Benefit of Point of Care testing for Faecal Calprotectin

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AgPlus diagnostics

CONTENTS

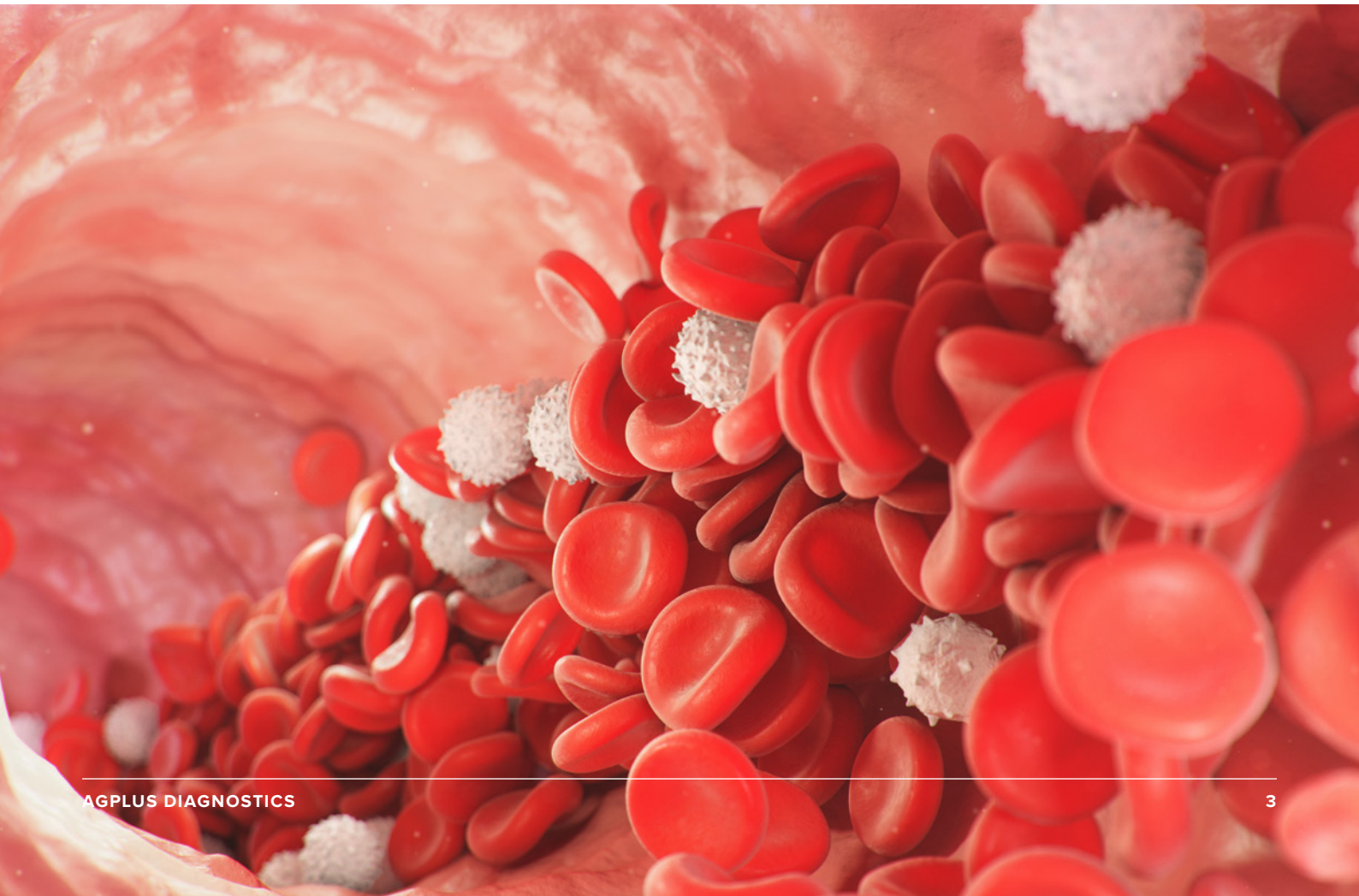
BENEFITS OF POC TESTING FOR CALPROTECTIN

- Increased compliance with recommendations for testing frequency and treatment adoption
- Improved clinical outcomes
- Facilitated patient education and motivation
- Improved patients' quality of life
- Contribute to cost/time savings both for health-care professionals and patients

INTRODUCTION

Calprotectin is one of the most abundant proteins in neutrophils, a type of white blood cell that is recruited in large numbers to sites of inflammation in the body. During inflammation in the intestine, recruited neutrophils are frequently shed into the gut and are then degraded by digestive fluids and enzymes.

