

**A MESSAGE FROM THE DEPARTMENT OF HEALTH ON BEHALF OF THE
PROTOCOL ADVISORY SUB COMMITTEE REGARDING THIS PROTOCOL**

**PLEASE NOTE: This is an applicant-prepared Consultation Protocol which has
not been ratified by the Protocol Advisory Sub Committee (PASC).**

MEDICAL SERVICES ADVISORY COMMITTEE

Quantitative measurement of Calprotectin in human stool

Protocol

Sponsor – Taylor Bio-Medical Pty Ltd – Andrew Wise

October 8th 2014

Title of Application

Quantitative measurement of Calprotectin in human stool , to distinguish Inflammatory bowel disease (IBD) from Irritable bowel syndrome , and to monitor disease activity in IBD.

1. Purpose of application

Symptoms such as chronic abdominal pain or discomfort, bloating, excessive flatus or a change in bowel habit are common to both irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). However, IBS does not produce the inflammation found in IBD. Surrogate biomarkers of inflammation are useful to distinguish organic from functional intestinal disease and to monitor disease activity in IBD.

Faecal calprotectin is a marker for intestinal inflammation. Calprotectin concentration in faeces correlates with the severity of inflammation: it is significantly increased in patients with bowel inflammation (IBD), but not elevated in patients with functional disorders like IBS. As a screening tool, faecal calprotectin tests (by bench-top, quantitative lateral flow analyzer or laboratory-based enzyme-linked immunosorbent assay [ELISA]) differentiate IBD from functional bowel disease (IBS), reducing the need for invasive diagnostic procedures (such as colonoscopy), potentially leading to earlier diagnosis of IBD and IBS and subsequently improving patient management.

Recent studies have shown the cost-effectiveness of faecal calprotectin testing to rule out IBD (CEP 2010a; van Rheenen et al. 2010; Mindemark and Larsson 2012).

2. Population and medical condition eligible for the proposed medical services

The population comprises two patient groups. The first group comprises patients presenting with chronic gastrointestinal symptoms suggestive of either IBD or IBS where infective causes have been excluded.

Measurement of Calprotectin is used to differentiate between IBS and IBD.

The second group comprises patients with an established diagnosis of IBD such as Crohn's disease (CD) or Ulcerative Colitis (UC). Measurement of Calprotectin is used to monitor these patients to assess disease activity.

The patient population is that presenting to a doctor with gastrointestinal symptoms suggestive of either organic (e.g. inflammatory bowel disease [IBD]) or functional (irritable bowel syndrome [IBS]) bowel disease, namely:

- chronic abdominal pain and discomfort > 6 weeks
- urgency and bloating > 6 weeks
- diarrhoea > 6 weeks
- constipation . 6 weeks
- alternating bouts of diarrhoea and constipation > 6 weeks
- 3 changes in bowel habits
- in the absence of alarm symptoms such as rectal bleeding or abnormal blood tests.

Irritable bowel syndrome (IBS) is unrelated to IBD, although frequently confused with IBD: symptoms of IBD can mimic functional disease (IBS), leading to misdiagnosis and delays in instigating appropriate treatment. IBS is approximately 50 times more common than IBD in Australia (10-15% of the community with IBS compared to 0.3% for IBD); it is therefore the most likely important differential diagnosis. IBS is typically longstanding, with fluctuating severity, but without alarm features or abnormal blood tests. IBS and IBD require different management.

The term inflammatory bowel disease (IBD) encompasses the two conditions of ulcerative colitis (UC) and Crohn's disease (CD). These are diseases in which the intestines are inflamed. The conditions are chronic, relapsing and remitting diseases that can cause diarrhoea, abdominal pain, weight loss, rectal bleeding and anaemia. These diseases require long-term and often lifelong treatment with medication.

The principal symptom of UC is bloody diarrhoea with abdominal pain and urgency or tenesmus (the constant feeling of needing to pass stools, even though the bowels are empty) as UC gets more severe. Typical symptoms of CD can include abdominal pain, diarrhoea and weight loss.

IBD, a chronic disease for which there is no cure, leads to significant morbidity and impaired quality of life, generally without affecting mortality (Andrews et al. 2010). IBD can be diagnosed at any age, with a typical age of onset in the twenties: the peak prevalence in Australia is reported to be among 30-39-year old otherwise healthy, active people (Access Economics 2007). Most people living with IBD spend many productive years coping with their life-long condition. The age of these patients has important implications for diagnosis and management of IBD.

In 2005, it was estimated that approximately 61 000 Australians were living with IBD, making IBD more common than epilepsy or road traffic accidents; its prevalence is comparable with type 1 diabetes or schizophrenia. Each year in Australia, there are around 1622 new cases of the two most common forms of IBD, CD and UC. By 2020, the number of people with IBD is projected to increase to 74 500 (Access Economics 2007). Australia has among the highest reported incidence of IBD worldwide (Wilson et al. 2010).

Because the main symptoms of IBD and IBS are common to both, differential diagnosis based on a clinical assessment alone is unsatisfactory. As the key difference between IBD and IBS is inflammation present in IBD, measuring intestinal inflammation in patients presenting with gastrointestinal symptoms suggestive of IBD and IBS is one possible way of differentiating between the two conditions. Eligible patients will be those with chronic diarrhoea (more than 6 weeks duration) where infective causes have been excluded.

IBD patients for monitoring of their disease with faecal calprotectin will be all of those who have a diagnosis of IBD based on endoscopic, radiologic or histologic findings consistent with IBD.

Define the proposed patient population that would benefit from the use of this service. This could include issues such as patient characteristics and /or specific circumstances that patients would have to satisfy in order to access the service.

1) Chronic diarrhoea (more than 6 weeks duration) where infective causes have been excluded. The patient population is that presenting to a doctor with gastrointestinal symptoms suggestive of

either organic (e.g. inflammatory bowel disease [IBD]) or functional (irritable bowel syndrome [IBS]) bowel disease, namely:

- chronic abdominal pain and discomfort
- urgency and bloating
- diarrhoea
- constipation
- alternating bouts of diarrhoea and constipation
- changes in bowel habits
- in the absence of alarm symptoms such as rectal bleeding or abnormal blood tests.
-

IBS does not produce inflammation found in IBD, and does not result in permanent damage to the intestines, intestinal bleeding or harmful complications often associated with IBD. IBD can put some patients at risk for colon cancer, whereas IBS does not lead to any increased risk.

Currently in Australia colonoscopy is frequently used to investigate these non-specific bowel symptoms, although IBS is far more common than IBD, and can usually be accurately diagnosed on history. Colonoscopy is used as both patients and doctors need reassuring that nothing has been missed.

Measurement of faecal calprotectin can differentiate between functional (low-risk IBS) and high-risk (IBD) patients: identification of low-risk patients would greatly reduce the number of unnecessary invasive endoscopic procedures and the identification of high-risk patients would justify prompt endoscopy. Appropriate treatment can be instigated after early diagnosis.

