NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 3 July 2013

Comment number	Name and organisation	Section number	Comment	Response
1	Consultee 1: (NHS Professional)	1	Make cancer suspicion much much more explicit. Never (NEVER) use faecal calprotectin in over 60s - possibly not in over 50's. Negative faecal calprotectin does not exclude serious non-IBD causes of diarrhoea such as medications, bile salt malabsorption and collagenous colitis.	Thank you for your comment. The Committee notes that age is an important risk factor for cancer when considering people with lower gastrointestinal symptoms. In this regard, the Committee notes that there is differing opinion on what age cut-off to use for faecal calprotectin testing. The Committee is aware that other guidelines are, or will shortly be, in the process of being updated (for example, the BSG guidelines for IBS). Therefore, this guidance does not include specific ages in the recommendations but refers to NICE clinical guideline 27 “Referral for suspected cancer”, which cites age as one of a range of risk factors for consideration. Recommendations for faecal calprotectin to distinguish between IBD and non-IBD are limited to children who have been referred for specialist assessment. The Committee believes that specialists have the expertise to recognise the appropriate use and interpretation of faecal calprotectin testing.

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			More needs to be made of the results in the 50-200 or 300 range - in an earlier document it was suggested that it be repeated after 3 months - very sensible. How to deal with these results will be key to the effect on practice and costs - if it starts to be used more it could lead to increased referrals if all borderline results are referred and especially if they get colonoscopy and small bowel imaging/capsule endoscopy etc. More detail is needed to make it 'suitable guidance for the NHS'	Investigation of thresholds was included in the scope for the assessment and assessed by the External Assessment Group (and presented in the diagnostics assessment report). Upon consideration, the Committee believed that further data are needed before a recommendation could be made. Therefore, the Committee has recommended research into optimal cut-off values for tests and the investigation of repeat testing strategies in people with intermediate levels of faecal calprotectin (see section 7 of the guidance).
2	Consultee 2: (NHS Professional)	1	It appears from 1.1 that NICE is recommending that FCP is adopted as part of routine clinical practice within primary care IBS pathways and secondary care. If that is not correct or there are potential caveats then these need to be made clear However there does not yet appear to be evidence to support the commissioning of FCP in primary care IBS pathways outside of research studies It is inevitable that FCP will be used with the aim of providing reassurance to symptomatic IBS patients whom the GP has diagnosed IBS and did not initially plan to referral. This appears to have happened in Brighton and Hove PCT where FCP is part of the primary care IBS pathway. There is a significant risk that introducing FCP testing into primary care will lead to increased referrals of IBS	Thank you for your comment. The Committee was mindful that there are limited data on the use of faecal calprotectin testing in primary care. However, the Committee concluded that the assessment had demonstrated the benefit of using faecal calprotectin testing in adults who meet the specific criteria set out in section 1.1 of the guidance and the benefits were, on balance, generalisable to testing in primary care. The Committee recognised the potential for testing patients who were not originally considered for referral and the knock-on effect of

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			patients for endoscopy who do not ultimately have pathology and that the demands on endoscopy will increase If the intention is that FCP should only be used in the selected subgroup patients whom the GP's would otherwise have referred this should be made explicit as should the negative effects on cost savings. These are briefly mentioned including projections based on testing 25% and 50% of IBS patient	increased referrals to specialists. This was investigated in the assessment using an assumption of GPs testing 50% of symptomatic patients (pilot data suggest that approximately 25% of symptomatic patients would normally be referred for specialist assessment). The analysis showed that although the benefits from faecal calprotectin testing were reduced, faecal calprotectin testing is still cost saving. To ensure faecal calprotectin testing is used optimally, the Committee recommended that locally agreed pathways are in place for testing. It is envisaged that a range of local stakeholders will participate in such care pathway discussions.
3	Consultee 3: (Patient Organisation policy officer)	1	Crohn's and Colitis UK welcomes the provisional recommendations and supports further research in this area as recommended elsewhere in the guidance.	Thank you for your comment.
4	Consultee 5: (Manufacturer – Merck Sharp & Dohme Ltd)	1	MSD welcomes the opportunity to engage in the consultation process for the diagnostics guidance "Faecal calprotectin diagnostic tests to differentiate inflammatory bowel disease from irritable bowel syndrome".	Thank you for your comment.
5	Consultee 1: (NHS Professional)	2	Point of care tests have been evaluated in small controlled studies and not widely in routine practice. In studies practices will be well supported by the sponsor, a situation which is unlikely to pertain when in widespread use. This is likely to lead to reduced accuracy in practice outside of studies. Laboratory based tests are much more likely to be consistent.	Thank you for your comment. Comment noted.

