Debate & Analysis

Low-risk bowel cancer symptoms:

is it time for FIT?

STOOL TEST TO DETECT BOWEL CANCER

In 2017, 30 710 patients were diagnosed with bowel cancer in the UK.[1] The disease carries a poor prognosis, being the second most common cause of cancer death in the UK.[2] There is a drive to detect cancer earlier as it correlates to a better outcome. In 2017, the National Cancer Patient Experience Survey published its results, showing that 36.4%[3] of patients with bowel cancer have seen their GP two or more times before they are diagnosed with cancer. One of the many initiatives to address this issue is through detecting small amounts of blood in the stool of patients with low-risk symptoms. In 2015, the National Institute for Health and Care Excellence (NICE) suggested the use of guaiac-based faecal occult blood tests (gFOBT) for this purpose. This, however, was met with opposition due to concerns about its relatively high false-negative value.[4] Hence gFOBT for this purpose never materialised.

In the meantime, GPs continue to find patients with low-risk bowel symptoms diagnostically challenging, as GPs often have to rely on their own clinical judgement to decide if cancer is a possible diagnosis. This year, we will see a new stool test, the faecal immunochemical test (FIT), replacing the gFOBT, which NICE proposes as the way forward. This article first defines the low-risk symptomatic patient, followed by a brief description of the two stool tests. It then analyses evidence that has informed NICE recommendations for FIT, concluding with a summary and a future recommendation.

WHO IS THE LOW-RISK SYMPTOMATIC PATIENT?

NICE guidelines[5] have set clear criteria on what are considered high-risk bowel symptoms that require urgent 2-week wait (2WW) referral. These can be referred to in Box 1. Patients with bowel symptoms outside these criteria are considered to have low-risk symptoms. They are deemed to have <3% risk of having bowel cancer. With reference to the current guideline, these patients can be summarised in Box 2.

Box 2 shows that low-risk patients must have two important features: first, they have no rectal bleeding, and, second, they should have only a single bowel symptom. Patients who are aged <40 years are less likely to have bowel cancer, and other possible causes should be excluded in the first instance.

Box 1. High-risk symptoms/signs warranting 2-week wait referral

Bowel symptoms/signs	<40 years	40–49 years	50–59 years	≥60 years
Rectal/abdominal mass	2ww	2ww	2ww	2ww
Unexplained rectal bleeding *and* abdominal pain/change in bowel habit/weight loss/ iron deficiency anaemia	2ww	2ww	2ww	2ww
Unexplained weight loss *and* abdominal pain		2ww	2ww	2ww
Unexplained rectal bleeding			2ww	2ww
Iron deficiency anaemia				2ww
Change in bowel habit				2ww

Shaded cells = low-risk bowel cancer symptoms. 2WW = 2-week wait.

GFOBT AND FIT

Both gFOBT and FIT can detect microscopic blood in the stool, which is indicative of bowel cancer, especially with older patients. However, they have different detection methods. gFOBT indirectly detects the presence of blood through the oxidation of guaiac, by hydrogen peroxidase. FIT on the other hand uses antibodies to detect human globin very specifically. There are two FIT types available: the qualitative FIT, which is a visual dipstick technique, and the quantitative FIT, which is analysed using automated devices. The quantitative FIT is the stool test proposed by NICE.

All subsequent references to FIT will refer to quantitative FIT.

IS FIT BETTER THAN GFOBT?

FIT is the tool of choice for bowel cancer screening in many countries, including Japan, South Korea, the Netherlands, Spain, and Australia. This is because it has substantive evidence of being better than gFOBT at detecting bowel cancer.[6] We should be wary of not extrapolating this evidence to include symptomatic patients, as incidence rates of bowel cancer are likely to be higher.

Currently, evidence for FIT is not as robust in low-risk symptomatic patients. Many types of FIT are manufactured worldwide, and each of them can be set up to detect blood in the stool at different calibrations. There seems to be no agreed standards on which FIT manufacturer or which Hb concentration cut-off to use, hence studies are not comparing the same type of FIT. This leads to difficulties in determining any outcome.