Unlike other proteins, however, calprotectin is highly resistant to enzymatic degradation and can be detected in bodily samples even when other proteins have been broken down. Over the last 15 years, the ability to detect calprotectin in faeces has provided a useful surrogate for measuring intestinal inflammation (1). This is particularly important since the symptoms of diseases like Crohn's disease, which can cause serious intestinal damage, are often similar to the symptoms of conditions like irritable bowel syndrome, which does not cause any lasting damage. The ability to determine which symptoms require further investigation, and which do not, has led to faecal calprotectin becoming an invaluable tool in assessing patients with intestinal symptoms (2).



CURRENT USES OF FAECAL CALPROTECTIN

1. Discriminating irritable bowel syndrome from inflammatory bowel diseases

Faecal calprotectin has been approved by the National Institute for Clinical Excellence (NICE) for helping distinguish between possible Crohn's disease or ulcerative colitis (collectively termed inflammatory bowel disease or IBD) and irritable bowel syndrome (IBS) (3). This is important because IBS is common in the general population (affecting 10-20% of people (4)) and is the predominant cause of lower bowel symptoms in patients attending GP appointments. Unlike IBD, IBS is not associated with the development of serious complications or co-morbidities, but the overlap in the symptoms of IBD and IBS often make a definitive diagnosis difficult without invasive investigations, such as a colonoscopy. Indeed, there is no specific diagnostic test for IBS, meaning that its diagnosis relies on excluding other, more serious conditions. Prior to the approval of faecal calprotectin as a diagnostic test, clinicians would rely on measuring C-reactive protein (CRP) to assess for the presence of inflammation. CRP is a protein that increases in response to inflammation anywhere in the body, but an elevated result gives no indication as to where the inflammation is coming from. Unfortunately, some patients with IBD will not have an elevated CRP (5), while patients with IBS could have an elevated CRP because of unrelated inflammation elsewhere in their bodies. Faecal calprotectin has been repeatedly shown to outperform CRP as a screening test (2, 6) and is a highly sensitive and specific tool for identifying patients who require further investigation for possible IBD (sensitivity 0.93; specificity 0.96 in adults) (7). It is particularly useful since the negative predictive value is exceptionally high (>99.8%) meaning that a normal result in a symptomatic patient effectively excludes IBD (7), and thereby reduces the need for unnecessary endoscopic investigations. An elevated result, on the other hand, does not diagnose IBD – since there are other causes of neutrophils entering the intestine – but rather indicates that further tests are necessary (8).

2. Assessing disease activity in IBD

Another important use of faecal calprotectin is in the assessment of patients with an established diagnosis of IBD. Because faecal calprotectin is more sensitive and specific than CRP, and correlates better with disease activity – whether assessed endoscopically (9) or histologically (10) – it has become an invaluable tool in assessing symptomatic IBD patients. Importantly, even in a patient with a confirmed diagnosis of IBD, abdominal symptoms are not always due to intestinal inflammation. Indeed, IBS and other intestinal disorders, such as bile acid malabsorption or bacterial overgrowth, are common and can mimic active IBD (11).

Ensuring that IBD treatments are not erroneously used for non-inflammatory gastrointestinal disorders – or vice versa – is not only important to ensure patients get symptomatic relief, but is necessary in order to avoid exposing patients to the risks or side-effects of immunosuppressive treatment that they do not require.

3. Deciding when to stop treatments in IBD.

Once IBD patients have entered clinical remission, a common question is whether they can now stop their medication. In this situation, it is important to distinguish between a patient who is well because of the medication they are taking (and who would become unwell if it were stopped) and a patient who is well and no longer needs to be on regular treatment. In the STORI trial, an elevated faecal calprotectin was shown to predict subsequent relapse in Crohn's disease patients who stopped infliximab following a period of sustained remission (12). Similar data have since been published for a range of other IBD treatments (13) leading to faecal calprotectin being routinely checked prior to considering whether to de-escalate a patient's treatment. In this way, it is possible to avoid future disease flare-ups by not stopping treatment that patients still require.

4. Assessing for post-operative recurrence of Crohn's disease.

In Crohn's disease patients who require an intestinal resection, a standard part of the subsequent management is to assess for disease recurrence at 3-6 months post-operatively (14). This is done because Crohn's disease frequently recurs, and early recurrence carries the highest risk of further disease complications. Historically, this assessment has been done endoscopically by examining the anastomosis for evidence of recurrent inflammation or ulceration. It has been shown, however, that faecal calprotectin normalises following an intestinal resection and is a sensitive marker of disease recurrence. Importantly, the negative predictive value (NPV) of faecal calprotectin in this setting is high meaning that colonoscopy could potentially be avoided. For example, in a prospective study of 135 post-operative Crohn's disease patients from Australia and New Zealand, the NPV was 91% which meant that colonoscopy could have been avoided in 47% of patients (15). Other studies have found similar results (16, 17) although it is clear that the positive predictive value is lower, emphasising that the true value of faecal calprotectin is in identifying patients who do not require a colonoscopy.

