NICE National Institute for Health and Care Excellence

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| NHS Professional | 1 | All | All | This report is an excellent, comprehensive, well laid out and relatively easy to read and follow piece of work. Dr Westwood and her team are to be congratulated on producing this important evidence-based work.<br><br>If the final redrafted report ratifies the overall cogent conclusions reached in this confidential version circuited to stakeholders, then use of FIT to triage patients presenting in primary care with lower abdominal symptoms will be more widely adopted. The scarce colonoscopy resource currently available will be better directed to those who will benefit most. As a result, patient satisfaction should be enhanced. The use of FIT as THE test to fulfil the NG12 recommended “test for occult blood in faeces” will see evolution of a new FIT-based paradigm for the detection of all significant colorectal disease in symptomatic patients, not only colorectal cancer.<br>.<br>As a professional in laboratory medicine, my comments will mainly concern FIT in clinical practice. I shall not comment in any detail on Section 4 – or other sections concerned with costs - since I have no expertise in this field.<br><br>I have three major concerns as explained | We thank the stakeholder for these kind remarks |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | (undoubtedly repetitively) in the comments below, which might affect the detail in the report: If accepted, some recasting will be needed. However, it is important to note that the key overall and cogent conclusions will NOT be affected by any of my comments.<br><br>1. I do not think that the work of Parente et al should be included as a study on HM-JACKarc: it is clear that the analytical system used was the older HM-JACK, unavailable in the UK or Europe. I advocate that all references to the work, save the very interesting material on FIT v calprotectin v M2-PK should be deleted.<br><br>2. There seems to be considerable confusion about the units used for faecal haemoglobin concentration. The recommendation is µg Hb/g faeces. However, much of the literature cited uses the older FIT-specific ng Hb/ml buffer. While there are well known conversion factors for OC-Sensor (multiply by 0.20) and FOB-Gold (multiply by 0.17), the conversions are not always done correctly through the report. The report needs very careful scrutiny to ensure the correct units and correct conversion factors are made in text, Tables and footnotes to Tables.<br><br>3. In routine practice, the threshold applied as the | 1. Parente, reference 54, has been removed from the results sections of the systematic review and added to the excluded studies table (erratum provided to NICE)<br><br>2. Conversion factors have been re-checked and corrected, as needed<br><br>3. The issues around the "undetectable" |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | criterion for referral for endoscopy or otherwise cannot be “undetectable” if that implies 0 µg Hb/g faeces. While very interesting for research purposes and casting much light on relationships between faecal haemoglobin concentration and symptoms and colorectal disease of all types, this threshold cannot be used in routine practice. Neither can the manufacturers’ quoted limit of detection or limit of quantitation. The lowest cut-off that can be used in routine practice is the lower limit of the analytical working range given by manufacturer. Thankfully, this correlates well with the thresholds recommended in many of the studies evaluated in this report and in the conclusions reached in the report itself (10 µg Hb/g faeces). However, much of the report will need recast if this is accepted.<br><br>My other comments are somewhat less important, but I hope these are seen, as I meant them to be, as constructive suggestions. | thresholds are familiar and are something that we have encountered previously (NICE DG15 – high sensitive troponin assays). We feel that it remains worthwhile to include these data in the review for research interest and so that the committee can consider whether research recommendations may need to include extending the working range of assays.<br><br>We will consider adding some explanatory text before the HTA report is published. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | Minor corrections have been made (see below) and will be applied to the HTA journal version of the report ahead of publication |
| NHS Professional | 2 | 15/16 | Glossary | Perhaps the “glossary” should include the terms: positive predictive value and negative predictive value. Should the definitions of guaiac faecal occult blood test and faecal immunochemical test for haemoglobin (FIT) not also be included at this point in the report? Should what is actually meant by the term colorectal cancer also be defined? Should the term “screening” also be defined here to make sure that asymptomatic and/or apparently healthy are highlighted? | These items have been added to the Glossary |
| NHS Professional | 3 | 17 | Scientific summary | It is stated (sic); Quantitative FIT assays allow the detection of very low levels of blood in the faeces. This seems subjective – what is very low or low or high? Should this say something like that earlier in the report, viz: “Quantitative FIT assays allow the estimation of quantities of blood that are not | The suggested change has been made |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | detectable by normal visual inspection"? | |
| NHS Professional | 4 | 17 | Scientific summary | The statement is: FIT has been approved for the Scottish Bowel Screening Programme and has been recommended for adoption in the NHS Bowel Cancer Screening Programme in England.<br><br>In fact, FIT have now been approved for use in the NHS BCSP. See - https://healthmedia.blog.gov.uk/2016/06/07/new-bowel-screening-test-to-save-hundreds-of-lives/ | This statement has been corrected |
