# FIT Negative Follow-Up

## Safety-netting patients with a low faecal haemoglobin concentration and modifying the current patient pathway to improve patient care.

Dr. James Turvill, Consultant Gastroenterologist,
York Teaching Hospital NHS Foundation Trust

NHS
York Teaching Hospital
NHS Foundation Trust

Dr. James Turvill is a screening endoscopist within the Bowel Cancer Screening Programme and has an interest in inflammatory bowel disease and gastrointestinal cancer. Since 2008 he has developed a research interest in the use of biomarkers to facilitate the diagnosis and monitoring of gastrointestinal disease. Currently he is working with Y&H AHSN in the implementation of a faecal calprotectin (fCAL) care pathway to support NICE DG11 and with the Y&H Cancer Alliance in the introduction of faecal immunochemical testing (FIT) in patients with suspected colorectal cancer.

Here Dr. Turvill summarises his presentation made at the Digestive Diseases Day, where he discussed his study at York Hospital and the importance of negative FIT follow-up for patients.

### BACKGROUND

*"NICE guidance is about finding people with cancer so that we can make a difference. FIT should be seen as a technology designed to facilitate this process. So I am a little unsettled about the concept of using FIT as a test to 'rule-out' colorectal cancer (CRC), though this is what it is good at. Instead we need to use it to 'rule-in' patients and so find CRC early. And here lies the challenge.*

### INTRODUCTION

*In thinking about FIT negative follow up we need to understand what is currently happening in primary and secondary care and then, what a FIT positive result will mean for the future.*

*Then for the FIT negative patient we need to consider* ***consequentialism*** *over* ***essentialism****.*

*If you look at a cohort of patients referred from primary care fulfilling NICE NG12, that is at high risk of CRC, around two-thirds of patients will have 'functional disorders' (predominantly the irritable bowel syndrome (IBS), but also benign anal canal bleeding and iron deficient anaemia of unknown cause).*

*Currently it is this group of patients that secondary care clinicians are focussing on since these are judged to increase healthcare costs by the time constrained consumption of resource in achieving a diagnosis.*

*Then 4% of patients will have CRC and a further 4% will have significant polyps (those 10mm or larger). Then there will be a complex, non-malignant group of patients, making up 12%, generally termed 'organic enteric disease' that will need secondary care intervention.*

*This includes patients with IBD, microscopic colitis and diverticulitis.*

*There will be another similarly sized group with diminutive polyps (<1 cm). Lastly, around 4% of the cohort will have non-enteric disease and within this group there will be other cancers, which FIT will not identify. This means that around 40% of all the cancers in patients referred through NICE NG12 with suspected CRC will be non-CRC.*

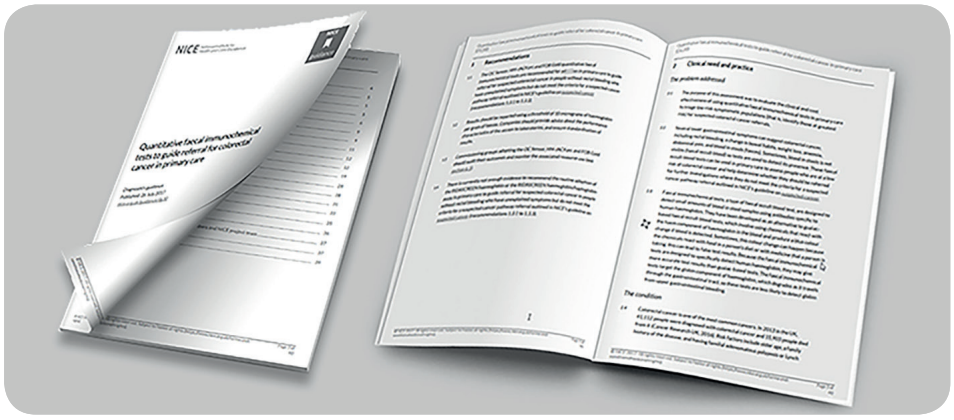
*Therefore, the success of using FIT will not depend on how well it identifies CRC but on how well it helps us identify the 40% of cancer patients without CRC that are currently being referred through NG12.*

### *So how does FIT allow us to untangle this disparate group?*

*We have looked prospectively at 700 patients referred from primary care under NG12 with suspected CRC. Each patient provided two stool samples prior to investigation allowing us to perform two FIT and two fCAL tests. We had hypothesized that a repeat test might improve the specificity-sensitivity profile of the assays and so enhance diagnostic accuracy.*

*We tested FIT using the Kyowa Medex HM-JACKarc and calprotectin using BÜHLMANN fCAL® ELISA (both supplied by Alpha Laboratories Ltd).*