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6	Consultee 1: (NHS Professional)	3	The report seriously underplays the effect that IBS has on patients - it does have a serious impact, SF36 shows that qol is just as bad in IBS as IBD. Thus 'prognosis' in terms of qol and work ability etc is seriously impaired in some patients. The differential also should include bile salt malabsortion in watery diarrhoea and collagenous colitis. These are severe, have specific treatments and would need hospital referral probably. The criteria for cancer suspicion need to be much more explicit (i.e. should not be used in over 60s with cobh or in 40-60 with cobh and bleeding) and also need Hb check to rule out IDA before cancer unlikely. The fact that around 40% of patients with cancer do not have red flags should be mentioned. Delays in diagnosis of IBD are very common and faecal calprotectin should be helpful here, agreed. average wait to diagnosis has been reported as 2.5 years.	Thank you for your comment. The Committee agrees that IBS can have a serious impact on a person's quality of life. This is captured in 3.13 of the guidance. Amendments have been made in sections 2 and 3 of the guidance to better reflect the impact of IBS on quality of life.
7	Consultee 2: (NHS Professional)	3	What is the recommended maximum age at which FCP screening is recommended as part of an IBS pathway. The TAC Pilot study seemed to consider FCP as appropriate test for patients up to 60 with change in Bowel Habit. This seems to old and a number of patients with colorectal cancer would end up with the incorrect reassurance of a negative FCP without colonoscopy.	Thank you for your comment. The Committee notes that age is an important risk factor for cancer when considering people with lower gastrointestinal symptoms. In this regard, the Committee notes that there is differing opinion on what age cut-off to use for faecal calprotectin testing. The Committee is aware that other guidelines are, or will shortly be, in the process of being updated (for example, the BSG guidelines for IBS). Therefore, this guidance does not include specific ages in the recommendations but refers to NICE clinical guideline 27 "Referral for

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				suspected cancer", which cites age as one of a range of risk factors for consideration.
8	Consultee 5: (Manufacturer – Merck Sharp & Dohme Ltd)	3	We would like to comment that in order to fully understand the context in which decisions regarding these technologies are made, it would be beneficial to fully reference the data provided in the draft guideline. For example, in Section 3.15, the proportion of patients with mild, moderate, or severe UC is not clearly explained and the supporting data are not referenced, which may hinder the understanding of the clinical background. In other instances, it is unclear why particular data sources have been chosen, i.e. the prevalence and incidence values for UC given in this guideline contradict values used in other current NICE guidance. We are pleased that the role of anti-TNF drugs in the treatment paradigm for both UC and Crohn's disease is recognised within the guideline.	Thank you for your comment. Full referencing can be found in the diagnostics assessment report.
9	Consultee 4: (Manufacturer - Thermo Fisher Scientific)	4	Please change "Thermo Fisher Scientific" into "Phadia AB, part of Thermo Fisher Scientific" (on both pages 15 and 60 of the pdf circulated)	Thank you for your comment. Amend accepted.