| NHS Professional | 5 | 17 | Scientific summary | Last line – should the term "advanced neoplasia" be defined here simply as CRC plus advanced adenoma (AA) and significant bowel disease also defined as perhaps CRC + AA + inflammatory bowel disease (IBD: Crohn's and ulcerative colitis) – see comment #6 also. | Additional definitions have been added |
| NHS Professional | 6 | 19 | Scientific summary | Here again the term "high risk adenoma" is used without any definition: the term advanced adenoma is also used later in the report. I wonder if these terms are actually interchangeable. The BSG recommendations (cited in the reference list) have three classes of adenoma – low risk, intermediate risk and high risk, In fact, the three Scottish studies combine high risk and intermediate risk and call this | The document has been checked for consistency and edited as needed |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | (sometimes) higher risk adenoma. Perhaps the Specialist Committee Members can advise on the best semantics for the report?<br><br>I did note that this was very well explained later in the report, for example, on page 66 at the beginning of section 3.2.4. I wonder if this explanatory material, or at least a short summary, needs to come in the Scientific Summary. | |
| NHS Professional | 7 | 19 | | The report states: the **only** study of HM-JACKarc…..I presume that this is Godber et al. However, the abstract of Thomas et al states …. Using **FIT alone at a cut-off of 10 µg Hb/g faeces,** gave an NPV of 99.6% for CRC (sensitivity 92.3%, specificity 85.2%), and 99.6% for other significant bowel disease (sensitivity 94.4%, specificity 86.6%). So, I think that there are two studies with data from HM-JACKarc, albeit one without CI, See my later comment on following this up. The study by Auge et al does not dissect out CRC from ACRN. | The abstract by Thomas et al. Reports the threshold used as 7 µg Hb/g faeces and the text states that the one study referred to is for the target condition CRC. – No change needed |
| NHS Professional | 8 | 20 | Scientific summary conclusions | I should like to see this "Suggested Research Priorities" section in the summary expanded to include:<br><br>(a) comparison of FIT analytical systems through patients collecting samples with more than one | These suggestions have been added to the research recommendations, subject to discussion at the appraisal committee meeting. Any further suggestions, arising from discussions at the meeting, will also be added. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | specimen collection device from a single bowel motion,<br><br>(b) further evaluation of the merits of other faecal biomarkers, especially faecal calprotectin, which is recommended by NICE in DG 11 and advocated recently as an alternative to FIT by some (Turvill J, et al. Faecal calprotectin in patients with suspected colorectal cancer: a diagnostic accuracy study. Br J Gen Prac. 2016;66(648):e499-506) and<br><br>c) comparison of approaches for safety-netting of those who have negative FIT results but continue to have symptoms. This last is also mentioned, and expanded upon, in my comment 38.<br><br>Further, in view of the interesting quandary about what is the lowest possible reportable faecal haemoglobin concertation, as mentioned in point 3 above and discussed later, perhaps this section could also state something along the lines of the following:<br><br>Since at least half of patients providing specimens for FIT have undetectable f-Hb, but the dogma is that everyone has some blood in their faeces, would the development of “high sensitivity” methods for estimation of f-Hb be of any clinical value? | |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | If it is not wished to expand this section at this point in the report, than these could be included in section 6.2. | |
| NHS Professional | 9 | 25 | 2.1 | In this Introduction, for balance, should there not be a short statement after the three bulleted referral criteria telling that the recommendation of gFOBT was very controversial the subject of much concern and discussion and then cite Steele R, et al. Use of faecal occult blood tests in symptomatic patients. BMJ. 2015;351:h4256, Benton S, et al. NICE referral guidelines for suspected cancer: colorectal cancer and faecal occult blood testing. Ann Clin Biochem. 2016;53:7-9, and Fraser CG, Strachan JA. A nicer approach to the use of 'faecal occult blood tests' in assessment of the symptomatic. Ann Clin Biochem. 2016;53:5-6. This would make for a good introduction and explain the rationale for NICE having set up a DAC on the topic of FIT in the symptomatic. Otherwise, the rationale for the DAC is somewhat vague, in my opinion. | This is a difficult area, as there seems to be some debate around whether the intention of NG12 was to recommend guaiac testing or faecal occult blood tests more generally.<br><br>We will consider introducing some text about how the NG12 has been interpreted ahead of the publication of the HTA monograph. |
| NHS Professional | 10 | 28 | 2.2 | The report states …….a very small amount of faeces into a small volume of stabilising buffer in the device. Can the report not be more “scientific” and state that a few mg of faeces into a few ml volume of stabilising buffer…..? | This change has been made |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| NHS Professional | 11 | 28 | 2.2 | An additional disadvantages of qualitative FIT is that the colour development is dynamic and early reading leads to false negative results and late reading to false positive results.<br><br>Further, there is lot-to-lot variation in FIT obtained from a single manufacturer (see - McDonald PJ, Anderson CM, Fraser CG. Acceptance quality checks for qualitative fecal immunochemical tests ensure screening program consistency. Int J Cancer. 2011;128(1):247-8). | Background only, no change needed. We would prefer not to introduce statements about lot-to-lot variation based on one study |