2) Patients with a known diagnosis of IBD.

Once diagnosed and placed on treatment, the regular measurement of faecal calprotectin will allow the patient to be monitored for levels of inflammation to determine the efficacy of therapy.

Currently, the activity of IBD is either judged on patients' symptoms or on the appearance of the affected area of the bowel with either colonoscopy, endoscopy or radiology (high-radiation dose computed tomography (CT) scan or magnetic resonance imaging (MRI), unfunded and variably available).

Patient selection for colonoscopy based on symptoms is not reliable as symptoms correlate poorly with disease activity and bowel damage, so that many patients will be overtreated with immunosuppressing drugs if they have symptoms but are healed (it is very common for these patients to have functional symptoms after the inflammation resolves); or undertreated if they have ongoing inflammation yet few symptoms (the risk is that these patients then have surgery and complications potentially leading to disability which could have been avoided if their IBD were better controlled). Due to the invasive nature of colonoscopy and the associated risks (1/1000 of perforation), IBD specialists are cautious about using it too frequently to monitor disease activity. Likewise the radiation dose associated with a computed tomography (CT) scan and the costs and lack of access to magnetic resonance imaging (MRI), make these radiology procedures unsuitable techniques for regularly monitoring disease activity. This patient group therefore currently has inconsistent and inaccurate monitoring of disease activity, leading to both under and over treatment. Faecal calprotectin tests would reduce radiology and

colonoscopy in these patients. In the longer term, it may also enhance disease control and reduce surgery, complications and disability.

In summary, any patient in whom there is a question as to whether their chronic GI symptoms are due to functional (IBS) or organic (IBD) disease, and all patients with IBD, will benefit from the use of faecal Calprotectin measurement.

Indicate if there is evidence for the population who would benefit from this service i.e. international evidence including inclusion / exclusion criteria. If appropriate provide a table summarising the population considered in the evidence.

1. Chronic diarrhoea (more than 6 weeks duration) where infective causes have been excluded

Faecal calprotectin as a parameter in the diagnostic process for a patient with non-specific abdominal pain and irregular stools. The test is used in the case of functional bowel diseases to rule out inflammatory (organic) bowel diseases in undiagnosed, symptomatic patients with abdominal complaints and chronic diarrhoea, as it has a high negative predictive value (NPV > 93%) to detect colorectal inflammation (Fagerberg et al. 2005; Manz et al. 2012). A high NPV is needed to provide doctors with the assurance that they do not need referral for secondary care investigations and unnecessary endoscopy (CEP 2010b).

In general practice, faecal calprotectin measurements should be determined early in the diagnostic evaluation of patients with abdominal pain and chronic diarrhoea. In patients with calprotectin concentrations below 50 µg/g, organic disease of the upper or lower gastrointestinal tracts is very unlikely, unless alarm symptoms (unexplained weight loss, unexplained rectal bleeding, family history of bowel or ovarian cancer, change in bowel habit lasting more than 6 weeks in people over 50 years [Australian Cancer Network 2005]) or pathologic laboratory results (positive inflammatory biomarkers erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)) are present. Calprotectin concentrations of 50 µg/g usually suggest an organic disease and further investigation is necessary. A high faecal calprotectin measurement can lead to an early colonoscopy and a more timely instigation of appropriate treatment (Gearry et al. 2005).

A recent health technology assessment concluded that calprotectin testing was a reliable way of differentiating inflammatory diseases of the bowel from non-inflammatory ones (Waugh et al 2013).

2. Evaluation of disease activity in patients with inflammatory bowel disease

Using the faecal calprotectin assay to evaluate disease activity has now been carried out in a number of studies (Tibble et al. 2000; D'Inca et al. 2008; Gisbert and McNicholl 2009; Kallel et al. 2010).

The underlying pathological process of IBD is intestinal inflammation and current treatment strategies are aimed at reducing or eliminating the associated inflammation. Measuring faecal calprotectin allows physicians to monitor a patient's response to therapy and to predict the recurrence of IBD.

In active Crohn's disease (CD) and ulcerative colitis (UC), the faecal calprotectin level should be above 50 µg/g (unless only the upper gut is affected). The goal of monitoring the course of therapy is to better adjust the dose of medication to the stage of the disease. Successful therapy reduces inflammation and thus leads to a decrease in the faecal calprotectin level. The dose can be reduced when the disease is in remission. On the other hand,

elevated faecal calprotectin levels in patients in clinical remission are associated with increased risk of disease relapse (Burri and Beglinger 2012). An incipient relapse can be recognised earlier by a rise in the calprotectin level, thus avoiding or ameliorating a recurrent attack through timely therapy adjustment.

A recent publication by Waugh et al 2013 , indicates that Faecal Calprotectin is very worthwhile and well regarded by other regulatory agencies

Protocol for assessment of faecal calprotectin.

8th October 2013

HTA reference number 2012/48

Title: faecal calprotectin in the differential diagnosis of chronic bowel disease.

Aim: to review the clinical accuracy and cost-effectiveness of faecal calprotectin testing for distinguishing between inflammatory and non-inflammatory bowel disease in people with chronic lower GI symptoms.

NB. This protocol may evolve in the course of the assessment.

Assessment group – Warwick Evidence

Project lead: Norman Waugh

Professor of public health medicine and health technology assessment

Warwick Evidence

Division of Health Sciences

Warwick Medical School

Coventry CV4 7AL

norman.waugh@warwick.ac.uk 02476 151585

Project team;

Dr Ewen Cummins, health economist

Dr Pamela Royle, senior research fellow

Dr Deepson Shyangdan, research fellow

Dr Ramesh Arasaradnam, consultant gastroenterologist, UHCW and associate professor of gastroenterology, Warwick Medical School

Dr Ngianga-Bakwin Kandala, principal research fellow

Introduction

Chronic abdominal pain or discomfort, accompanied by diarrhoea or constipation, is common and the symptoms can be due to a number of different conditions, some more serious than others.

The conditions include irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). The commonest forms of the latter are ulcerative colitis and Crohn's disease, which make up about 90% (to be checked) of IBD.

Irritable bowel syndrome

Provide details on the expected utilisation, if the service is to be publicly funded.

The symptoms of chronic diarrhoea and abdominal pain can be due to either inflammatory bowel disease (IBD)

or irritable bowel syndrome (IBS), a chronic functional gastrointestinal disorder that does not generally require medication or lead to complications. IBS is a syndrome with a diagnosis made on a cluster of symptoms in the absence of structural abnormalities. It does not produce the inflammation found in IBD. It does not result in permanent damage to the intestines, intestinal bleeding, harmful complications and the risk of colon cancer, often associated with IBD. Although there are limited Australian data on the current incidence and prevalence of IBD and IBS (AIHW 2012), IBS in the community is common with a considerable physical and psychological impact on sufferers; it has been estimated to affect about 10% of the Australian population (Gibson 2012). It represents a substantial proportion of the workload of GPs and gastroenterologists (Talley 2006; Quigley et al. 2012). IBS accounts for up to 12% of primary care consultations and 28% of referrals to specialist GI practice (Mitchell and Drossman 1987; Thompson et al. 2000; Dolwani et al. 2004).

