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**Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration - can a repeat test be used?**

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# Annals of Clinical Biochemistry

**Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration – can a repeat test be used?**

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Manuscripts

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3 **Editorial**  
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8 **Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of**  
9 **patients with symptoms and low faecal haemoglobin concentration – can a**  
10 **repeat test be used?**  
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51 **Short title:** FIT in safety-netting  
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55 **Keywords:** colorectal cancer, colonoscopy, COVID-19, faecal immunochemical test,  
56 faecal haemoglobin, lower bowel symptoms,  
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10 Quantitative faecal immunochemical tests for haemoglobin (FIT) are increasingly  
11 being used in the UK and elsewhere to assist in the assessment of patients  
12 presenting to primary care with lower bowel symptoms to guide referral for further  
13 investigation, often colonoscopy. A very low or undetectable faecal haemoglobin  
14 concentration (f-Hb) has been demonstrated in multiple studies to have a very high  
15 negative predictive value for colorectal cancer (CRC).<sup>1</sup> In 2017, the National  
16 Institute for Health and Care Excellence (NICE) issued Diagnostics Guidance DG30  
17 which encouraged the use of FIT in the assessment of patients at low risk of CRC.<sup>2</sup>  
18 These guidelines were then incorporated into the NICE guidance NG12 on referral of  
19 patients considered at risk of CRC.<sup>3</sup> DG30 advises that patients with symptoms  
20 considered low risk for CRC and with f-Hb < 10ug Hb/ g do not need to be referred  
21 on the NHS England two week wait pathway and can instead be monitored in  
22 primary care.  
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43 There are an ever-growing number of publications demonstrating the value of FIT as  
44 a rule-out investigation for CRC, in high-risk as well as low-risk symptomatic  
45 patients, particularly as a rule-out test for CRC.<sup>4</sup> The reason for this significant  
46 interest was that the rapidly evolving evidence was that FIT provides a simple and  
47 inexpensive test that might stem some of the ever increasing demands on scarce  
48 endoscopy services, which do not actually lead to significantly more CRC being  
49 detected.<sup>5</sup>  
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9 Then, the COVID-19 pandemic arrived, which led to almost complete cessation of  
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11 endoscopy. This stimulated much discussion about how the many patients already  
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13 referred for investigation of symptoms, and the new patients presenting with  
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15 symptoms, could be provided with the best care in the challenging circumstances.  
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17 Recent NHS England and NHS Improvement guidance stated: <sup>6</sup> Clinicians may  
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19 prioritise referrals using patient-reported symptoms together with blood test results  
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21 (including full blood count (FBC) and FIT. The accompanying clinical guidance  
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23 stated that patients should therefore be prioritised for further investigation according  
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25 to a triage process, not documented here in detail, which involved FIT. The  
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27 guidance from the Scottish Government is similar and states that, when colonoscopy  
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29 is either severely restricted or not available, a numerical f-Hb result and a FBC  
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31 should be available whenever possible before a patient is considered for  
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33 investigation of large bowel symptoms.<sup>7</sup> Both English and Scottish guidances have  
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35 higher thresholds (f-Hb >100 µg Hb/g faeces in England; f-Hb >400 µg Hb/g faeces  
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37 in Scotland) whereby patients require urgent investigations.  
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47 In both sets of guidance, patients with a f-Hb <10 µg Hb/g faeces are considered  
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49 very low risk for CRC. In England, the guidance states these patients with NCI2  
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51 symptoms and f-Hb <10 µg Hb/g faeces should be safety-netted to a patient tracking  
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53 list and, in Scotland, those with a f-Hb <10 µg Hb/g faeces should only be offered  
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55 investigation where there is significant on-going clinical concern.  
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3 The guidance from England states that appropriate safety-netting should be put in  
4 place for patients who do not require immediate investigation, to allow for a further  
5 clinical assessment should their symptoms worsen. The Scottish guidance has  
6 details on use of FIT: if a patient has a FIT result  $<10 \mu\text{g Hb/g faeces}$ , but has  
7 persistent symptoms, a primary care review within six weeks is recommended and, if  
8 there is still doubt as to whether or not to refer, a repeat FIT may be of value.  
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10 Further, in the Scottish guidance, it is documented that, in the recovery phase of  
11 COVID-19, repeating FIT in patients on the waiting list may help prioritisation.  
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25 It is well documented that FIT are not the perfect diagnostic test and, although FIT  
26 are far better than symptoms alone in the detection of CRC,<sup>8</sup> some cases of CRC do  
27 have f-Hb  $<10 \mu\text{g Hb/g faeces}$ . In consequence, for such patients, especially if their  
28 symptoms continue, safety-netting is unequivocally recommended. Safety-netting  
29 strategies are designed so that people at low risk, but not at no risk, of having CRC  
30 are actively monitored in primary care to see if the risk of CRC changes.<sup>9</sup>  
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32 Interestingly, as per the Scottish guidelines, recent reviews,<sup>10</sup> a “best practice”  
33 guidelines paper commissioned by the Royal College of Pathologists,<sup>11</sup> and a recent  
34 paper,<sup>12</sup> all propose that repeat FIT *might* be of value, if symptoms persist, as a  
35 component of safety-netting approaches.  
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52 However, the current problem is that there is no objective evidence to support or  
53 refute the use of repeat FIT in patients with f-Hb  $<10 \mu\text{g Hb/g faeces}$ , who are  
54 probably at very low risk of CRC and other significant bowel diseases. Several  
55 asymptomatic population-based CRC screening programmes use two or three faecal  
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specimens, but these are taken from consecutive bowel motions with a view to enhancing sensitivity for the detection of CRC: lowering the f-Hb threshold achieves the same laudable aim. Some FIT-based post polypectomy screening programmes use two samples, for example, that conducted in South Australia.<sup>13</sup> There are only three studies, to our knowledge, that examine multiple specimen collection in the clinical setting of assessment of patients with symptoms: two have used quantitative FIT on sequential bowel motions<sup>14,15</sup> and one has used a qualitative FIT and three specimens.<sup>16</sup> However, again these replicate specimens have been collected to investigate whether sensitivity for CRC detection can be enhanced by using more than one specimen, not repeat specimens for the safety-netting of patients with f-Hb <10 µg Hb/g faeces.