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10	Consultee 1: (NHS Professional)	4	It is critical that the tests used have very clear cut offs for normal, indeterminate and positive. Lab based tests generally work well with <50 as negative, 50-300 as indeterminate and >300 as abnormal. It is not at all clear whether the point of care tests and semi-quantitative tests perform as well in giving indeterminate results of the same meaning. More evidence is required on rapid and point Â of care tests and we need to be quite sophisticated in how we deal with indeterminate or else it will result in a lot more referrals. Otten shows this well with low sensitivity at 60 cut off for that test.	Thank you for your comment. Investigation of thresholds was included in the scope for the assessment and assessed by the External Assessment Group, with the results being presented in the diagnostics assessment report. Upon consideration, the Committee believed that further data are needed before a recommendation could be made. Therefore, the Committee has recommended research into optimal cut-off values for tests and the investigation of repeat testing strategies in people with intermediate levels of faecal calprotectin (see section 7 of the guidance). The External Assessment Group note that Otten's low sensitivity at 60ug/g is an outlier in figure 3 of the diagnostics assessment report. As specificity is high, it would be reasonable to expect fewer referrals rather than more.
11	Consultee 4: (Manufacturer - Thermo Fisher Scientific)	5	Section 5.55: It should be noted somewhere that the POCT CalDetect evaluation is based on one unique study (Otten et al 2008), whereas the accuracy of the ELISA tests is assessed by means of a diagnostic meta-analysis. As a consequence, the calculations for the POCT test might be less representative and their significance might be limited.	Thank you for your comment. The differing levels of evidence are captured earlier in section 5 (5.11 – 5.14) of the guidance and also considered by the Committee in section 6 of the guidance.
12	Consultee 1: (NHS Professional)	5	The economic modelling here is far too speculative to be useful. It assume so many things over a 10 year period. It would be much more realistic to assess the	Thank you for your comment. The methods used for the economic modelling

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			costs up until a diagnosis has been made. we cannot know what the sensitivity of GP diagnosis is (it is clearly wrong to assume it is 100% based on Durham!!) and we cannot estimate costs of IBD treatment - these are so variable and will change in 10 years as new treatments come on line or old treatments get cheaper. What clinicians want to know is how many patients will be managed in primary care not secondary care and what the effect on use of endoscopy will be - that will be metrics that mean something on a day to day basis. QALYs are too abstract. If this information could be provided it will have a significant influence on take up of this technology as it will enable clinicians and commissioners to see what effect it will have on them. In our current practice I think it is accurate to assume that all patients with FC>300 will be offered colonoscopy but many at levels of 50-100 will not and even at 100-300 we may well repeat and do some watchful waiting. This is using a lab based elisa test.	are consistent with the Diagnostics Assessment Programme manual. By using our standard method of cost-utility analysis, the impact of QALYs of missed IBD, or IBD with delayed diagnosis can be captured in the assessment. The analysis mentioned in the comment can be found in the existing literature. This comment will be forwarded to the Implementation team at NICE. In particular, the need for estimates of how many patients will be managed in primary care not secondary care and what the effect on use of endoscopy will be highlighted.
13	Consultee 2: (NHS Professional)	5	It is unfortunate that the TAC primary care pilot studies that NICE has used have not been peer reviewed given their significant weight that they have been given as the only primary care based studies The TAC FCP states ‘as no pre implementation data was available it is not possible to assess the impact of the project’ 5.21 and 5.22 appears to differ from the management pathway as set out in TAC FCP. It is unclear at which	Thank you for your comment. The External Assessment Group notes there are limitations in the pilot data. However, these were the best data available for the assessment. It is understood that GPs made diagnosis decisions based on clinical assessment without

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			point FCP testing was performed. Was this pre or post the decision to refer to secondary care? If the testing was post selection then this is in effect a secondary care study. In which case it is unclear why the incidence of IBD diagnosed in the selected subgroup of patients who were then screened with FCP pre referral seems similar to the incidence of IBD in unselected general gastroenterology clinics. This suggests that the availability of FCP changed GP practice even in this small pilot and patients were tested who GP's wouldn't normally have referred. Hence the assumption that all patients would have otherwise been referred may not be correct and the cost benefits more modest. The introduction of FCP may have generated potential referral	knowledge of the faecal calprotectin test result. Upon review, the External Assessment Group believes that 5.21 and 5.22 are consistent with pathway as described in the pilot study. The External Assessment Group notes that the similarity in prevalence is to be expected - the selected subgroup make up those seen in unselected gastroenterology clinics. The Committee recognises the potential for testing patients who were not originally considered for referral and the knock-on effect of increased referrals to specialists. This was investigated in the assessment using an assumption of GPs testing 50% of symptomatic patients (pilot data suggest that approximately 25% of symptomatic patients would normally be referred for specialist assessment). The analysis showed that although the benefits from faecal calprotectin testing were reduced, faecal calprotectin testing is still cost saving. To ensure faecal calprotectin testing is used optimally, the Committee recommended that locally agreed pathways are in place for testing. It is envisaged that a range of local stakeholders will participate in such care pathway discussions.