| NHS Professional | 12 | 29 | 2.2.2 | Pedantic comments – the document has OC Sensor and OC-Sensor. Consistency of hyphen use is required. I think that OC-Sensor IO is actually lower case io - http://www.eiken.co.jp/en/product/fit/index.html – Table I requires correction too as do later materials on this system, eg, page 41. In 2.2.5, please leave a space between numbers and their units - >2µg/g should be >2 µg/g and similar. | The document has been checked for consistency and edits made throughout |
| NHS Professional | 13 | 31 | 2.2.5 | I think that the paragraph in the lower half of page 31 needs a new heading – 2.2.6 - since what follows does not apply to Ridascreen discussed above.<br><br>Further, the report has, in this single paragraph, data for sensitivity and specificity in two formats – as | An additional heading has been included and the formatting inconsistency has been corrected |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | fractiles and percentages - 0.XY and as XY.Z%. Should these data not be in consistent format throughout? | |
| NHS Professional | 14 | 32 | Fourth line from foot | Please insert the word recommendations at the end of the sentence to read …… best non-invasive screening modality in all national and international recommendations.[31] | Correction made |
| NHS Professional | 15 | 32 | 2.4.1 | The report mentions that a pilot of FIT in the NHSBCSP has been done: the excellent paper on this is out and should be cited here and above (instead of reference 30) –<br><br>Moss S, Mathews C, Day TJ, Smith S, Seaman HE, Snowball J, Halloran SP Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England. Gut. 2016 Jun 7. pii: gutjnl-2015-310691. doi: 10.1136/gutjnl-2015-310691. [Epub ahead of print].<br><br>A full paper on uptake in screening using FIT in Scotland has also been published: Digby J, McDonald PJ, Strachan JA, Libby G, Steele RJ, Fraser CG. Use of a faecal immunochemical test narrows current gaps in uptake for sex, age and deprivation in a bowel cancer screening programme. J Med Screen. 2013 ;20(2):80-5. | Comment on implementation – no response needed.<br><br>We will add the citation for publication on the NHSBCSP pilot, ahead of publication of the HTA monograph. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | I think there is no reason why uptake of FIT in primary care should not be very high indeed – do most patients not do as the GP tells them to do (at least a far as tests and investigations are concerned)? Perhaps an analogy of value would be the uptake of colonoscopy after a positive screening test result in the NHS BCSP?. | |
| NHS Professional | 16 | 33 | 2.4.2 | The SIGN Guideline 126 (section 3.7) has just been updated (August 2016) and the new wording, available on the SIGN website, may not have the same sense as what is documented here in this report. Please review and consider this point. | There are no substantive changes in the quoted section of the up-dated guideline. The citation will be up-dated ahead of publication of the HTA monograph. |
| NHS Professional | 17 | 36 | 3.1.1 | To be pedantic, AACC is the American Association for Clinical **Chemistry** and Laboratory Medicine - not Biochemistry. | Correction made |
| NHS Professional | 18 | 41 | 3.2 | Very importantly, as stated in comment 1 above, the study of Parente et al (54) does not use the HM-JACKarc. Review of the paper and the others by this group cited as relevant references clearly shows that the study was done with the HM-JACK. The HM-JACKarc and the HM-JACK are very different FIT analytical systems, the HM-JACKarc being a newer version: see - http://www.kyowamx.co.jp/en/products/device/ - for | Parente, reference 54, has been removed from the results sections of the systematic review and added to the excluded studies table (erratum provided to NICE) |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | details. The sampling devices are different, HM-JACKarc taking 2 mg faeces into 2.0 ml buffer, but HM-JACK takes 10 mg into 2.0 ml buffer. The HM-JACK is unavailable in Europe, to my knowledge. Thus, I think that there are three and not four relevant studies with HM-JACKarc and many of the later statements, calculations, data, Tables and appendices require modification if Dr Westwood, her colleagues and the SCM agree with my assessment of the paper. | |
| NHS Professional | 19 | 44 | Table 3 | Table 3 has 507 for the Godber et al study: this is the number who accepted the invite. However, only 484 had both FIT and colonoscopy data. This number seems more consistent with the data from the other studies detailed in this Table. And this applies elsewhere in the report. | Correction made |
| NHS Professional | 20 | 44 | Table 3 | It is pleasing to be able to inform that the COLONPREDICT study, of much value to this report, has now appeared in print –<br><br>Cubiella J, Vega P, Salve M, Díaz-Ondina M, Alves MT, Quintero E, Álvarez-Sánchez V, Fernández-Bañares F, Boadas J, Campo R, Bujanda L, Clofent J, Ferrandez Á, Torrealba L, Piñol V, Rodríguez-Alcalde D, Hernández V, Fernández-Seara J; COLONPREDICT study investigators. Development and external validation of a faecal immunochemical | AiC mark-up has been removed |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | test-based prediction model for colorectal cancer detection in symptomatic patients. BMC Med 2016;14:128.. This paper is open access. | |
| NHS Professional | 21 | 44 | Table 3 and elsewhere | The Mowat et al paper is now out in print: Gut.2016;65:1463-9. This too is open access. Should the report have Mowat 2016 now rather than Mowat 2015 (eg, on page 49) – although it did appear on-line in 2015 (Gut takes a very long time to get a paper into a print issue). | The reference is given as it was used for the report – No change needed |