*If we extrapolate our data to a population of 1000 patients and apply 'detectable' haemoglobin as the FIT cut-off value you get 290 positive, and 710 negative results. You will pick up almost all, but importantly not all, CRC (I am reconciled to the fact that regardless of what the cut-off is, some, but very little CRC will be missed).*



*Using this FIT cut-off most 'IBS' patients and those with diminutive polyps will be spared, initially at least, investigation. But FIT will miss half of those with organic enteric disease, over half of those with significant polyps and, importantly, half of those with other non-enteric cancers.*

### *So clearly FIT is a game changer.*

*But not perfect.*

*If you apply FIT using 10 µg/g cut off [Figure 1], the proportion of missed CRC will double. But, the numbers will still be very small.*

*Three patients in 1000 will be missed who would have been picked up using FIT for 'detectable' haemoglobin. But you will have reduced the number of FIT positive patients with IBS to a third. The total number of patients with a positive FIT will now be 140 patients.*

*This then allows you to start to use healthcare resource much more efficiently. You have the starting potential to spare 860 patient investigations from the original 1000 patient cohort. That resource can be directed at other patient groups, such as those fulfilling NICE DG30.*

*Our findings suggest that using the FIT ≥10µg/g cut off you get the optimal sensitivity (82%) and specificity (88%), with a high NPV (99%) and an acceptable PPV (27%).*

## FIT NEGATIVE PATIENTS

*So I have made the presumption that FIT negative care begins when a high risk patient has one FIT <10 µg/g.*

*In our putative population of 1000 patients we now have 860 such patients and within this group <1% will have CRC, 3% will have significant polyps and 3% non-CRC cancer. A significant number of patients with organic enteric disease will remain, but over 90% will have 'IBS'.*

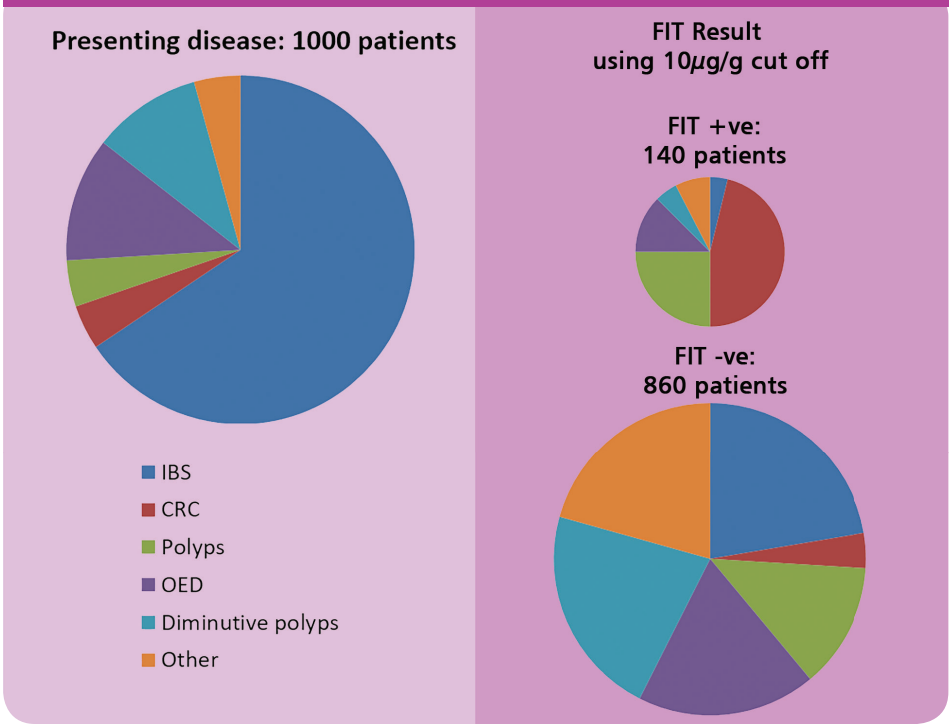
### *What do we do next? What if you repeat the FIT or add in a fCAL?*

*If you repeat the FIT and you are looking solely for CRC you will want either of, rather than both, of the two FIT to be positive (to 'rule in' not 'rule out'). In so doing we found that you could marginally increase the sensitivity and specificity of FIT, but not significantly.*

*Furthermore the repeat FIT requires additional cost, time and may reduce patient compliance.*

*We conclude that in symptomatic patients at high risk, a repeat FIT prior to referral would fail to detect CRC in those who were initially FIT negative. Perhaps their biology is different. Two FITs may prove useful for screening (it may offer cost savings) but not in the work up of symptomatic patients.*

**Figure 1: Applying FIT using a cut off of 10µg/g**




*Adding fCAL gives no diagnostic advantage because it reduces the PPV.*

### *Can you identify the FIT negative patients with CRC if you apply particular patient symptomatology?*

*The short answer here is no. Symptoms are no less specific in FIT negative patients than they are in the unselected cohort.*