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14	Consultee 1: (NHS Professional)	6	I agree that more info is needed from primary care - the data examined apply to just 111 attenders. 100% sensitivity was assumed not demonstrated - that is an important difference. I understand that 1 cancer was missed in Durham using this strategy - how should this be taken into account in the qualy calculation and does it have any implications for its use in certain age groups. In my very very strong opinion it should never be used in over 60s, probably never in over 50's and between 40 and 50 they need to be used with caution. This really needs to be emphasised much more in the guidance as GPs reading superficially could easily miss this.	Thank you for your comment. Quantitatively, the QALY can capture both the impact on quality and quantity of life – as would be expected from cancer. Qualitatively, the Committee discussed the importance of optimal conditions for faecal calprotectin testing as described in section 6 of the guidance. The Committee notes that age is an important risk factor for cancer when considering people with lower gastrointestinal symptoms. In this regard, the Committee notes that there is differing opinion on what age cut-off to use for faecal calprotectin testing. The Committee is aware that other guidelines are, or will shortly be, in the process of being updated (for example, the BSG guidelines for IBS). Therefore, this guidance does not include specific ages in the recommendations but refers to NICE clinical guideline 27 “Referral for suspected cancer”, which cites age as one of a range of risk factors for consideration.
15	Consultee 2: (NHS Professional)	6	Is it recommended that FCP is adopted in both primary and secondary care with a cut off for endoscopic investigation at 50micrograms/g? If there are risks or areas of uncertainty with this then these need to be made explicit and separated out for primary and secondary care. Setting the level of referral trigger at 50 micrograms/g seems to be too low based on King’s College Hospital data and local data from Brighton. Please contact Dr	Thank you for your comment. Investigation of thresholds was included in the scope for the assessment and assessed by the External Assessment Group (and presented in the diagnostics assessment report). Upon consideration, the Committee believed that further data are needed before a recommendation could be made. Therefore, the Committee has recommended research into optimal cut-off

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			Tibble who can provide local data in which FCP has been used as part of a primary care based IBS pathway with a referral cut of at 50 micrograms/g. In discussion with our local CCG this has just been raised to 150micrograms/g because of the increased numbers of IBS referrals which were generated at FCP levels between 50-100 microgram/g in whom no significant pathology was found. Does NICE recommend setting levels locally and if so on what criteria? Based on local tests? Based on local referral patterns? CCG's will look at this section to address whether or not they should now adopt FCP into a primary care pathway and if clear cost and resource savings have been demonstrated. Have they?	values for tests and the investigation of repeat testing strategies in people with intermediate levels of faecal calprotectin (see section 7 of the guidance), however, the Committee has not recommend cut-off values in section 1 of the guidance. The Committee agreed that cut-offs should be discussed and agreed locally as part of the implementation process for this testing pathway (see section 6 of the guidance). Faecal calprotectin testing has been found to dominate current practice. That is, the use of the technology produces greater benefit at reduced cost. This is presented initially in the evidence section (section 5) and considered by the Committee in section 6 of the guidance.
16	Consultee 1: (NHS Professional)	7	It could be argued that basing evidence for primary care use on one study of 111 people using a non-lab method is very very poor evidence. The risk of assuming translation from secondary care studies to primary care is that differing prevalence of IBD and milder cases of IBD will seriously affect performance of the test. For example, in primary care patients seen soon after gastroenteritis will give false positives that would not occur in secondary care as more time will have passed before testing. Also secondary care has more expertise so will use tests 'better' and be able to evaluate indeterminate results more accurately.	Thank you for your comment. Comment noted. The Committee is aware of the limitations in the evidence and discussed this issue at length (see section 6 of the guidance). As a result, the Committee strongly emphasised that, when uncertainty remains in primary care around whether to refer a patient for specialist assessment based on faecal calprotectin testing, the clinician will benefit from further specialist