| NHS Professional | 22 | 50 | Accuracy of OC-Sensor for the detection of CRC | Very importantly as stated in comment 1, here, and elsewhere, the idea of using “undetectable” faecal haemoglobin as the cut-off is documented. This cut-off was discussed in detail in Mowat et al (OC-Sensor) and Auge et al (HM-JACKarc) and documented in Table 2 in the paper of Rodríguez-Alonso et al (OC-Sensor). While it is of significant research interest to examine cut-off concentrations above zero and investigate people with concentrations of 1,2,3 µg Hb/g faeces and so on through the integers to the lower limit of the analytical working range documented by the manufacturers (called the measurement range in Table 1 of the report), it is very unlikely that this could not be done in routine practice when the FIT (either analyser) was used in ISO 15189 accredited laboratories (as required in the UK). The lowest cut-off that can be applied is the lower analytical working | Please see response to comment 1 |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | limit. I advise that this be discussed with the Specialist Committee Members who are consultants in laboratory medicine, namely Dr Godber and Mrs Strachan. If they agree with this thesis, then a comment on this should be clearly documented in the report in the many sections where undetectable and 0 µg Hb/g faeces are used. Moreover, although the limit of detection and limit of quantitation as documented by manufacturers (Table 1) do inform much about the analytical performance characteristics of the f-Hb examinations, neither of these should be applied as cut-off. | |
| NHS Professional | 23 | 50 | Third line from foot | It is stated (sic): two CRCs would be missed using the 10 µg Hb/g faeces threshold. That is correct since Mowat et al missed three and Rodríguez-Alonso et al had one. Interestingly, I believe that all three in the Mowat et al study were female: it is not known what sex the one of Rodríguez-Alonso was. This might be worthy of comment since the known difference in faecal haemoglobin concentrations in men and women, well documented in the report, might have ramifications for design of strategies involving use of FIT in the symptomatic, as is discussed in a number of sections of the report. | The text relates to a hypothetical cohort, not to an individual study. – No change needed. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| NHS Professional | 24 | 53 | Figure 5 and those similar later | This Figure and other similar has + FIT Test and – FIT Test – the T in FIT means Test so this legend actually uses a double "test test". I think that it would be far better to have: + FIT result and – FIT result in all such Tables. | These figures have been corrected |
| NHS Professional | 25 | 54 | Figure 5 and Table 4 and elsewhere | I think that there is a conflict in the report between 0 µg Hb/g faeces (undetectable) 4 µg Hb/g faeces (said to be the limit of detection of the OC-Sensor assay) and 10 µg Hb/g faeces (the lower limit of the analytical working range – according to the manufacturer). As above, it may not be possible (ISO 15189) to use either 0 or 4 µg Hb/g faeces as cut-off and 10 µg Hb/g faeces would be the lowest possible cut-off, all samples with less than this having to be reported as "less than" or "not detected" or "normal" or "low risk" or whatever local circumstances and practices dictate. | Please see response to comment 1 |
| NHS Professional | 26 | 59 | Table 5 | The footnote has: Converted from ng Hb/ml buffer using a multiplication factor of 0.17. This is OC-Sensor and, as per the previous Table, the appropriate factor is 0.20 (and that is what has been used, in fact, since 20 µg Hb/g faeces = 100 ng Hb/ml buffer for OC-Sensor). | The footnote has been corrected |
| NHS Professional | 27 | 62 | Second paragraph | It is the Colorectal Cancer Screening **Committee.** | Correction has been made |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| NHS Professional | 28 | 66 | 3.2.4 | As above, I do not think that the study of Parente et al can be included here and in many following sections (not enumerated separately), because it is clearly documented to be done with HM-JACK and not HM-JACKarc – different systems. | Parente, reference 54, has been removed from the results sections of the systematic review and added to the excluded studies table (erratum provided to NICE) |
| NHS Professional | 29 | 67 | Accuracy of HM-JACKarc … | The study of Parente et al (which should be excluded in any case) did not use 100 µg Hb/g faeces.as cut-off. The paper documents 100 ng Hb/ml buffer: with the HM-JACK analyser (not the arc) and this is equivalent to 20 µg Hb/g faeces. I think Figure 8 wilt thus be incorrect also. | Parente, reference 54, has been removed from the results sections of the systematic review and added to the excluded studies table (erratum provided to NICE) |
| NHS Professional | 30 | 69 | Auge et al | Another pedantic comment – one cannot have the highest of two samples or results – the adjective really has to be higher, not highest! This error is repeated later in the report. | Correction made |
| NHS Professional | 31 | Tables 12,13 and 14 | 3.2.4 | The report states in the footnote: limit of detection for the assay is 0.6 µg Hb/g faeces or 0.6 ng/ml buffer, As above, I think that this is irrelevant and the important analytical performance characteristic is the lower limit of the analytical working range cited by the manufacturer. No results less than that should be reported numerically in real practice. I think all such footnotes should be deleted since the interesting but mainly irrelevant information is clearly documented in Table 1. I also think that the report needs editing to | Please see response to comment 1 |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | convey these concepts clearly throughout. | |
