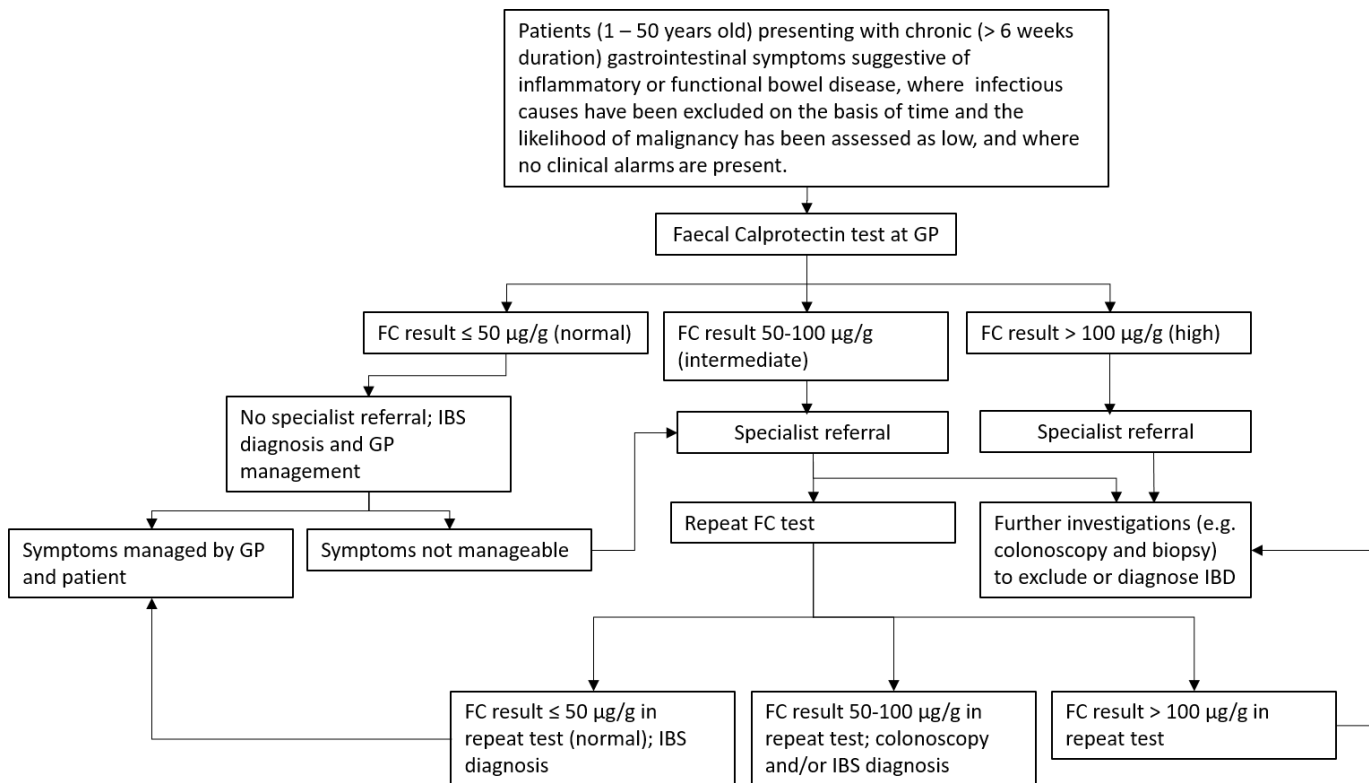
The FC test is proposed to be used as a “rule-out” test for eligible patients (whether IBD or organic gastrointestinal disorders [OGID] can be ruled out or not), to determine whether specialist referral and further investigations are necessary. It is proposed to be used in primary care, with a repeat test to be ordered by the specialist if the initial FC test result is indeterminate (FC between 50 µg/g and 100 µg/g).

The current and proposed clinical management algorithms are presented in Figure 1 and Figure 2, respectively.



**Figure 1 Current diagnostic algorithm for usual care without the use of FC testing**

The introduction of FC testing is expected to replace the need for more invasive and expensive medical testing, namely referral and endoscopies (colonoscopies, and/or upper endoscopies with biopsies), for patients with a negative FC test.