With these symptoms, the crucial diagnostic step is deciding which patients should receive endoscopic and radiological investigations. Differentiating between IBD and IBS often cannot be determined solely on symptoms. A large number of patients are referred for specialist opinion and will undergo endoscopy and colonoscopy for a definitive diagnosis. These investigations carry risks, are costly and require time (1-2 days) to prepare and to undergo. In addition, audits of patients having colonoscopy consistently reveal a large number of inappropriate investigations (Lasson et al. 2008; Chey et al. 2010).

There are limited Australian data on the current incidence and prevalence of IBD and IBS (AIHW 2012). Based on surveys using IBS-specific diagnostic criteria, an estimated 1 in 10 Australians experience symptoms associated with IBS at some time (Boyce et al. 2006); however, not all seek medical care (AIHW 2012). Based on recent incidence surveys in Australia, there are an estimated 70 000 people living with IBD (Wilson et al. 2010).

A population-based study found that IBS costs the Australian community in terms of loss of time from work, medication use, repeated doctor visits and hospitalisations, inappropriate investigations, and generally poor treatment outcomes (Koloski 2002).

A significant proportion of the referrals to specialist hospital-based gastroenterology clinics consist of patients with diarrhoea and or abdominal pain. A significant proportion of these may not have a clear diagnosis on clinical grounds alone and may require further investigations. IBS accounts for up to 12% of primary care consultations and 28% of referrals to specialist GI practice (Dolwani et al. 2004).

There is a growing awareness of a significant number of colonoscopies being performed in clinical practice in developed countries for indications not listed in the American Society for Gastrointestinal Endoscopy (ASGE) guidelines (ASGE 2012). These countries have also seen an increased demand of gastrointestinal endoscopy, causing a strain on health-care resources. A multicentre study in Italy investigated the appropriate use of colonoscopy in an open access system, using the ASGE guidelines (Minoli et al. 2000). The study found a high rate of colonoscopies being performed for chronic diarrhoea and IBS symptoms. The rate of generally not indicated colonoscopies (according to the ASGE guidelines) was 21%. This finding corresponds to other studies in the United States, Europe and the Middle East indicate that 20-50% of colonoscopies are performed for inappropriate indications (Telford 2012).

Such data are as yet unavailable in Australia. Available data to monitor bowel cancer screening shows a 90.1% increase in the number of colonoscopies performed in Australia in the ten-year period from 1995/96 to 2005/06 (based on claims for Medicare benefits) (DoHA 2010). Data are also available showing the number of colonoscopies performed from 2000 to 2010 for both 32090 and 32093 MBS item numbers showing an increase in all states and territories and for Australia as a whole, however it is not possible to define the number of colonoscopies performed specifically for IBS symptoms (DoHA date missing).

Data from the Royal Brisbane and Women's Hospital in Queensland show that in the 12-month period 1/10/211 to 1/10/2012, 2205 referrals of a total of 4817 referrals were coded from a list of 25 provisional diagnoses and symptoms; of these 2205, 316 were coded as altered bowel habit, 67 were known or likely IBD and 379 as abdominal pain, dyspepsia or non cardiac chest pain. Significantly, the group of patients referred because of altered bowel habit (316/2205) represent 14% of all referrals.

As resources are limited with regard to medical services, a test that can assist in differentiating those patients who do not need endoscopic exploration would avoid subjecting them to unnecessary investigative procedures and free up resources for people who need to access them in a more timely way. Waiting times for specialist review and endoscopic investigations have been increasing, resulting in concerns of delayed diagnoses and initiation of appropriate treatment. It has been estimated that screening by measuring faecal calprotectin levels would result in a 67% reduction in the number of adults requiring endoscopy (van Rhee et al. 2010).

3. Intervention – proposed medical service

Provide a description of the proposed medical service.

a. Quantum Blue® Calprotectin Lateral Flow Assay

The BÜHLMANN Quantum Blue® Calprotectin Assay is an immunoassay designed for the quantitative determination of Calprotectin in human stool samples in combination with the BÜHLMANN Quantum Blue® Reader.

After a short extraction procedure, the test allows for the selective measurement of Calprotectin antigen by sandwich immunoassay. A monoclonal capture antibody (mAb) highly specific for Calprotectin is coated onto the test membrane. A second monoclonal detection antibody conjugated to gold colloids is deposited onto the conjugate release pad and released into the reaction system after addition of the extracted and diluted stool sample. The Calprotectin/anti-Calprotectin gold conjugate binds to the anti-Calprotectin antibody coated on the test membrane (test line; test band) and the remaining free anti-Calprotectin gold conjugate binds to the goat anti-mouse antibody coated on the test membrane (control line; control band). The signal intensities of the test line and the control line are measured quantitatively by the BÜHLMANN Quantum Blue® Reader.

b. Quantum Blue® Calprotectin

Limit of Detection (LoB): <7 µg/g calprotectin.

Working range: 30 -300µg/g of calprotectin.

Time to Result – 20 minutes.

c. Quantum Blue® Calprotectin High Range

Limit of Detection (LoB): <60 µg/g calprotectin.

Working range: 100 -1800 µg/g calprotectin.

Time to Result – 20 minutes.

d. Quantum Blue® Calprotectin Extended Range

Limit of Detection (LoB): <20 µg/g calprotectin.

Working range: 30 -1000 µg/g calprotectin.

Time to Result – 20 minutes.

1. **BÜHLMANN Calprotectin ELISA**

The BÜHLMANN Calprotectin ELISA kit is designed for the extraction and quantitative determination of human Calprotectin in stool samples.

PRINCIPLE OF THE ASSAY

After a short extraction procedure, the test allows for the selective measurement of Calprotectin-antigen by sandwich ELISA. A monoclonal capture antibody (mAb) highly specific to the Calprotectin heterodimeric and polymeric complexes, respectively, is coated onto the microtiter plate. Calibrators, controls and patients extracts are incubated at room temperature for 30 minutes. After a washing step a detection antibody (Ab) conjugated to horseradish peroxidase (HRP) detects the calprotectin molecules bound to the monoclonal antibody coated onto the plate. After incubation and a further washing step, tetramethylbenzidine (TMB) will be added (blue color formation) followed by a stopping reaction (change to yellow color). The absorption is measured at 450 nm.

Assay specifications:

Lower Range Procedure:

Working range: 10 – 600 µg/g

Detection limit (LoB): <10 µg/g.

Extended Range Procedure:

Working range: 30 – 1800 µg/g

Detection limit (LoB): <30 µg/g.