CURRENT CHALLENGES FOR COLLECTING AND TESTING OF FAECAL CALPROTECTIN

Although the introduction of faecal calprotectin testing has substantially helped in discriminating IBD from IBS and in the management of IBD patients, its use in clinical practice is not without logistical challenges. It is clear, for example, that calprotectin is not as stable as was first thought, with levels being significantly lower after 7 days storage at room temperature (18).

Current recommendations are therefore that samples should be kept for no longer than 3 days at room temperature since this does not appear to affect the result (18). It is also clear that there is variability between available assays, precluding direct comparison of results if they have not been performed using the same assay (19). In practical terms, however, one of the biggest challenges is in the delay between requesting the test and receiving the result. Samples are frequently not received at the laboratory because they have been lost in transit or patients forget to provide them (or choose not to) (20).

Some ELISA-based assays are also performed in batches, requiring a certain number of samples to be accrued before the batch is run – leading to potential delays. Indeed, even when results are received, the time that has elapsed between the request and the result often means that clinicians must re-examine the notes to remind themselves of the clinical details before decisions can be made. This is compounded by the fact that patients will have left the clinic, and so additional letters / phone-calls are required to inform patients of any treatment changes that may now be required.

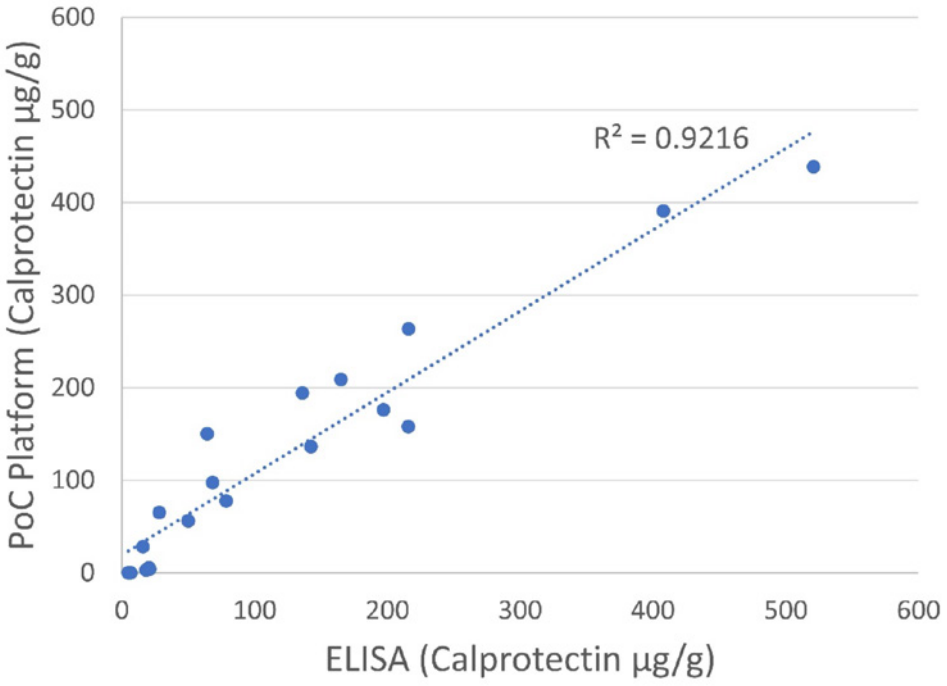
THE BENEFITS OF POINT-OF-CARE TESTING

In other areas of medicine, point-of-care (POC) testing has provided significant benefits for patient care. For example, patients taking warfarin, an oral anticoagulant that requires regular monitoring to ensure that the effect is within the therapeutic range, POC testing has been shown to significantly increase the time that patients are in the therapeutic range, compared to lab-based testing which involves an inevitable delay between in the test being performed and the result being received (21).

Similar benefits have been reported for POC testing of CRP for identifying potential bacterial infections (22), of HbA1C in identifying pre-diabetic patients (23), and of HbA1c and cholesterol testing in primary prevention of cardiovascular disease (24). As well as reducing delays in decision making, leading to better disease control, POC testing has also been shown to facilitate more frequent testing, to improve patient satisfaction, and reduce unnecessary treatment / referrals (25). A POC faecal calprotectin test, such as the one developed by AgPlus Diagnostics, would potentially overcome many of the logistical challenges around using faecal calprotectin in clinical practice. If used to distinguish between IBS and possible IBD, for example, a rapid POC result would enable GPs to immediately reassure patients with normal levels that they do not have IBD and begin treatment for IBS, while also expediting referrals for patients with elevated levels. This would be cost and time saving both for healthcare professionals and patients and – by facilitating earlier referral, diagnosis and treatment – lead to better clinical outcomes. Similarly, in IBD patients, the ability to regularly check for the presence of intestinal inflammation would be expected to reduce unnecessary clinic visits, empower patients to have more ownership of their condition (leading to improved knowledge and motivation), more rapidly identify ineffective treatments, and ultimately lead to improved disease control. These benefits, which should all lead to improvements in patients' quality of life, would require a POC faecal calprotectin test to perform as well as lab-based testing. Data from AgPlus Diagnostics demonstrates a high correlation between POC and lab-based faecal calprotectin results, suggesting that the potential benefits of POC testing could realistically be achieved (Figure 1).