**Figure 2 Clinical management algorithm for the proposed FC test**



## 9. Comparator

The comparator is clinical workup without the FC test, possible referral to specialist and endoscopy<sup>1</sup> + biopsy (e.g. colonoscopy/endoscopy and biopsy).

Current MBS item descriptors for the different forms of endoscopy + biopsy include MBS items 32084, 32090, 32095, 72823 and 72824. Note, there are draft items on the MBS scheduled to replace MBS item 32090.

## 10. Comparative safety

No comparative studies on the safety of FC testing relative to possible endoscopy + biopsy were identified. However, no safety concerns for FC testing were reported, and this non-invasive test is generally considered safe.

## 11. Comparative effectiveness

Fifty-nine studies were included in the systematic review. No studies on direct effectiveness of FC testing were identified. Of the eligible studies, 55 were included providing evidence on analytical validity, and eight were included on clinical utility (four studies were included in both sections). For therapeutic effectiveness a separate (non-systematic) search was done and the studies identified through this search were narratively discussed.

### *Diagnostic performance*

Overall, FC testing showed acceptable diagnostic performance. The pooled, median and point estimates for sensitivity and specificity of ELISA<sup>2</sup> FC testing to detect OGID over FGID were similar for adults and children in both a primary and specialist care setting. Generally, as the FC threshold increased, the sensitivity decreased and the specificity increased.

### *Clinical validity*

ELISA FC testing is likely to be useful for ruling out the presence of either OGID or IBD in the primary care setting at any FC threshold between 50 µg/g and 200 µg/g.

- Only 3–6% of adult patients with a negative FC test result in primary care would actually have OGID. Therefore only a small proportion of patients would receive a delayed diagnosis.
- It is estimated that only 2–3 children out of every one hundred with a negative FC test result in primary care would actually have OGID. These children would eventually be diagnosed on follow-up (delayed diagnosis).
- In primary care only one patient (adult or child) out of every one hundred with a negative FC test result would actually have IBD.

ELISA FC testing to determine the presence of either OGID or IBD is likely to only be useful in a specialist care setting.

- 81–92% of adults with a positive FC test ( $\geq 100$  µg/g) result would actually have OGID, meaning that only 8–19% of these patients would receive invasive tests such as colonoscopy unnecessarily.
- At least 95% of children with a positive FC test result in specialist care would actually have OGID.
- In the specialist care setting ELISA FC testing with a threshold of at least 100 µg/g may be useful to determine the presence of IBD over IBS in adults.

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<sup>1</sup> Type of endoscopy mostly used to diagnose IBD is a colonoscopy (or in the case of suspected Crohns disease, capsule endoscopy).

<sup>2</sup> Other FC tests include chemiluminescence immunoassay (CLIA), fluoro-enzyme immunoassay (FEIA), lateral flow immunoassay (LFIA) and particle enhanced turbidimetric immunoassay (PETIA)

- In the specialist care setting ELISA FC testing with a threshold of at least 100 µg/g may be useful to determine the presence of IBD over FGID or non-IBD in children.

*Therapeutic efficacy (change in management)*

- One UK based cohort study reported that 25% of adult patients in the group undergoing FC testing (66/262) received a lower endoscopy, compared with 53% in the comparator group (55/103; not receiving FC testing). A larger proportion of patients receiving a lower endoscopy were diagnosed with an organic gastrointestinal disorder (OGID) such as IBD in the FC test group compared with the comparator group (29.4% vs 10.9%).
- One study investigated whether FC testing changed referral behaviour by including a hypothetical comparator: GPs were asked to report their referral intentions before receiving the FC result. This was compared with the actual referral behaviour after receiving the FC result. In the absence of the FC test, GPs intended to refer 409 patients. With receipt of the FC test, only 271 were referred. Of the 409 patients who the GP would have referred in the absence of FC testing, 336 (82.1%) had an FC result under 100 µg/g. Of these 336 patients with a low FC level, 147 (44%) were not referred after receiving the low FC test result. This indicates the FC could be used to target referrals more appropriately.
- Of the 43 patients which GPs did not intend to refer in the absence of FC testing, seven had an FC test result over 100 µg/g, and 6/7 (86%) consequently received a specialist referral. However, of the 36/43 patients with a low FC result (< 100 µg/g) who the GP did not intend to refer prior to receiving the FC result, eleven (31%) were referred despite receiving a low score. These results clearly demonstrate that decision making regarding whether to refer patients incorporates more information than the FC test alone. Overall, 38.1% of patients had a change in referral from what the GP had planned, possibly due to the FC result (although not always concordant with what would be expected).
- No evidence on change in patient management due to FC testing was found in paediatric populations.