| NHS Professional | 32 | 74 | 3.2.4 | The data from Thomas et al were contained in a detailed abstract available presented in Warwick earlier this year and available on the Internet. I understand that a full paper with a larger quantum of data is either submitted or at an advanced stage of drafting for submission: would it be worth contacting the authors for clarification since the data would enhance the report's analysis of the performance of the HM-JACKarc? I believe that the "senior author" is: Professor R Arasaradnam; r.arasaradnam@warwick.ac.uk | The conference abstract reported a complete data set, which was included in the review. Inclusion of possible additional data in the DAR is not practical at this stage<br><br>We will seek this information before any further journal article is produced, and any new data will be available for inclusion in any future up-dates to guidance |
| NHS Professional | 33 | 76 | 3.2.5 | Although there are few data on the performance of FOB Gold, as well as the "closed" systems available from Sentinel Diagnostics (Milan, Italy) – SENTiFIT and SENTiFOB - http://www.sentinel.it/en/fob-gold-line/ - the reagents are available for use on many "open" clinical chemistry analytical platforms. This is mentioned earlier in the report. In the description of the different options for FIT in the UK. Is it not likely that the performance characteristics will be influenced by the analytical system actually used? That comes across in Table 1 regarding the recommended cut-off. I wonder if that consideration merits a short comment here. | This is a relevant point for discussion by the committee. The report provides what detail was available from the one un-published study of FOB gold and it is for the committee to consider whether this is applicable to the UK setting. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | |
| NHS Professional | 34 | 79 | Table 19 | The data from Krivec et al has ≥9.35 µg Hb/g faeces as the threshold: this figure is obtained by conversion from ng Hb/ml buffer using a factor of 0.17. The factor is correct, but due to the variability of the faecal matrix and the inherent imprecision of the analytical system, I do not think that use of so many significant figures is at all warranted. Although some of the literature uses similar data, I feel very strongly that faecal haemoglobin concentrations should be reported throughout as whole integers only (≥9 µg Hb/g faeces). | The suggested change has been made |
| NHS Professional | 35 | 102 and others | 4 (as an example) | The term “stool” is used on this page (second last paragraph) and elsewhere in the report. I wonder if readability and understanding would be enhanced if this awful (in my opinion) term were replaced by faeces or faecal as appropriate to keep the term for the matrix analysed by FIT consistent throughout. | The suggested substitution has been applied throughout the report |
| NHS Professional | 36 | 104 | Table 34 | One of the cost estimates in this Table was provided by me. I think that I misunderstood – sorry. The cost that I thought that I had gave was for the gFOBT test materials only and did not include any labour and the many other overhead costs. Could a footnote to that effect be included, please? | This information has been added to the footnote |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | |
| NHS Professional | 37 | 107 | CRC Markov model | Cubiella et al did not use ≥17 µg Hb/g faeces as their cut-off in reference 55 as documented here: ≥100 ng/ml as in the paper is equivalent to 20 µg Hb/g faeces with OC-Sensor. | Correction made |
| NHS Professional | 38 | 142 | Section 5 | This section will need updating if my comments above are taken into account, particularly the following: Parente et al (54) should be excluded, COLONOPREDICT is now in print., and "undetectable" faecal haemoglobin cannot be used as a threshold – the lower limit if the analytical working range is most appropriate, See comment 1 | Parente, reference 54, has been removed from the results sections of the systematic review and section 5.1.1 of the discussion, and added to the excluded studies table (erratum provided to NICE) |
| NHS Professional | 39 | 142 and repeated on page 148 | 5.1 | The report tastes that: None of the included studies reported data comparing different FIT assays. In fact, the presentation of Auge at http://www.worldendo.org/wp-content/uploads/2016/08/5_josep_maria_auge_spain_ueg2015.pdf shows (slide 4) a rather nice comparison of HM-JACKarc, SENTiFIT 270 and Kroma IT – linear systems in assessment of the symptomatic. Not a lot of information, for sure, but essentially states that these three systems have apparently similar performance in use for assessment of the symptomatic (with subtle analytical differences in | This slide reports % agreement between the systems for proportions of patients with stratified levels of Hb. It does not provide comparative accuracy data and, therefore, does not meet the inclusion criteria for our systematic review. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | estimation of faecal haemoglobin at very low concentrations). | |
| NHS Professional | 40 | 151 | 5.1.1 | I wonder if Section 5.1.1 should end with a caveat statement such as.<br><br>The evidence used in the analyses in this report was generated in a small number of research studies which had few subjects. Should FIT be adopted as a routine test for assessment of patients presenting with lower abdominal symptoms, it is highly likely that the clinical performance characteristics, particularly sensitivity, will be less good.<br><br>As an alternative, I recognise that section 5.3.1 explains the caveats in some detail, but I wonder if a succinct statement as above at the beginning of this section might help understanding. | We believe that these issues are fully covered in sections 5.2.1 and 5.3.1, - No change needed |