Time to Result – 75 minutes – N.B. Samples will be batched to make the test run cost-effective. Therefore , the individual result may not be available for approx 2-3 weeks.

Both applications – Quantum Blue as well as Buhlmann fCAL ELISA – are suitable for both groups of patients, because both intervention methods offer the calprotectin tests requested for both of the patient groups (Based on diagnostic range , clinical cut-offs as well as clinical validation data). The choice between the two intervention methods is not with regard to the targeted patient group , but rather due to the laboratory environment , number of tests requested , or acceptable time to receive results.

N.B. Age (> 3 years) , sex , or race do not influence calprotectin levels.

For potential confounding effect of other inflammatory GE disorders refer: 2012 – Manz & 2014 – Kennedy.

Cut-off values have been established for differentiation between IBS and IBD , but there are no cut-offs for severity ranges of acute inflammation. Currently there are no clinical validation studies indicating such threshold cut-offs of acute inflammation.

Re longitudinal changes in calprotectin levels , and subsequent changes to patient management , the evidence indicates.....Refer :

Group 2: Therapy monitoring of diagnosed IBD patients

2014 – Naismith

2014 – Guardiola

2013 – De Vos

2013 – Lobaton

2013 - Ortega

2012 – de Haenes

If the service is for investigative purposes, describe the technical specification of the health technology and any reference or “evidentiary” standard that has been established.

Faecal calprotectin is a marker for intestinal inflammation. Calprotectin concentration in faeces correlates with the severity of inflammation: it is significantly increased in patients with bowel inflammation (IBD), but not elevated in patients with functional disorders like IBS. As a screening tool, faecal calprotectin tests (by bench-top, quantitative lateral flow analyser or laboratory-based enzyme-linked immunosorbent assay [ELISA]) differentiate IBD from functional bowel disease (IBS), reducing the need for invasive diagnostic procedures (such as colonoscopy), potentially leading to earlier diagnosis of IBD and IBS and subsequently improving patient management.

2. Quantum Blue® Calprotectin Lateral Flow Assay

The BÜHLMANN Quantum Blue® Calprotectin Assay is an immunoassay designed for the quantitative determination of Calprotectin in human stool samples in combination with the BÜHLMANN Quantum Blue® Reader.

After a short extraction procedure, the test allows for the selective measurement of Calprotectin antigen by sandwich immunoassay. A monoclonal capture antibody (mAb) highly specific for Calprotectin is coated onto the test membrane. A second monoclonal detection antibody conjugated to gold colloids is deposited onto the conjugate release pad and released into the reaction system after addition of the extracted and diluted stool sample. The Calprotectin/anti-Calprotectin gold conjugate binds to the anti-Calprotectin antibody coated on the test membrane (test line; test band) and the remaining free anti-Calprotectin gold conjugate binds to the goat anti-mouse antibody coated on the test membrane (control line; control band). The signal intensities of the test line and the control line are measured quantitatively by the BÜHLMANN Quantum Blue® Reader.

a. Quantum Blue® Calprotectin

Limit of Detection (LoB): <7 µg/g calprotectin.

Working range: 30 -300µg/g of calprotectin.

b. Quantum Blue® Calprotectin High Range

Limit of Detection (LoB): <60 µg/g calprotectin.

Working range: 100 -1800 µg/g calprotectin.

c. Quantum Blue® Calprotectin Extended Range

Limit of Detection (LoB): <20 µg/g calprotectin.

Working range: 30 -1000 µg/g calprotectin.

3. BÜHLMANN Calprotectin ELISA

The BÜHLMANN Calprotectin ELISA kit is designed for the extraction and quantitative determination of human Calprotectin in stool samples.

PRINCIPLE OF THE ASSAY

After a short extraction procedure, the test allows for the selective measurement of Calprotectin-antigen by sandwich ELISA. A monoclonal capture antibody (mAb) highly specific to the Calprotectin heterodimeric and polymeric complexes, respectively, is coated onto the microtiter plate. Calibrators, controls and patients extracts are incubated at room temperature for 30 minutes. After a washing step a detection antibody (Ab) conjugated to horseradish peroxidase (HRP) detects the calprotectin molecules bound to the monoclonal antibody coated onto the plate. After incubation and a further washing step, tetramethylbenzidine (TMB) will be added (blue color formation) followed by a stopping reaction (change to yellow color). The absorption is measured at 450 nm.

Assay specifications:

Lower Range Procedure:

Working range: 10 – 600 µg/g

Detection limit (LoB): <10 µg/g.

Extended Range Procedure:

Working range: 30 – 1800 µg/g

Detection limit (LoB): <30 µg/g.

Endoscopy:

Endoscopy is an important diagnostic and therapeutic modality in inflammatory bowel disease (IBD), being useful for both Crohn's disease (CD) and ulcerative colitis (UC). Endoscopy is used to make an initial diagnosis of IBD, distinguish CD from UC, assess the disease extent and activity, monitor response to therapy, allow for surveillance of dysplasia or neoplasia, and provide endoscopic treatment, such as stricture dilation. Colonoscopy with ileoscopy allows direct visualization and biopsy of the mucosa of rectum, colon, and terminal ileum. Unless contraindicated because of severe colitis or possible toxic megacolon, a full colonoscopy with intubation of the terminal ileum is performed during the initial evaluation of patients with a clinical presentation suggestive of IBD.

Indicate whether the service includes a registered trademark with characteristics that distinguish it from any other similar health technology.

Lab-based ELISA technology is not trademarked.

Quantum Blue Lateral Flow technology is the only Lateral Flow technology providing quantitative results (refer to Sydora et al.: Validation of a point-of-care desk top device to quantitate fecal calprotectin and distinguish inflammatory bowel disease from irritable bowel syndrome, Journal of Crohn's and Colitis (2012) 6, (207–214).

Indicate the proposed setting in which the proposed medical service will be delivered and include detail for each of the following as relevant: inpatient private hospital, inpatient public hospital, outpatient clinic, emergency department, consulting rooms, day surgery centre, residential aged care facility, patient's home, laboratory. Where the proposed medical service will be provided in more than one setting, describe the rationale related to each.

The service will be provided by:

1)NATA accredited public or private pathology laboratories (ELISA or POCT) or

2) in the consulting rooms of physicians (general physician, paediatrician, gastroenterologist) who manage patients referred for gastrointestinal specialist advice (bench-top test). The Point-of-Care test could also be performed in a Day Surgery Centre, or Laboratory.

The ELISA would be on request from a GP or Specialist.

The ability to perform the bench-top test in the consulting rooms of consultant general physicians, paediatricians and gastroenterologists will allow a result to be available within the consultation time period and thus provide important information as to whether the patient with known IBD has elevated levels of gastrointestinal inflammation and therefore aid with clinical decision making. In physician's rooms the performance of the test may be by delegated staff (i.e. nurse) under direct consultant supervision. Training and practices with regard to the bench-top testing is to be in line with the Australian National Pathology Accreditation Advisory Council: Policies, procedures and guidelines for point-of-care testing.