In the UK, NICE has decided to recommend only three types of FIT. These are the OC Sensor, HM-JACKarc, and FOB Gold quantitative unit, at 10 µg of haemoglobin per gram of faeces as the cut-off.[7] The main source of evidence for the above FIT types that informed NICE

Box 2. Bowel cancer risk according to symptoms and age[a]

Single bowel symptoms/signs	40 years	50 years	≥60 years
Iron deficiency anaemia	Low risk	Low risk	High risk
Change in bowel habit	Low risk	Low risk	High risk
Unexplained weight loss	Low risk	Low risk	Low risk
Unexplained abdominal pain	Low risk	Low risk	Low risk

[a]Patients considered low risk must only have a single symptom/sign as above and no other additional symptoms/ signs.

Table 1. Diagnostic accuracy estimates of stool test, adapted from NICE guidelines[7]

	gFOBT, % (95% CI)	OC Sensor (FIT), % (95% CI)	HM-JACKarc (FIT), % (95% CI)
Sensitivity	50.0 (15.0 to 85.0)[8]	92.1 (86.9 to 95.3)[9]	100 (71.5 to 100)[9]
Specificity	88.0 (85.0 to 89.0)[8]	85.8 (78.3 to 91.0)[9]	76.7 (72.6 to 80.3)[9]
False-negative	50.0	7.9	0
False-positive	12.0	14.2	23.2

gFOBT = guaiac-based faecal occult blood test.

guidance was Westwood *et al*[9] in their systemic review in 2017. They followed strict systemic review methodology and managed to compile nine diagnostic cohort studies from a total of 113 eligible. However, as the study pointed out, one of the most important weaknesses was that most of the studies in their review included patients with rectal bleeding, which is a high-risk bowel symptom. The results are summarised in Table 1. Note that evidence for FOB Gold quantitative unit is yet to be published.[7]

Referring to Table 1, the specifications of the gFOBT and the two FIT can begin to be compared, which at a glance shows FIT is much better in terms of sensitivity and false-negative value. It has been argued that the slightly lower specificity for FIT in detecting bowel cancer is negated by its ability to detect high-risk adenoma and other serious bowel pathology in patients.

However, caution should be taken with such a comparison, as results from the gFOBT were taken from a different study, van Rheenan *et al*.[10]

RULE-OUT TEST?

Earlier in the text, it was highlighted that gFOBT for the low-risk symptomatic group never became popular due to concerns about its high false-negative percentages, values ≤50%. The risk of false reassurance to patients was deemed too high, as it could lead to even more delay in cancer diagnosis. Referring to values on Table 1, the false-negative for FIT would be between 0–7.9%. If compared with other 'rule-out tests' often used in the primary care setting, the rate would seem acceptable. For example, stool tests to detect calprotectin for the investigation of inflammatory bowel disease has a false-negative of 6%,[10] and a chest X-ray to detect lung cancer has a false-negative rate of ≤20%.[11]

SUMMARY

NICE's suggestion of using FIT as a stool test in low-risk bowel cancer patients has met with some hesitancy from the medical community, as 3 years ago similar guidance using gFOBT was rejected due to a high false-negative value. However, the low false-negative value of 7.9% with FIT would be considered by many as an acceptable risk, with the upside of potential benefits in earlier bowel cancer detection and a moderate false-positive rate. Hence, we should consider embracing FIT as a 'rule-in test' to warrant onward referral if positive and be comfortable that a negative result is relatively reassuring.

It is important that future research should try to look into methods to standardise results from different FIT companies at multiple Hb/g faeces thresholds. This will allow large-scale collaboration studies internationally.

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Provenance
Freely submitted; externally peer reviewed.

Competing interests
The author has declared no competing interests.

DOI: https://doi.org/10.3399/bjgp19X704501

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