*Therapeutic effectiveness (health benefit from change in management)*

- Evidence on ‘change in management’ indicated that it is expected that fewer lower endoscopies will be performed if FC testing becomes available in primary care. In general, an endoscopy is seen as a safe procedure, however, complications may occur. No data on the safety of endoscopies in patients *suspected* of having IBD were identified. Two large cohort studies reported the incidence rates of colonic perforation to be 0.60 and 1.61 perforations per 1,000 endoscopies in patients with IBD. Based on the two studies, the perforation rate due to endoscopy was 0.86 per 1,000 procedures (weighted average: 0.086%). Two Australian cohort studies on endoscopies in children reported 2/999 and 0/652 perforations, a perforation rate of 0.12% in children (1.2 per 1,000 endoscopies) when combining the two studies. Limiting unnecessary endoscopies would lead to fewer serious endoscopy-related complications.
- Ten studies were identified from a review on diagnostic delay in IBD patients. These studies assessed the impact of early versus late diagnosis. Those who had a delayed diagnosis were more likely to have strictures, stenoses, fistula and require surgery, and had poorer quality of life compared to those with an earlier diagnosis. Those appropriately referred earlier would therefore have superior health outcomes.

## Clinical claim

On the basis of the evidence profile, it is suggested that, relative to specialist referral and endoscopy and biopsy, FC testing has superior safety and non-inferior effectiveness. The resubmission stated that non-inferior effectiveness comes with uncertainty, and will depend on the actual false negative rate of FC testing in Australian primary care and the decision making by general practitioners (GPs) (the uptake of FC testing by GPs and how the FC result influences referral behaviour by GPs in Australia). However, the avoidance of unnecessary referrals to specialists would be of particular benefit to rural and remote patients, as it would mean that the patient would not need to travel to a specialist centre.

## 12. Economic evaluation

A summary of the key characteristics of the economic evaluation is provided in Table 3.

**Table 3 Summary of the economic evaluation**

Perspective	Australian healthcare system
Population	Patients aged $\leq 50$ years with GI symptoms suggestive of inflammatory or functional bowel disease of more than 6 weeks' duration who are presenting to a GP or Specialist; where infectious causes have been excluded on the basis of time and the likelihood of malignancy has been assessed as low, and where no clinical alarms are present.
Intervention	Faecal calprotectin test
Comparator	Possible referral to specialist and invasive testing (colonoscopy or upper endoscopy, and histopathology)
Type of economic evaluation	Cost-effectiveness
Outcomes	Cost per colonoscopy avoided, cost per initial correct diagnosis, cost per adverse event avoided and time to true diagnosis
Sources of evidence	Systematic review of the literature and expert opinion where required.
Methods used to generate results	Decision analytic model
Cohorts modelled	Adults (patients 18 years or above) Children (patients below 18 years)
Time horizon	To the time of diagnosis (assumed to be less than one year)
Discount rate	Not applicable (modelled time horizon is less than one year)
Software packages used	TreeAge Pro 2019

GI = gastrointestinal; GP = General Practitioner or General Physician

Key structural assumptions of the model are:

- In the model, all first FC tests are assumed to be requested by GPs and the repeat tests by specialists.
- In the economic model it is assumed that all the IBD diagnoses will need specialist review and confirmatory colonoscopy/endoscopy + biopsy.
- It is assumed that all referred patients utilise the referral that is, the uptake of referral is assumed to be 100% in the model.
- Endoscopy and biopsy is considered to be 100% sensitive and 100% specific.

Two cohorts were modelled based on the age: adults, age  $\geq 18$  years (Table 4); and children, age  $< 18$  years (Table 5). The base-case analysis assumed that the FC testing is used for differential diagnosis of IBD vs IBS (or FGIDs) in adults, and IBD vs non-IBD in children. Additional scenario analyses considered the alternative differential diagnostic options for each of the populations.