Describe how the service is delivered in the clinical setting. This could include details such as frequency of use (per year), duration of use, limitations or restrictions on the medical service or provider, referral arrangements, professional experience required (e.g.: qualifications, training, accreditation etc.), healthcare resources, access issues (e.g.: demographics, facilities, equipment, location etc.).

Gastroenterologists or delegated staff (i.e. nurse) should collect the samples which they either analyze directly (by POC test) or send to the lab, for POC test or ELISA method. All other requesters should collect the sample and send it to a certified pathology laboratory for analysis.

All other requesters, including GPs should NOT be allowed to use POC/bench-top methods.

Training needs to be considered for the following categories:

Lab-based ELISA testing: This can only be performed by NATA accredited Pathology laboratories. Individual laboratory proficiency is assessed periodically by NATA. Interpretation of the test result will be done by the pathologists.

Bench-top/Point-of-Care test: Training is conducted by appropriately qualified, "Factory-trained" scientists. This training is provided at installation, and consists of 1 full day of tuition in sample preparation, performance of tests, functions of analyser, review of results and general maintenance of reader. This should be in keeping with the recommendations of the Australian National Pathology Accreditation Advisory Council: Policies, procedures and guidelines for point-of-care testing. Interpretation of the test result will be by the specialist gastroenterologist only.

Guidelines for interpretation of results in terms of Cut-Offs , Grey-Zone and Relapse/Remission , can be found in the following documents:

Group 1: Testing for IBS/IBD differentiation

2013 - Pavlidis/Tibble

2012 – Manz/Beglinger

2012 – Mindemark

2014 – Kennedy

2012 - Sherwood

Group 2: Therapy monitoring of diagnosed IBD patients

2014 – Naismith

2014 – Guardiola

2013 – De Vos

2013 – Lobaton

2013 Ortega

2012 – de Haenes

Frequency of use:

1) For people with suspected IBS and a calprotectin value < 50 µg/g, it would not be justified >1 per year. A measurement within the “grey area” (50-150) would require a repeat measurement in 1-2 weeks.

2) For people with IBD (Calprotectin > 150 ug/g) they may require up to 4 tests per year (every 3 months for monitoring) + an extra one if they have a flare, but on maintenance therapy flare rate per year is <50%. For well IBD patients, annual faecal calprotectin measurement should be appropriate. This would be lifelong.

With regard to any required changes in capital equipment, and/or issues of location of the medical service or associated health technology:

For Laboratory ELISA , nil changes.

For POC test , require purchase of reader (< \$4,000.00).

Regarding any direct practice cost components:

a. What is the staff component of the direct costs (hourly rate and time typically taken)?

A: Bench-Top analyser – \$24.67 (\$37.00 hourly rate , over 40 Mins).

B: Lab-based ELISA test – \$24.67 (\$37.00 hourly rate , over 40 Mins).

b. What is the consumable component of the direct costs (cost of consumables used when the proposed medical service is typically provided)?

A: Bench-Top analyser – \$32.25 per sample

Includes: Kit components (\$27.00) , Extraction Device (\$4.30) , Pipette Tips and tubes (\$0.50) , Control Material (\$0.45)

B: Lab-based ELISA test – \$32.20 per sample Includes: Kit components (\$27.40) , Extraction Devices (\$4.30) , Pipette Tips and tubes (\$0.50).

c. What is the equipment component of the direct costs (annual cost of each piece of equipment used and the other MBS items for which it is also used)?

Based on equipment life-time of 5 years & 125 samples per quarter

A: Bench-Top analyser – \$3.82 per sample.

Includes: Reader (\$3,600) , Printer (\$1,800) , Pipettes (\$800) , Vortex (\$350) , Centrifuge (\$3,000).

B: Lab-based ELISA test – \$4.01 per sample.

(N.B.) – The ELISA equipment can be used for other tests.

Includes: ELISA Reader (\$8,500) , ELISA Washer (\$4,500) , Printer (\$400) , Pipettes (\$800) , Centrifuge (\$3,000) , Vortex (\$350) , Plate Rotator (\$2,500).

Fully-Comprehensive Service Contracts after warranty are costed in d. below. This includes any upgrades.

d. What are other components of the direct cost in delivering this service?

Total direct practice costs (separated into per service and annual costs as necessary):

A: Bench-Top analyser – \$60.74 per sample , Plus \$895.00 annual Service Contract.

B: Lab-based ELISA test – \$60.88 per sample , Plus \$1,295.00 annual Service Contract.

4. Co-dependent information (if not a co-dependent application go to Section 6)

Please provide detail of the co-dependent nature of this service as applicable

5. Comparator – clinical claim for the proposed medical service

Please provide details of how the proposed service is expected to be used, for example is it to replace or substitute a current practice; in addition to, or to augment current practice.

The Reference standard (Comparator) for both patients groups is the Colonoscopy – References:

2014 – Guardiola , 2013 – Lobaton , 2013 – Ortega – These are recent examples for vast clinical evidence over more than 10 years.

Other comparators such as CRP and ESR could be used for the patient Group 1 – But these are non-specific inflammation markers , as opposed to Calprotectin which is highly specific for Gastrointestinal Inflammation. Ref – 2010 Schoepfer.

There are two distinct clinical pathways for the use of the quantitative measurement of calprotectin in stool samples: one (Comparator A) to discriminate between organic and functional bowel disorders and the second (Comparator B) to monitor disease activity in known inflammatory bowel disease (IBD).

A) Colonoscopy in functional bowel disease to exclude the diagnosis of organic diseases

Cost per colonoscopy examination: \$1200.00

Facility fee:

Specialist fee (public):

Specialist fee (private):

Anaesthetist fee:

Biopsy costs (performed in 30-50% of cases):

Current standard diagnostic pathway for a clinical presentation of a patient with abdominal symptoms suggestive of either irritable bowel syndrome (IBS) or IBD.

A patient will usually present first to a general practitioner (GP) with chronic (more than 6 weeks) lower gastrointestinal symptoms (abdominal pain or discomfort, bloating or a change in bowel habit). The GP will take a patient history and perform an examination. At this first GP consultation, in the absence of alarm symptoms (red flag symptoms such as unexplained weight loss, rectal bleeding without cause, iron deficiency in men over 40 years or women over 50 years or a high-risk family history for colorectal cancer [Australian Cancer Network 2005]), the necessary pathology tests are sometimes instigated (full blood count (FBC) with differential, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) with or without stool specimen to rule out infectious causes) to help to discriminate between IBS and IBD. At the following GP consultation, if symptoms persist, pathology is ordered (FBC, CRP and ESR with or without stool specimen to rule out infectious causes), or initial workup if not previously done. The patient is then often referred to a specialist physician for colonoscopy to provide absolute assurance that IBD can be ruled in or out. Although colonoscopy is not always done, it is frequently performed even if the specialist suspects functional bowel disorder, as patients and GPs want a definite answer for reassurance. In Australia, an expectation of the procedure has been created as the one method of providing certainty for both doctors and patients. Moreover, colonoscopy is currently covered on Medicare whereas faecal calprotectin testing is not so in public medicine many unnecessary colonoscopies are performed where a faecal calprotectin test could have served as well.