| NHS Professional | 41 | 157 | 5.3.1 | Although the study of Parente et al does not use HM-JACKarc, the material on the study comparing FIT (if you mention that it is not with the analyser that is available in the UK and the subject of the report) and faecal calprotectin and M2-PK is interesting and is, in my opinion, worthy of retention. Again note that the threshold is not 100 µg Hb/g faeces but 100 ng Hb/ml buffer and this is equivalent to 20 µg Hb/g faeces which changes the conclusions in the report. | Parente, reference 54, has been removed from the results sections of the systematic review and added to the excluded studies table (erratum provided to NICE) |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | |
| NHS Professional | 42 | 157 | 5.3.1 | Note that the studies of Mowat et al and Thomas et al also have information on FIT and calprotectin. Both studies consider faecal calprotectin inferior to FIT in assessment of the symptomatic. Would it be worth stating their findings here in the context of FIT and/or faecal calprotectin? This is important because, see comment 6, there is a recent paper recommending calprotectin that might be used until this DAC reports! Turvill J, et al. Faecal calprotectin in patients with suspected colorectal cancer: a diagnostic accuracy study. Br J Gen Prac. 2016;66(648):e499-506.<br><br>Further, there is a very interesting recent study, unfortunately using a qualitative FIT, which investigates FIT, calprotectin and blood haemoglobin and anaemia markers. Would this be worthy of mention, even if only to stimulate future studies using quantitative FIT (since many patients with symptoms will have full blood count and anaemia markers done when attending primary care with lower abdominal symptoms. Interestingly, these authors seem to consider calprotectin as an unnecessary investigation.<br><br>Högberg C, Karling P, Rutegård J, Lilja M. Diagnosing colorectal cancer and inflammatory bowel disease in primary care: The usefulness of tests for faecal | The assessment of the accuracy of tumour makers (including faecal calprotectin), or a comparison of their accuracy with that if FIT, were outside the scope of this assessment. However, the discussion section of our report (section 5.3.1) considers the possible value of using tumour markers in combination with FIT. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | haemoglobin, faecal calprotectin, anaemia and iron deficiency. A prospective study. Scand J Gastroenterol. 2016 Sep 14:1-7. [Epub ahead of print]. | |
| NHS Professional | 43 | 159 | 5.3.1 | In the description of the trial planned for Denmark, the cut-off is reported as ≥50 µg/L Hb. In https://clinicaltrials.gov/show/NCT02308384 it is stated that the cut-off is 50 ng/ml and, of course, this is 10 µg Hb/g faeces with the OC-Sensor which is to be used, I believe. | This information has been added to the text |
| | 44 | 159 | 5.3.1 | The report states that: "The full potential benefits of FIT in symptomatic patients, including those relating to diagnoses other than CRC, remain unclear. This issue may be particularly important in younger patients, where the prevalence of CRC is lowest and other diagnoses are more likely." Should the NICE DG11 guidance be mentioned here since this does advocate using faecal calprotectin in IBS/IBD differential diagnosis, particularly since Crohn's and UC are more likely in the younger age group? However, there is an important caveat (as best shown by Mowat et al) that there is ever increasing literature that shows, exactly as for use in assessment of CRC in people with lower abdominal symptoms, that FIT is better than calprotectin!<br><br>One recent example is: Nakarai A, Kato J, Hiraoka S, | Comment only – no response needed |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | Takashima S, Takei D, Inokuchi T, et al. Ulcerative colitis patients in clinical remission demonstrate correlations between fecal immunochemical test results, mucosal healing, and risk of relapse. World J Gastroenterol. 2016;22:5079-87. | |
| NHS Professional | 45 | 162 | 6.2 | This is a very good section which I hope does stimulate further important research on the use of FIT in assessment of the symptomatic. The last proposal is that: A post-implementation audit would also be valuable. For example, this could be used to investigate the proportion of FIT negative patients who go on to have a colonoscopy as well as the delay to getting the colonoscopy.<br><br>I wonder if this could be expanded to encourage research on strategies to deal with people who have a negative FIT result but still have symptoms: a formal comparison between simply reassurance, referral to an outpatient gastroenterology clinic, a repeat FIT, an upgraded referral to endoscopy, or another strategy, would be of great value.<br><br>Moreover, there are some thoughts that patients with a negative FIT result might, especially the younger, benefit from a calprotectin test, so pathways involving sequential (rather than simultaneous) testing might be well worth exploring too. | These suggestions have been added to the research recommendations, subject to discussion at the appraisal committee meeting. Any further suggestions, arising from discussions at the meeting, will also be added. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| NHS Professional | 46 | 217 and following | Appendix 2b | Is the cut-off for Cubiella COLONPREDICT not 20 rather than 100 µg Hb/g faeces? It is the 100 ng Hb/ml buffer used in the paper that confuses!<br><br>Krivec – the Table has 55 µg Hb/g faeces but this is ng Hb/ml buffer and, earlier in the report, this is correctly converted (factor 0.17) to 9 µg Hb/g faeces.<br><br>McDonald et al is 10 µg Hb/g faeces (50 is ng Hb/ml buffer).<br><br>Parente et al, if included, is 20 µg Hb/g faeces and not 100 µg Hb/g faeces (that, again, is ng Hb/ml buffer).<br><br>Terhaar sive Droste et al – these data are likely to be in ng Hb/ml buffer and should probably read ≥10, ≥15, ≥20, ≥30, ≥40 in µg Hb/g faeces. | Corrections made |