**Table 4 Costs and effectiveness for base-case analysis (IBD vs FGID) in adults**

	Average cost per adult	Clinical Outcomes				
		Endoscopies	Correct initial diagnoses	Time to correct diagnosis (weeks)	Specialist Referrals	Adverse events
FC testing	\$1,565	40.11%	56.06%	10.42	60.11%	0.05%
No FC testing	\$2,594	74.49%	29.93%	16.80	95.40%	0.09%
<b>Increment (FC testing – No FC testing)</b>	<b>-\$1,028</b>	<b>-34.39%</b>	<b>26.12%</b>	<b>-6.39</b>	<b>-35.29%</b>	<b>-0.04%</b>

Endoscopy = refers to upper endoscopy or colonoscopy here; FC = faecal calprotectin; FGID = functional gastrointestinal disorder; IBD = inflammatory bowel disease

**Table 5 Costs and effectiveness for base-case analysis (IBD vs non-IBD) in children**

	Average cost per child	Clinical Outcomes				
		Endoscopies	Correct initial diagnoses	Time to correct diagnosis (weeks)	Specialist Referrals	Adverse events
FC testing	\$1,490	38.49%	66.68%	8.68	53.74%	0.06%
No FC testing	\$2,612	74.97%	30.71%	16.93	95.49%	0.11%
<b>Increment (FC testing – No FC testing)</b>	<b>-\$1,121</b>	<b>-36.48%</b>	<b>35.98%</b>	<b>-8.24</b>	<b>-41.75%</b>	<b>-0.05%</b>

Endoscopy = refers to upper endoscopy or colonoscopy here; FC = faecal calprotectin; IBD = inflammatory bowel disease

The results of the base-case analyses for both adults and children suggested that the FC testing strategy is less costly and more effective (i.e. dominant – in the South-East quadrant of cost-effectiveness plane) compared with no FC testing, for all clinical outcomes assessed.

The modelled results were robust for all sensitivity analyses. The results predicted that the proposed FC test would be dominant (have cost-savings and more effectiveness) compared to the current practice of specialist referrals and colonoscopies across all ranges of tested variables. This included the results from scenario analyses. However, the average cost per patient (and therefore cost-savings) and other clinical outcomes are sensitive to the specialist referral rate chosen and percentage of endoscopies performed in both adults and children.

### 13. Financial/budgetary impacts

A market based approach was used to estimate the financial implications of a potential listing of FC testing on the MBS (Table 6).

**Table 6 Net costs to the MBS associated with FC testing**

Description	2019–20	2020–21	2021–22	2022–23	2023–24
<b>FC test</b>					
Number of services	61,945	71,237	81,922	94,210	108,342
Cost to MBS	\$4,212,248	\$4,844,085	\$5,570,698	\$6,406,302	\$7,367,248
<b>Cost of other medical services</b>					
Estimated cost savings to MBS due to reduction in the use of other Medical services <sup>a</sup>	\$8,310,475	\$9,557,047	\$10,990,604	\$12,639,194	\$14,535,073
<b>Net costs to MBS</b>	<b>-\$4,098,227</b>	<b>-\$4,712,962</b>	<b>-\$5,419,906</b>	<b>-\$6,232,892</b>	<b>-\$7,167,825</b>

FC = faecal calprotectin; MBS = Medicare Benefits Schedule

<sup>a</sup> The introduction of FC testing is expected to replace the need for more invasive and expensive medical testing, namely referral and endoscopies (colonoscopies, and/or upper endoscopies with biopsies), for patients with a negative FC test.

In addition to the expected net cost-savings of \$4–7 million per year to the MBS due to reduction in the use of other medical services (specialist referrals and endoscopies with biopsies), it is also expected that FC testing will reduce public hospital expenditure on equivalent services provided in public hospitals (around \$11–\$20 million). Other than MBS and government health budgets, FC testing will result in cost-savings of \$32–\$73 million per year to the private sector (private health insurers and patients) by avoiding gap payments for specialist consultations and hospital costs associated with endoscopies + biopsies.

Sensitivity analyses indicated that net costs (or cost-savings) to the MBS are found to be sensitive to the growth in uptake rate of FC test, number of referrals and endoscopies avoided due to the listing of FC test.