Patients with a clear need for colonoscopy (that is, those patients with alarm indicators on history) should be excluded from this diagnostic pathway. These patients are referred immediately for specialist care and further investigations including colonoscopy.

B) Investigations to follow disease activity in known inflammatory bowel disease (IBD)

Cost per colonoscopy examination: \$1200.00

Cost of endoscopy:

Cost of radiology (CT scan or Barium follow-through procedure):

Facility fee:

Specialist fee (public):

Specialist fee (private):

Anaesthetist fee:

Current standard diagnostic pathway for a clinical presentation of a patient with a known diagnosis of IBD.

Currently, the activity of IBD is either judged on patients' symptoms or on the appearance of the affected area of the bowel with either colonoscopy, endoscopy or radiology (high-radiation dose

computed tomography (CT) scan or magnetic resonance imaging (MRI), unfunded and variably available).

Patient selection for colonoscopy based on symptoms is not reliable as symptoms correlate poorly with disease activity and bowel damage, so that many patients will be overtreated with immunosuppressing drugs if they have symptoms but are healed (it is very common for these patients to have functional symptoms after the inflammation resolves); or undertreated if they have ongoing inflammation yet few symptoms (the risk is that these patients then have surgery and complications potentially leading to disability which could have been avoided if their IBD were better controlled). Due to the invasive nature of colonoscopy and the associated risks (1/1000 of perforation), IBD specialists are cautious about using it too frequently to monitor disease activity. Likewise the radiation dose associated with a computed tomography (CT) scan and the costs and lack of access to magnetic resonance imaging (MRI), make these radiology procedures unsuitable techniques for regularly monitoring disease activity. This patient group therefore currently has inconsistent and inaccurate monitoring of disease activity, leading to both under and over treatment. Faecal calprotectin tests would reduce radiology and colonoscopy in these patients. In the longer term, it may also enhance disease control and reduce surgery, complications and disability.

Results for both ELISA and bench-top testing within the grey area (50-100ug/g) would be treated alike and are mainly important in trying to determine if a patient with greater than 6 weeks of gastrointestinal symptoms suggestive of IBD should proceed with colonoscopy to establish a diagnosis. Initially a repeat calprotectin in one to two weeks is recommended. If this is <50 ug/g this would indicate non-inflammatory disease and no further diagnostic studies would be indicated. If the result is ≥ 50 ug/g a decision should be made based on clinical grounds as to whether the patient should proceed with colonoscopy.

6. Expected health outcomes relating to the medical service

Identify the expected patient-relevant health outcomes if the service is recommended for public funding, including primary effectiveness (improvement in function, relief of pain) and secondary effectiveness (length of hospital stays, time to return to daily activities).

The proposed new service is superior regarding time, cost efficiency, and with lower risk exposure for patients (no risk of perforation as with colonoscopy).

Identification of low risk (of lesion) patients would reduce the number of unnecessary invasive procedures. Conversely, there would be a substantial advantage in being able to identify those at high risk of finding organic disease so that their colonoscopies can be expedited, and therapy started. In Australia, savings of about \$1,105 per spared endoscopy, depending on the charge for the Calprotectin determination. Mid-term savings of about 35,000 to 50,000 endoscopies per year could be realized, which represents about 38 to 55 \$AU Mio. In this way, substantial cost savings could be achieved through effective disease management.

It would also free-up colonoscopic resources so that those procedures can be better targeted.

It will also be reduce the number of colonoscopies done simply to monitor inflammatory activity in people with known IBD.

As the Reference Standard is colonoscopy in both population groups , the following publications for group 1 and group 2 offer analytical validity data for calprotectin vs colonoscopy.

Group 1: Testing for IBS/IBD differentiation

2013 Pavlidis/Tibble

2012 – Manz/Beglinger

2012 – Mindemark

2014 – Kennedy

2012 - Sherwood

Group 2: Therapy monitoring of diagnosed IBD patients

2014 – Naismith

2014 – Guardiola

2013 – De Vos

2013 – Lobaton

2013 Ortega

2012 – de Haenes

Describe any potential risks to the patient.

Risks to patients are potential delay in diagnosis as a result of a false negative result, or unnecessary colonoscopy with the potential of associated risks (bleeding, perforation) in those with a false positive result.

Specify the type of economic evaluation.

The cost of the current diagnostic pathway being endoscopy, as per the current cost of the diagnostic work-up to differentiate between IBD and IBS is approximately \$1,200.00. By using faecal Calprotectin measurement as a new diagnostic pathway to identify patients that require endoscopy (those with elevated Calprotectin levels – indicating inflammation of the gut), and accordingly to identify patients with IBS (those with low levels of Calprotectin – indicating non-inflammation of the gut), the proposed cost re-imburement is \$95.00 per patient test.

Savings of about \$1,105 per spared endoscopy, depending on the charge for the calprotectin determination. Mid-term savings of about 35,000 – 50,000 endoscopies/year could be realized, which represents about 38 – 55 \$A Mio. In this way, substantial cost savings could be achieved through effective disease management.

7. Fee for the proposed medical service

Explain the type of funding proposed for this service.

MBS funding for appropriate Labs and Gastroenterology units covered by the following categories:

ELISA and bench-top testing performed in NATA-accredited Laboratories - Category 6 – Pathology Services

Bench-top testing performed in Non-Pathology settings - Category 2 – Diagnostic Procedures & Investigations

Please indicate the direct cost of any equipment or resources that are used with the service relevant to this application, as appropriate.

For the ELISA laboratory-based test there is no special equipment necessary to perform the service as the equipment is generic for laboratories and thus already available.

For the Bench-Top analysis , there would be approximately \$4,800.00 cost for goods required – i.e. QB Reader , Vortexer , Pipettes and Rack.

With regard to any required changes in capital equipment, and/or issues of location of the medical service or associated health technology:

For Laboratory ELISA , nil changes.

For POC test , require purchase of reader (< \$4,000.00).

Regarding any direct practice cost components:

a. What is the staff component of the direct costs (hourly rate and time typically taken)?

A: Bench-Top analyser – \$24.67 (\$37.00 hourly rate , over 40 Mins).

B: Lab-based ELISA test – \$24.67 (\$37.00 hourly rate , over 40 Mins).

b. What is the consumable component of the direct costs (cost of consumables used when the proposed medical service is typically provided)?

