## What calprotectin cut-offs should apply for IBD in general practice?

To the Editor

We write in response to the recent article by Dhaliwal *et al*[1] in *Frontline Gastroenterology*, which discussed the utility of faecal calprotectin (FC) levels in discriminating between inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). We applaud the authors' investigation of this important topic given the high prevalence of IBS in general practice, the understandable concern of practitioners in reliably excluding inflammatory conditions in patients with IBS and the imperative to avoid unnecessary diagnostic evaluations.

The main reported results of the Dhaliwal study support previous findings in the published literature that, at a cut-off of 50 µg/g, FC determination demonstrates adequate sensitivity and specificity to distinguish between IBS and IBD.[2] The authors note, however, that raising the cut-off to 100 µg/g 'does further improve' sensitivity and specificity of the FC test, and improves the negative predictive value (NPV) to 97% from 87%. This statement highlights several practical concerns that we believe are of substantial importance for both general practitioners and medical policy decision-makers when interpreting the extensive literature on the role of FC in differentiating IBS and IBD.

First, it is essential for readers to understand which condition (IBS or IBD) is selected as the 'target' when constructing receiver operating characteristic curves for sensitivity and specificity of FC. Although the authors state that '[performance characteristics] for diagnosing IBD… were calculated at different FC cut-off values', it appears they actually use IBS as the target condition for IBS versus IBD in table 3, as evidenced by the increase in sensitivity and (slight) reduction in specificity produced by raising the cut-off. Using the authors' data and switching the target condition to IBD for an indication of IBS versus IBD at FC 50 µg/g yields a sensitivity of 77.7 and specificity of 87.5, the inverse of what is reported in table 3.

Unfortunately, this inconsistency in selecting the target condition is not unusual in the published literature for FC and may contribute to the widespread perception among medical policy decision-makers in the USA that there is a 'lack of consensus for appropriate cut-off values for FC'.[3]

Second, we would like to remind readers that, unlike sensitivity and specificity, which are fixed performance characteristics of a test, the NPV and positive predictive value (PPV) of a test are dependent on the prevalence of the target condition in the practitioner's population.[4] Although Dhaliwal *et al* do not explicitly state the prevalence figures that they used to calculate NPV and PPV, it is readily shown that the authors, by convention, used the prevalence of IBS and IBD in their study population (144 of 292 (49%) subjects had Rome II confirmed IBS; 148/292 (51%) had IBD) to calculate their reported predictive values.

However, the prevalence of IBD and other inflammatory aetiology of symptoms (cancer, microscopic colitis, etc.) in patients who meet Rome III criteria without alarm features in a typical general practice setting is 3% or less.[5–8] Since the primary concern of general practitioners when initially evaluating a patient with altered bowel patterns and abdominal pain is to exclude the presence of these relatively uncommon but serious organic inflammatory conditions, a lower cut-off of 50 is optimal for this clinical setting because it minimises false negatives. Therefore, using Dhaliwal's sensitivity/specificity values for IBS versus IBD at FC 50 µg/g (77.7 and 87.5, respectively, when the target condition is IBD), it can readily be shown that the NPV of FC in Rome III qualified patients presenting to a general practitioner is ~100% (assuming a 1% prevalence of IBD).

It has been shown that much of the cost attributed to IBS arises from the time and resources used to establish the diagnosis and to rule out inflammatory conditions; 50%–75% of the overall costs attributable to IBS arise from the use of invasive endoscopic procedures.[9 10] Like others, we argue that use of the FC test, at the manufacturer's recommended cut-off of 50 µg/g, is clinically useful and cost-effective, with little risk of an error that would pose serious risks.[2] Indeed, previous work has shown that the routine use of calprotectin to exclude inflammatory changes results in substantial economic savings.[2 11]

In summary, while we applaud the work of Dhaliwal *et al*, in confirming the value of FC in the clinical setting where IBD and IBS are the primary concerns, we caution that greater insight is required in the interpretation of such studies, particularly with regard to establishment of the target condition against which test performance characteristics are measured. We also reiterate that FC has high clinical utility in general practice settings to exclude IBD or other inflammatory conditions of the colon, is Food and Drug Administration (FDA)-cleared for this indication, and is also recommended by National Institute for Health and Clinical Excellence (NICE) guidelines and several gastrointestinal (GI) specialty societies for this purpose.

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