There is an urgent need for research into several crucial aspects of the application of repeat FIT in patients presenting with symptoms and with f-Hb <10 µg Hb/g faeces. Necessary prerequisites to the optimum care of this large group of patients include generation of objective evidence on :

- should recommendations be developed regarding the most appropriate time interval that should elapse before a second FIT is requested: should this depend on symptom severity,
- should more than one repeat FIT be done if symptoms persist beyond the finding of two low f-Hb,

- if the repeat result is f-Hb  $\geq 10$   $\mu\text{g Hb/g faeces}$ , should this be the criterion for referral for further investigation, or should a further repeat FIT be performed for confirmation of an increase in f-Hb,
- should a threshold of  $<10$   $\mu\text{g Hb/g faeces}$  be applied as the criterion for reassurance, watching and waiting, or further safety-netting, since available FIT analytical systems have detectability characteristics<sup>17</sup> that are below this f-Hb,<sup>18</sup> allowing f-Hb to be detected at very low f-Hb and quantitated at lower f-Hb than this threshold: lower thresholds do increase diagnostic sensitivity for CRC, although positivity and colonoscopy demands do increase,<sup>19</sup>
- should repeat or serial estimates of f-Hb in specimens from an individual patient be performed on one type of FIT system, since different systems give different numerical f-Hb results, especially at low f-Hb,<sup>18</sup> and
- should professional bodies provide further best practice guidelines on how the sources of pre-analytical, analytical and post-analytical variation can be minimised to ensure that any changes seen in an individual are due to important physiological or pathophysiological deterioration.

We urge all those involved in application of FIT in assessment of patients with symptoms, especially those with f-Hb  $<10$   $\mu\text{g Hb/g faeces}$ , to undertake pure or applied research, and/or report their findings to date, on repeat FIT, so that evidence can be gathered, lessons learned and best practice identified and ubiquitously translated into routine practice.

#### **Declaration of conflicting interests**



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45 Both authors participated equally in the generation of this work.  
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