#### 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Item descriptor	Population definition needs to be tightened (e.g. specify prior testing) to minimise leakage.
Financial impact highly uncertain	Financial estimates uncertain because of uncertainty in growth of testing. If growth is limited to the population that benefit there would be cost offsets but there is risk of leakage.
Unknown diagnostic yield in repeat testing of intermediate results	Between 25% (children) and 35% (adults) of initial tests produce an 'intermediate' result. Repeat testing of these is not captured in the model so the impact is unknown.
Model very sensitive to specialist referrals and ordering endoscopy in absence of testing	This has direct implications for the cost-effectiveness. If ordering endoscopies in the absence of FC testing is already low, there may be very little cost savings due to endoscopies avoided.
Patient acceptability/preference for the test	Suggestion that compliance for FC testing is low, which would lead to implementation challenges.

#### ESC discussion

ESC noted that issues raised by MSAC during initial consideration of this application have been addressed appropriately in the resubmission (Table 7).

**Table 7 MSAC's recommendations for resubmission for diagnostic FC testing**

Concerns raised by MSAC Application 1353	How the resubmission addressed MSAC's concerns
A clearer definition of the appropriate target population	The proposed item descriptor now specifies that the target population are those without alarm symptoms. However, the literature was too limited to restrict the included studies to those which were explicit about patients not having alarm symptoms.
More relevant and robust test performance data in a lower prevalence setting similar to that of the proposed target population, or more appropriate modelling of the likely operating point with its prediction area in summary receiver operating characteristic (SROC) curves;	Test performance data are provided separately for primary care and secondary care settings.
More realistic assumptions for the downstream consequences of FC testing versus no FC testing (such as for the estimated reduction in the extent of use of subsequent colonoscopy);	Assumptions regarding downstream consequences are based on the evidence from 8 studies regarding the change in management, and reduction in endoscopies, and do not assume that test results influence decisions in a direct 1:1 way.

Concerns raised by MSAC Application 1353	How the resubmission addressed MSAC's concerns
Appropriately amended economic model structure and inputs, which may simplify (if changes in health outcomes are estimated to be small) to a cost-minimisation analysis where the extra costs of add-on FC testing are equally offset by the estimated reduction in the proportion of patients undergoing colonoscopy (Public Summary Document [PSD] Application 1353, March 2018, pp1-2)	Decision analytic modelling is performed to assess the cost-effectiveness of FC test relative to the comparator. Clinical outcomes presented are cost per colonoscopy avoided, cost per initial correct diagnosis, cost per adverse event avoided and time to true diagnosis.

ESC accepted that the revised MBS item descriptor now more clearly defines the target population as: patients  $\leq 50$  years of age without any clinical alarm features. ESC also agreed with removing 'general physician' from the item descriptor and creating a separate item number for specialists to request repeat testing.

ESC considered it important that the descriptor reflects the purpose of the test as triage to avoid referral for colonoscopy/endoscopy, to be performed after other tests which have not yielded a diagnosis and not as an additional concurrent test. ESC considered that excluding infectious causes on the basis of time is inappropriate and too broad. ESC suggested that the descriptor wording should be more specific – for example, – “where other tests performed prior to colonoscopy/endoscopy have not confirmed a diagnosis” to more narrowly define the population that should have a triage FC test. However, ESC noted this would lower the pretest probability.

ESC also noted a grammatical error in the MBS item descriptor that needs to be corrected for clarity: 'diarrhoea, disturbing sleep' should be 'diarrhoea disturbing sleep' (i.e. remove the comma).

ESC noted consumer feedback that detection and management undertaken in primary care would improve access to appropriate care for rural/remote patients with IBD (IBD National Action Plan 2019). The Crohn's and Colitis Association argue that FC testing is valuable in primary care:

In the primary care setting where the prevalence of IBD is low (absolutely or compared with IBS), the emphasis is on 'ruling out' or lowering the probability of the IBD diagnosis to provide reassurance or to adopt a 'watchful waiting' strategy for the GP. In these instances, tests with a low negative likelihood ratio are preferred and guidance for GPs to prevent inappropriate use is important to maintain its utility.

ESC noted the Association's view that more GP education is needed for IBD/IBS diagnosis and care to be undertaken in primary care. This would benefit consumers who need extra support and save them the cost of specialist fees.

ESC considered the proposed algorithm for FC testing to be appropriate. However, ESC noted that the patient definition in the proposed clinical algorithm is the same as the item descriptor; the precise target population and where FC testing fits in the assessment pathway for a heterogeneous group of patients still need to be clarified.