| NHS Professional | 47 | 223 | Appendix 2b | The footnote should tell what HRA in the Table means. | This information has been added to the footnote |
| NHS Professional | 48 | 256 | Appendix 4 | I note that responses were not received from studies with Rozen P as an author: Paul, who contributed much to our knowledge of FIT in screening, died a couple of years ago. | We are aware of the death of Paul Rozen; co-authors were approached for information. A footnote has been added to the table in Appendix 4 to avoid any confusion |
| NHS Professional | 49 | 301 | Appendix 12 | Would it be worth having a section on NICE guidance relevant to colorectal disease other than CRC and | Comment only – No change necessary |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | include the interesting materials on faecal calprotectin – after all, this is mentioned in the report and the studies of Parente et al, Mowat et al and Thomas et al all (and a fair few others now) do comment on its use in assessment of lower abdominal diseases? I think that, once this report is out, and FIT are used more and more, then the role of calprotectin will diminish: it may be that NICE will have to review the existing guidance on calprotectin! | |
| NHS Professional | 50 | Perhaps on page 17 at the end of the last para of "Background" or on page 161 in 6.1? | Either in section 2 or section 6 | As I was finalising these comments, the following appeared:<br><br>http://www.itv.com/news/2016-09-26/new-bowel-cancer-test-could-cut-number-of-endoscopies/<br><br>http://www.express.co.uk/life-style/health/714368/bowel-cancer-test-blood-faces-endoscopy-GP<br><br>The study cited was done in The Netherlands with a qualitative FIT and is a follow up to the study described in the report by Kok et al (144). It is: Elias SG, Kok, L, de Wit, NJ, Witteman BJM, Goedhard G, Romberg-Camp MLJ, et al. Is there an added value of faecal calprotectin and haemoglobin in the diagnostic work-up for primary care patients suspected of significant colorectal disease? A cross-sectional | The article described was provided AiC, ahead of publication, and is mentioned in the discussion section of our report (section 5.3.1).<br><br>We believe that our report fully addresses the distinction between screening applications and the assessment of symptomatic patients. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | diagnostic study. BMC Medicine. 2016;14(1):141.<br><br>along with a critical commentary: Fraser CG. Diagnostic work-up of patients presenting in primary care with lower abdominal symptoms: which faecal test and triage strategy should be used? BMC Medicine. 2016;26;14(1):139<br><br>Both articles in the popular media quite clearly confuse, and mix up facts about, the two uses of FIT – in asymptomatic screening of the apparently healthy (not patients) and in assessment of patients with lower abdominal symptoms presenting in primary care. These two uses of the one test are very different. The target populations differ, The cut-offs used will differ greatly since screening is intended to pick up the small proportion of the population at highest risk of CRC and assessment of the symptomatic is intended to pick out those who would benefit most from colonoscopy. I think that this confusion will abound for the public and for healthcare professionals. I wonder if a strong statement about the two uses being complementary but very different would be useful in either the introduction, where screening is mentioned, or in the conclusions as a plea for wide education about the different uses of FIT and their benefits and drawbacks. | |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| NHS Professional | 51 | 163 | Acknowledgments | Finally, thank you for acknowledging my input into the preparation of this report. I very much enjoyed my interaction with Dr Westwood and always found our exchanges to be interesting (and sometimes challenging).<br><br>I hope that my comments above are of value and trust that I can continue to assist Dr Westwood and NICE as appropriate so as to progress the undoubtedly important role that FIT have in assessment of all patients with lower abdominal symptoms presenting in primary care (and certain secondary care outpatient clinics) | We thank the stakeholder for these kind remarks |
| Bowel Cancer UK | 52 | 5 | Conclusions | Bowel Cancer UK agrees that the evidence presented in the economic review provides a strong case for the introduction of the faecal immunochemical test to triage patients with lower abdominal symptoms, who are at low risk for CRC. Based on this evidence Bowel Cancer UK urges NICE to recommend that FIT is used in a primary care setting to triage those with low risk symptoms. The introduction of FIT would assist GPs to rule out bowel cancer first and not last, particularly as symptoms for bowel cancer are often symptoms of other, less serious, bowel conditions. The ability to rule out whether a person is likely to have bowel cancer quickly and conveniently is of significant benefit to patients. | Comment only – No response required |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| Bowel Cancer UK | 53 | 20 | Implications for service provision | Bowel Cancer UK supports the introduction of FIT, at its most accurate sensitivity level of 10 µg Hb/g faeces to allow for the greatest chance to detect people who may have bowel cancer early, when it is more treatable and chance of survival is higher. | Comment only – No response required |
| Bowel Cancer UK | 54 | 21 | Suggested research priorities | Bowel Cancer UK supports the NICE recommendations on suggested research priorities. We would also suggest that NICE considers making recommendations for research on how and to what extent the use of FIT in this setting and population can alleviate demand on endoscopy services that are currently struggling to cope with increasing demand for the service. | Comment only – No response required |