A: Bench-Top analyser – \$32.25 per sample

Includes: Kit components (\$27.00) , Extraction Device (\$4.30) , Pipette Tips and tubes (\$0.50) , Control Material (\$0.45)

B: Lab-based ELISA test – \$32.20 per sample

Includes: Kit components (\$27.40), Extraction Devices (\$4.30) , Pipette Tips and tubes (\$0.50).

c. What is the equipment component of the direct costs (annual cost of each piece of equipment used and the other MBS items for which it is also used)?

Based on equipment life-time of 5 years & 125 samples per quarter

A: Bench-Top analyser – \$3.82 per sample.

Includes: Reader (\$3,600), Printer (\$1,800) , Pipettes (\$800) , Vortex (\$350) , Centrifuge (\$3,000).

B: Lab-based ELISA test – \$4.01 per sample.

(N.B.) – The ELISA equipment can be used for other tests.

Includes: ELISA Reader (\$8,500) , ELISA Washer (\$4,500) , Printer (\$400) , Pipettes (\$800) , Centrifuge (\$3,000) , Vortex (\$350) , Plate Rotator (\$2,500).

Fully-Comprehensive Service Contracts after warranty are costed in d. below. This includes any upgrades.

d. What are other components of the direct cost in delivering this service?

Total direct practice costs (separated into per service and annual costs as necessary):

A: Bench-Top analyser – \$60.74 per sample , Plus \$895.00 annual Service Contract

B: Lab-based ELISA test – \$60.88 per sample , Plus \$1,295.00 annual Service Contract.

Training needs to be considered for the following categories:

Lab-based ELISA testing: This can only be performed by NATA accredited Pathology laboratories. Individual laboratory proficiency is assessed periodically by NATA. Interpretation of the test result will be done by the pathologists.

Bench-top/Point-of-Care test: Training is conducted by appropriately qualified, “Factory-trained” scientists. This training is included in the price of the reader and is provided at installation, and consists of 1 full day of tuition in sample preparation, performance of tests, functions of analyser, review of results and general maintenance of reader. This should be in keeping with the recommendations of the Australian National Pathology Accreditation Advisory Council: Policies, procedures and guidelines for point-of-care testing Interpretation of the test result will be by the specialist gastroenterologist.

Quality Assurance – An in-built Control is part of each Test-Cartridge , and this is measured , and the result stored , by the reader as part of each test. This can be complemented by performing a daily test on Control Material with assay defined ranges – The cost of this material is \$0.45 per test.

Provide details of the proposed fee.

We would request a fee of \$95.00 to cover the cost of the test kits , reader/s , consumables , labour , and inherent costs of operating a laboratory and/or Gastroenterology unit.

This fee would be applicable to both ELISA and Bench-top analysis.

Components of the test costs are explained in the above section.

8. Clinical Management Algorithm - clinical place for the proposed intervention

Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (6) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.

Current Diagnostic pathway :

In people with diarrhoea > 6 weeks , and infectious causes excluded:

Eligible for FC – BUT not funded:

Referral for colonoscopy, GE consult (110 - \$150.90), Colonoscopy (32090 - \$334.35) , Anaesthetic Fee (If private), Histopathology of biopsies.

No finding on colonoscopy of relevance – informed of IBS.

Finding of relevance (very low rate in this group) – treatment offered.

Patient with chronic (> 6 weeks) symptoms of loose stools, sees GP. If GP, or patient, is concerned, tests (blood and stool) are ordered (but may not be). Patient with on-going symptoms who is concerned may re-visit GP, and at one of these repeat visits, GP may refer patient for a colonoscopy, just “to exclude” organic disease. In this fashion, many people without concerning symptoms, get a colonoscopy purely for reassurance. The colonoscopy (at greater cost and greater risk) will then distinguish between functional (IBS) and organic causes for the loose stools.

Non-Specific markers of Inflammation in the blood : CRP, ESR.

Current process for monitoring therapy:

In people with known IBD:

Known IBD patient (Crohn’s or UC) receiving therapy, monitored Quarterly / As required. Colonoscopy performed to review efficacy of treatment. Result of colonoscopy will determine future of treatment.

Suspected flare in disease:

Colonoscopy (32090 - \$334.35), Anaesthetic Fee (If private), Histopathology of biopsies.

Appropriate treatment instigation

Provide a clinical management algorithm (e.g.: flowchart) explaining the expected management and any downstream services (aftercare) of the eligible population/s if public funding is recommended for the service proposed.

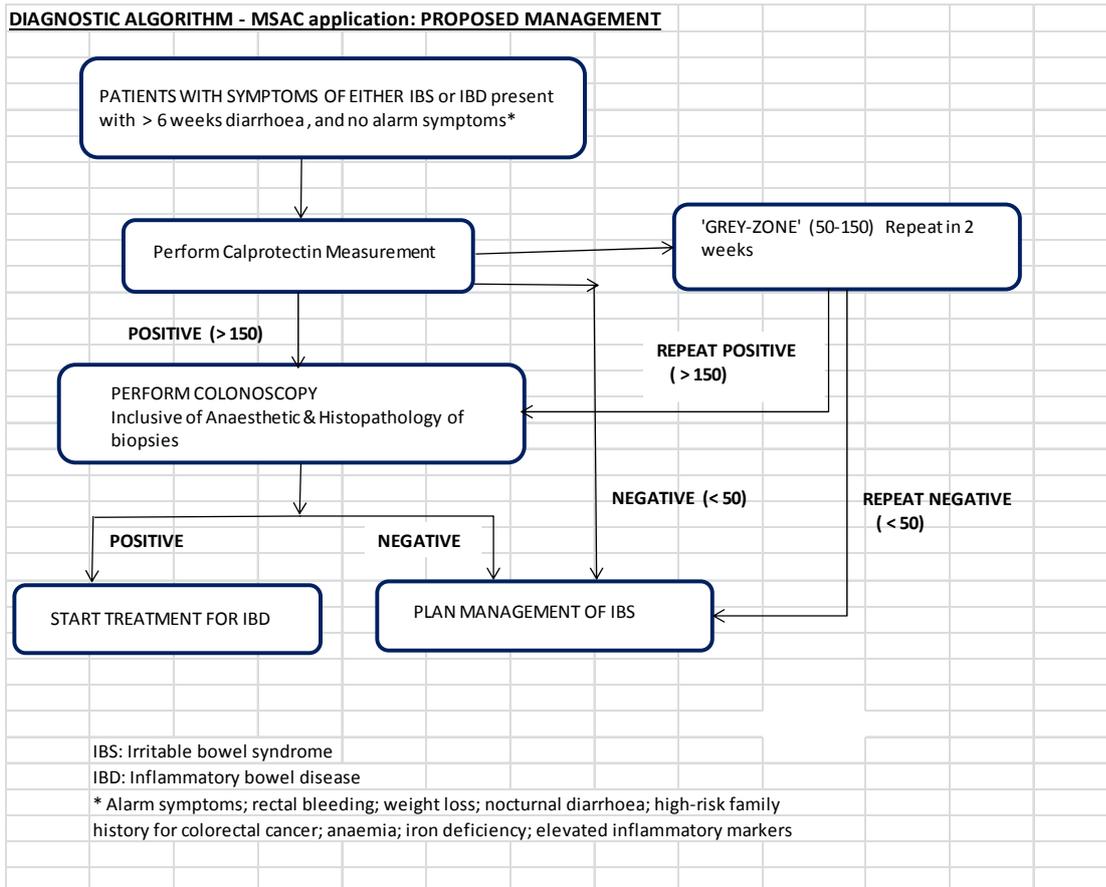
Diagnostic pathway with proposed new test:

Diagnosing IBS/IBD:

Chronic diarrhoea (more than 6 weeks duration) where infective causes have been excluded.