Figure 1. Correlation between ELISA and point-of-care faecal calprotectin results

Correlation in faecal calprotectin results between ELISA and point-of-care tests in 19 stool samples.



CONCLUSION

In summary, the introduction of faecal calprotectin testing has had a major positive impact on the allocation of healthcare resources – reducing unnecessary investigations and enabling ineffective treatments to be identified promptly without the need for multiple endoscopic investigations. Challenges still remain, however, and it is anticipated that point-of-care testing will be an important step in addressing many of these, as it has been in other clinical situations.

REFERENCES

1. J. A. Tibble, G. Sigthorsson, R. Foster, I. Forgacs, I. Bjarnason, Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. Gastroenterology 123, 450-460 (2002).
2. S. B. Menees, C. Powell, J. Kurlander, A. Goel, W. D. Chey, A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol 110, 444-454 (2015).
3. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. (2013 http://www.nice.org.uk/guidance/dg11).
4. C. Canavan, J. West, T. Card, The epidemiology of irritable bowel syndrome. Clin Epidemiol 6, 71-80 (2014).
5. S. Vermeire, G. Van Assche, P. Rutgeerts, Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 55, 426-431 (2006).
6. J. Langhorst et al., Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. Am J Gastroenterol 103, 162-169 (2008).
7. P. F. van Rheenen, E. Van de Vijver, V. Fidler, Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ 341, c3369 (2010).
8. N. A. Kennedy et al., Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16-50 years. J Crohns Colitis 9, 41-49 (2015).
9. A. M. Schoepfer et al., Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. Inflamm Bowel Dis 19, 332-341 (2013).
10. T. Sipponen et al., Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther 28, 1221-1229 (2008).
11. J. F. Colombel, A. Shin, P. R. Gibson, AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review. Clin Gastroenterol Hepatol 17, 380-390 e381 (2019).
12. E. Louis et al., Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 142, 63-70 e65; quiz e31 (2012).
13. A. Buisson et al., Faecal Calprotectin Is a Very Reliable Tool to Predict and Monitor the Risk of Relapse After Therapeutic De-escalation in Patients With Inflammatory Bowel Diseases. J Crohns Colitis 13, 1012-1024 (2019).
14. C. A. Lamb et al., British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 68, s1-s106 (2019).
15. E. K. Wright et al., Measurement of fecal calprotectin improves monitoring and detection of recurrence of Crohn's disease after surgery. Gastroenterology 148, 938-947 e931 (2015).
16. C. Mowat et al., Mercaptopurine versus placebo to prevent recurrence of Crohn's disease after surgical resection (TOPPIC): a multicentre, double-blind, randomised controlled trial. Lancet Gastroenterol Hepatol 1, 273-282 (2016).
17. F. Veyre et al., Low Levels of Fecal Calprotectin 3 Months After Surgery Predict Subsequent Endoscopic Postoperative Remission in Crohn's Disease. Dig Dis Sci, (2021).
18. A. Lasson et al., The intra-individual variability of faecal calprotectin: a prospective study in patients with active ulcerative colitis. J Crohns Colitis 9, 26-32 (2015).
19. S. J. Whitehead, J. French, M. J. Brookes, C. Ford, R. Gama, Between-assay variability of faecal calprotectin enzyme-linked immunosorbent assay kits. Ann Clin Biochem 50, 53-61 (2013).
20. A. Buisson et al., Comparative Acceptability and Perceived Clinical Utility of Monitoring Tools: A Nationwide Survey of Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 23, 1425-1433 (2017).
21. M. Smith et al., Warfarin management using point-of-care testing in a university-based internal medicine resident clinic. Am J Med Sci 344, 289-293 (2012).
22. Y. Huang, R. Chen, T. Wu, X. Wei, A. Guo, Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. Br J Gen Pract 63, e787-794 (2013).
23. H. P. Whitley, C. Hanson, J. M. Parton, Systematic Diabetes Screening Using Point-of-Care HbA1c Testing Facilitates Identification of Prediabetes. Ann Fam Med 15, 162-164 (2017).
24. A. El-Osta et al., Does use of point-of-care testing improve cost-effectiveness of the NHS Health Check programme in the primary care setting? A cost-minimisation analysis. BMJ Open 7, e015494 (2017).
25. C. P. Price, Point of care testing. BMJ 322, 1285-1288 (2001).

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