ESC noted that Gastroenterological Society of Australia (GESA) guidelines (updated in 2018) imply that FC testing should only be done if all other tests relevant to the patient's symptoms are normal. If other tests are positive, patients will be referred to a specialist anyway or treated appropriately. However, ESC noted that, following GESA guidelines, some patients with a normal FC level may still be referred to a specialist based on their history or risk factors, or if the GP or patient is still worried.

ESC emphasised that FC measurement is a test for inflammation, not a test for IBD; other confounding factors could cause an increase in FC levels.

ESC acknowledged that evidence presented in the report for primary care and specialist care are now well separated (as requested by MSAC). ESC considered that although most of the studies relate to specialist care, there is reasonable evidence to inform conclusions around safety, effectiveness and clinical utility of FC testing in the primary care setting.

ESC noted that intermediate results between 50 and 100  $\mu\text{g/g}$  would necessitate repeat testing. ESC considered that this testing would best be done by a specialist and a separate item number for repeat testing is therefore appropriate.

In specialist care, a threshold of 50  $\mu\text{g/g}$  resulted in lower specificity in adults than in children – that is, more adults than children would have a false-positive test result; however, the proportion of false-negative test results would be similar. In the lower prevalence primary care setting, most studies showed a very high negative predictive value. ESC considered that lower specificity may be acceptable in this setting because the FC test is intended as triage and a positive test does not give a specific diagnosis.

ESC noted that there is less evidence available for children than adults and that the range of cut-off values for diagnosis in children is broader than for adults. ESC considered that most children with symptoms will be referred to specialist care regardless of test result.

ESC emphasised that clinical decision-making regarding whether to refer patients would consider more than just the FC test, so referrals will not be reduced by a 1:1 ratio. ESC acknowledged that this is now reflected in the revised economic model.

ESC noted that between 25% (children) and 35% (adults) of initial tests produce an ‘intermediate’ result requiring retesting. However, this is not captured in the model because no data for the diagnostic accuracy or yield of sequential repeat FC testing in patients with intermediate results were available. The impact of repeat testing is therefore unknown.

ESC also confirmed that there may be some transformation issues related to the type and utilisation of investigative procedures used in Australia, the proportions of patients that undergo invasive procedures, the proportion that would be referred to a specialist in the absence of FC testing, and waiting times/time to diagnosis in the Australian setting.

ESC considered that some of the assumptions in the model (i.e. that all first FC tests are requested by GPs and repeat tests by specialists, and that all IBD diagnoses will need specialist review and confirmatory colonoscopy/endoscopy and biopsy) will only be appropriate if the population is defined correctly. ESC also noted the key drivers of the economic model in adults and children was the rate of specialists ordering endoscopy and referral rate (in the absence of FC testing).

ESC noted the market-based approach used the best available evidence to estimate financial implications. However, because of uncertainties in the data and assumptions used, especially the rate of uptake/growth in testing, ESC considered the estimates of financial impact and cost offsets to be highly uncertain.

ESC noted that FC testing is not currently widely used. Reasons reported in the contracted assessment (CA) include cost and availability of the test, and clinicians’ lack of familiarity with the test. ESC agreed that education of GPs will be important if FC testing is MBS listed. ESC also noted results of a prospective multicentre study of patient perceptions of FC testing (Kalla et al. 2018) reported in the CA. Of 109 Australian patients with experience of FC testing, 42% rated the test moderate, difficult or very difficult, with 58% reporting the sample collection as the reason. Blood testing was preferred to FC testing by 50% of Australian

patients. In the total survey population (n=585), 66% of patients opted for stool testing over endoscopy. However, of the patients who preferred endoscopy over stool testing 43% were from Australia.

ESC also noted consumer feedback relating patient hesitancy to undertake faecal collection. However, the Crohn's and Colitis Association report that patients who have experienced colonoscopy prefer FC testing.

ESC acknowledged that there may be implementation challenges if compliance with FC testing is low.

ESC queried which test is used in Australia and commented that the coefficient of variation between tests could affect decision-making. ESC noted that the Department will seek further information from pathologists about which test is done in accredited laboratories and the nature of the quality assurance program.

#### **15. Other significant factors**

Nil.

#### **16. Applicant's comments on MSAC's Public Summary Document**

The applicant had no comment.

#### **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)