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			Whilst I do agree with the direction of travel, there are risks and better quality evidence and rapid review of nice guidance are highly desirable. Tests in studies perform better than in practice - witness use of d-dimer and TnT in secondary care!	clinical or laboratory input prior to making a decision.
17	Consultee 2: (NHS Professional)	7	If 7.1 is correct then it is unclear as to why the recommendations of 1.1 are not limited to secondary care use and the recommendation is that FCP is only used in primary care as part of clinical trials. What does "clinical utility" mean? Does this mean for example that there is evidence for health economic benefit but not clinical There is an assumption that most IBS patients with normal faecal calprotectin will not be referred (11% were during the time frame of the pilot study). Unless there are new primary care models of support for these symptomatic patients, many will eventually be referred to secondary care. There is no evidence that a normal FCP will provide long term patient reassurance. There should be research into primary care support models such as community dieticians, CBT and community nurses and other primary care based support teams	Thank you for your comment. The Committee was mindful that there are limited data on the use of faecal calprotectin testing in primary care. However, the Committee concluded that the assessment had demonstrated the benefit of using faecal calprotectin testing in adults who meet the specific criteria set out in section 1.1 and the benefits were, on balance, generalisable to testing in primary care. In this context, clinical utility refers to the impact of faecal calprotectin testing on patient outcomes. The term has been used to encourage research into faecal calprotectin testing beyond diagnostic accuracy data generation, ultimately, to understand the affect on patients and outcomes that are important to them. The Committee agrees that support pathways for the long-term management of people in the community should be developed. It has recommended further research in the area (see section 7 of the guidance).
18	Consultee 1: (NHS	8	Implementation is critical. It needs to be set in the context of other guidance and holistic pathways. See	Thank you for your comment.

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	Professional)		below. Differentiation needs to be made between IBS with typical symptoms of pain, bloating and mixed bowel habit or constipation versus predominantly watery diarrhoea. Watery diarrhoea that affects quality of life has several treatable conditions and the idea that in primary care a negative faecal calprotectin means they definitely don't need referral or assessment for other conditions will lead to patients not receiving treatment that could improve their quality of life.	The Committee agrees that implementation is important and has recommended that locally agreed care pathways are in place for the testing. In addition, this comment will be forwarded to the Implementation team at NICE. The Committee strongly emphasised that, when uncertainty remains in primary care around whether to refer a patient for specialist assessment based on faecal calprotectin testing, the clinician will benefit from further specialist clinical or laboratory input prior to making a decision.
19	Consultee 1: (NHS Professional)	9	Diagnoses not prioritised in the IBS guidance or the faecal calprotectin guidance include bile salt malabsorption and collagenous colitis. The cancer referral guidance should be included in this section. There are now too many disparate guidance documents that refer to how patients with colorectal symptoms should be dealt with. An attempt should be made that draws together all of the guidance into one suggested diagnostic 'pathway' for patients with colorectal symptoms. It's hard enough for an interested person to tie them all together but for a GP they are just too disparate. 'NICE summary guidance on referral and management pathways for patients with colorectal symptoms taking into account age, symptoms and results of initial primary care investigations including faecal calprotectin'. I am working with others on producing something that encompasses all your guidance. Please get in touch if interested.	Thank you for your comment. The Institute agrees that NICE guidance on a particular topic should be easier to access. Therefore, NICE is investing in the Pathways programme. NICE Pathways is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. Visually representing everything NICE has said on a particular topic, the pathways enable you to see at a glance all of NICE's recommendations on a specific clinical or health topic. They provide an easier and more intuitive way to find, access and use NICE guidance. At present, NICE Pathways are available for

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				colorectal cancer and irritable bowel syndrome in adults. Appropriate NICE pathways will be updated when this guidance is published.