A Calprotectin determination usually precludes the need for colonoscopy if the value is < 50 ug/g. In the “grey area” between 50 and 150 ug/g, a repeat measurement in 1-2 weeks is recommended. If this is <50 ug/g this would indicate non-inflammatory disease and no further diagnostic studies would be indicated. If the result is ≥50ug/g a decision should be made based on clinical grounds as to whether the patient should proceed with colonoscopy.

DIAGNOSTIC ALGORITHM - MSAC application: PROPOSED MANAGEMENT



There is no reason that the algorithm for discrimination of IBS vs IBD be split to be initiated by either a GP and sent to a lab for ELISA , or by a Specialist with the test performed by Bench-Top POCT. Both technologies are similar , if not identical , in their performance and interpretation capacity. The choice of technology – Quantum Blue or ELISA – does not support such differentiation. Indeed , some Pathology Labs will have access to both technologies , and therefore it will be a case of selection of technology based on the urgency of result.

Proposed process for monitoring therapy:

Patients with a known diagnosis of IBD.

In active Crohn's disease of the lower GI tract and in ulcerative colitis, the Calprotectin level is > 150 µg/g; in these patients, monitoring for the level of inflammatory activity (and examining the trend, rising or falling) periodically using Calprotectin is helpful to predict disease behaviour, prognosticate and to pre-emptively adjust therapy. Successful management would be reflected by a reduction of the Calprotectin level.

A normal Calprotectin value in a patient clinically in remission may aid the decision to de-escalate therapy. Testing annually would be appropriate for patients in remission.

Known IBD patient (Crohn's or UC) receiving therapy , monitored Quarterly / As required.

Calprotectin Screening:

1. Result < Baseline or most recent level – continue current therapy.
2. Result > or = Baseline or most recent level - Colonoscopy performed to review efficacy of treatment. Result of colonoscopy will determine future/change of treatment.

There are no guidelines for monitoring therapy in IBD patients.

However , based on first clinical studies e.g. 2014 – Naismith , it seems that a testing interval of 3 months for diagnosed IBD patients in remission will be sufficient to make an early prediction of potential flares. In an acute exacerbation of symptoms , we would expect that testing interval shorten during the acute (flare) phase of the disease (2013 – de Vos).

Also , 2010 – ECCO CD consensus , 2012-ECCO UC consensus

9. Regulatory Information

Please provide details of the regulatory status. Noting that regulatory listing must be finalised before MSAC consideration.

- The ARTG listing or registration or inclusion number:

AUST L 59536

10. Decision analytic

Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC (as outlined in Table 1).

Population	Prior tests	Intervention	Comparator	Reference standard	Outcome claims
a). People with loose stools > 6 weeks with infection excluded where further reassurance is wanted.	a). NIL	a). Perform FC test and refer to GE opinion +/- colonoscopy if elevated.	a). Colonoscopy.		a). Reduce those referred for colonoscopy , provide better reassurance to patients , and also security to GPs.

For clinical evidence, to the HTA performed by van Rheenen et al.2010, BMJ 2010;341:c3369. The HTA has been accepted by the Swiss authorities in 2013 and thus reimbursement has been granted for Switzerland.



10 van
Rheenen_BMJ_Meta-

Population	Prior tests	Intervention	Comparator	Reference standard	Outcome claims
b). People with known IBD to monitor disease activity non-invasively.	b). An established diagnosis of IBD.	b). Perform regular FC tests to monitor & adjust therapy , & to judge whether new symptoms are due to inflammation.	b). Colonoscopy.		b). Better IBD control with more targeted therapy (And all the benefits which this drives). Plus , reduced colonoscopy demand.

11. Healthcare resources

Using tables 2 and 3, provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.

12. Questions for public funding

Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:

- Which health / medical professionals provide the service
- Are there training and qualification requirements
- Are there accreditation requirements

The service will be provided by NATA accredited public or private pathology laboratories or in the consulting rooms of physicians (general physician, paediatrician, gastroenterologist) who manage patients referred for gastrointestinal specialist advice or with a known diagnosis of IBD. The ELISA-based test would only be performed an accredited pathology laboratory.

The Bench-Top test could be performed in a multitude of settings, but most likely in an Outpatient clinic, Day Surgery Centre, or Laboratory.

Table 1: Summary of PICO to define research question

Refer to HTA by van Rheenen et al. 2010, attached to this form (10)

PICO	Comments
Patients	
Intervention	
Comparator	
Outcomes	
For investigative services	
Prior tests	
Reference standard	

Table 2: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MB S	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Resource 1	GP	Medical Centre								
Resource 2	Gastroenterologist	Gastro Unit								
Resources provided to deliver proposed intervention										
Resource 1	Gastro									
Resource 2	Pathology									
Resources provided in association with proposed intervention										
Resource 1	Colonoscopy if positive									
Resource 2										
Resources provided to deliver comparator 1										
Resource 1	GP	Medical Centre								
Resource 2	Gastroenterologist	Gastro Unit								
Resources provided in association with comparator 1										
(e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MB S	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resource 1										
Resource 2										
Resources provided to deliver comparator 2										
Resource 1										
Resource 2										
Resources provided in association with comparator 2										
Resource 1										
Resource 2										
Resources used to manage patients successfully treated with the proposed intervention										
Resource 1										
Resource 2										
Resources used to manage patients who are unsuccessfully treated with the proposed intervention										
Resource 1										
Resource 2										
Resources used to manage patients successfully treated with comparator 1										

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MB S	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resource 1										
Resource 2										
Resources used to manage patients who are unsuccessfully treated with comparator 1										
Resource 1										
Resource 2										

* Include costs relating to both the standard and extended safety net.

Table 3: Alternative summary of resources table for state transition models

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per cycle per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budgets (PBS, hospitals, etc)	Private health insurer	Patient	Total cost
Health state 1										
Resource 1										
Resource 2										
Health state 2										
Resource 1										
Resource 2										
Health state 3										
Resource 1										
Resource 2										

* Include costs relating to both the standard and extended safety net.