*Neither are we currently able to improve the sensitivity and specificity of FIT based on symptomatology (although this may come). Currently for example FIT cannot be applied in the low risk population (DG30) where there is rectal bleeding. However we found no difference in those presenting with or without rectal bleeding.*

### Managing FIT negative patients for the future

*In thinking about the negative FIT we need to leave the technology behind and return to the patient. Perhaps we need to look again at NICE CG27, the NICE guidance that pre-dated NG12.*

*Here it states that 'in patients with equivocal symptoms who are not unduly anxious, it is reasonable to use a period of 'treat, watch and wait' as a method of management'. Quite what this will mean in practice is as yet uncertain.*

*But the majority of patients will have functional disease and some will settle with expectant management. As many as 90% of younger, low risk patients will respond to local supportive measures but it is uncertain how many will do so in this population. Perhaps 50%, optimistically.*

*So the key question is whether we will give this disparate group of patients, time to declare themselves. Will we treat them expectantly or will they all be sent for abdominal-pelvic CT scans to find the non-enteric cancer in a newly defined suspected cancer pathway?*

*Surely for FIT to be of any health economic benefit the clinician must be able both to apply clinical judgment if suspicious and so refer into a two week wait pathway, even if FIT negative, but also to treat symptomatically and review locally if judged appropriate.*

*In this way patient care is central and FIT supports the efficient use of resource.*

### *And who is going to carry that risk?*

*Will primary care carry this cohort of FIT negative patients in whom it is known that there is missed cancer and in whom referral would otherwise have taken place if NICE NG12 were applied?*

*Should GPs refer all patients anyway, FIT positive or negative alike, but the former urgently and the latter routinely? Or perhaps GPs should both retain clinical suspicion and initial management decision; treating FIT negative patients symptomatically without automatic referral. Some would be referred urgently and others routinely should they remain symptomatic or early if suspicion was high. Would CT requesting from primary care become the norm?*

*In my mind what is needed is for clinical suspicion to help safety-net the patient and this would be my preferred option.*

*continued....*

# FIT Negative Follow-Up continued .....

*When thinking this through it is important to recognise the strength of primary care as 'the good gatekeeper' while secondary care is the obligate investigator. So this measured, safety netted, clinical risk assessment of FIT negative patients should lie with primary care.*

## THE FUTURE?

*Currently the role of FIT both to support DG30 and most particularly NG12 is uncertain. A great deal of work is going on at the moment and we will have a much clearer idea soon.*

*I have it in mind that a pathway will develop something like the diagram below [Figure 2]. The future pathway will start with patients with lower gastrointestinal symptoms in the broadest sense (though there may be a number of exclusions such as rectal mass/ iron deficient anaemia and possibly fresh rectal bleeding in the young).*

*We know that the specificity of FIT is lower in younger patients so you have to factor in a pragmatic age cut-off where fCAL may become a more useful test. I have chosen 50 years. All patients over 50 years with lower gastrointestinal symptoms, where there is diagnostic uncertainty, irrespective of whether they currently do not fulfil NICE NG12, will have a FIT. I do not think rectal bleeding will prevent the use of FIT.*

*GPs will also include patients younger than 50 years where CRC is suspected. Because FIT is such a good diagnostic I think it acceptable to widen the net and not to be proscriptive.*

*Those who are FIT positive will be referred into the 'two week wait' pathway.*

*Those under 50 years and in whom CRC is not suspected should enter the fCAL pathway[1].*

*For those who are FIT negative, if cancer is still suspected then an urgent referral should be made anyway. Perhaps a CT will be the first investigation here. Otherwise these patients should be treated symptomatically and then reviewed within primary care.*

*If still symptomatic and under 60 years they should then enter the fCAL pathway but if older than 60 years, a routine referral should be made.*

*In time I suspect a workable and pragmatic pathway such as this will evolve.*

Overall, Dr Turvill concludes FIT is an excellent test and will capture almost all CRC. However, we must remain cognisant of its limitations and ensure that FIT negative follow-ups are conducted to avoid excess referral, and therefore dilution of the benefits of FIT, and encourage the partnering of FIT with clinical suspicion to ensure we capture as many of those cancers as possible.

A video of Dr. Turvill's presentation can be seen at **www.faecal-immunochemical-test.co.uk/events.**

### Reference:

1. www.valeofyorkccg.nhs.uk/rss/data/uploads/gastroenterology/faecal-calprotectin/faecal-calprotectin-leaflet-gp-0180816.pdf

***Figure 2: Potential Digestive Diseases Patient Pathway as proposed by Dr. James Turvill***