| Bowel Cancer UK | 55 | 4 | Abstract/ background | The background information in the abstract states that colorectal cancer is the third most common cancer in the UK, however this is inaccurate. Bowel cancer is the fourth most common cancer in the UK, with over 41,000 people diagnosed each year. | This statement will be checked/corrected ahead of publication |
| Alpha Laboratories Ltd | 56 | | | Thank you for the opportunity to comment on the DAP33 report on "Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care." We have reviewed the document and have only 2 comments. One in relation to a cited article referencing the HM-JACK, which was an earlier system with a different collection system and cut-off. The other is in the calculation of the cost of controlling the HM-JACKarc.<br>Other than this reference (see comments below) and the associated pricing comments, we conclude that there is no | See responses below |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | statement required from Alpha Laboratories or the manufacturer of the HM-JACKarc system, Kyowa Medex. | |
| Alpha Laboratories Ltd | 57 | 66 | 3.2.4 | Reference 54, Parente F, Marino B, Ilardo A, Fracasso P, Zullo A, Hassan C, et al. A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. *Eur J Gastroenterol Hepatol* 2012;24(10):1145-52. This study used an earlier system to the HM-JACK arc and the sample size and latex reagent were different. Consequently the cut-off employed in the study is different to those of the HM-JACKarc studies, and any FIT comments from this publication should not be associated with the HM-JACKarc | See response to comment no. 1 |
| Alpha Laboratories Ltd | 58 | 103-4 | Table 32 | The cost of control calculation for HM-JACKarc is overstated. [redacted] | The costs used in the report were based on the information provided by the manufacturers in response to requests from NICE. We thank the stakeholder for this additional information. Using this information, the estimated cost for the HM-JACKarc would be £[redacted] (instead of £6.04 estimated in the DAR). This, in fact does not change the conclusions of the report but it would make the cost-effectiveness results slightly more favourable to HM-JACKarc than the current results. For example, using this updated cost estimate, the base case ICER for the HM-JACKarc compared to gFOBT would be |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | [redacted] I do not believe that this materially affects the conclusions of the report comparing the HM-JACKarc FIT method to FOBT. | £17,887 (instead of £18,296 reported in the DAR). PSA results with this cost estimate are nearly identical to those in the DAR. As noted by the stakeholder, the change in costs does not materially affect our conclusions.<br><br>Regarding differences between the list price/price provided by the manufacturer and price paid in practice: Analyses can only be based on the information provided; if a stakeholder wishes alternative costs to be considered then these should be supplied when NICE requests costs information. |
| Cancer Research UK | 59 | 91 | 4.2 | Only 5/10 specialists returned the questionnaire, and not all respondents answered every question. Annotations in the R source code for the base-case also indicate that parameters could be adjusted depending on further data being received – is it sufficient to rely on such a small sample? Could the questionnaire be circulated more widely? | A larger scale survey is desirable, however, this would constitute a major primary research exercise, which is beyond the scope of this assessment. As is generally the case, the elicitation of expert opinion to inform cost-effectiveness analyses reflects the balance between the need for additional data and the available time and resources.<br><br>Because we were aware of this limitation, sensitivity analyses were performed on the key parameters that were informed by the experts. The results of these showed that |

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | they have little impact on the cost-effectiveness results. |
| Cancer Research UK | 60 | 94 | 4.2.3 | "…it was assumed that patients with a negative colonoscopy result do not have the target condition [CRC]" – it is therefore assumed that colonoscopy is 100% accurate in diagnosing CRC, but evidence suggests ~6% of CRCs are missed by colonoscopy (e.g. Morris et al, "Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service", *Gut* 2015; **64**:1248-56) | The assumption that the reference standard is 100% sensitive and specific is core to diagnostic accuracy studies and, as such is a key limitation of this study design.<br><br>Whilst cancers missed at colonoscopy could, theoretically, be included in the model, this approach would also involve assumptions. Post-colonoscopy CRC rates are difficult to assess, as any estimate is likely to involve an element of follow-up over time, i.e. it is difficult to determine how many CRC were actually missed at colonoscopy and how many may have developed in the interim.<br><br>For the current modelling exercise, the inclusion of CRCs missed by colonoscopy would reduce the cost-effectiveness of the "no triage" option and thus would not change our overall conclusions. |
| Cancer Research UK | 61 | 95 | 4.2.4 | FOB Gold assay was not included in the base-case analysis due to lack of available data – there is no indication however of how frequently this method would be used in practice and therefore it is not possible to judge how much this might affect the | This is outside the scope of our assessment, but members of the specialist committee may be able to shed some light on the question. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | validity of the model. Further exploration of this would be informative. | |
| Cancer Research UK | 62 | 102 | 4.2.4 | It is assumed that there is one lab per 500,000 people but no explanation of how this figure was derived. | This was an assumption made based on expert opinion (personal communication: e-mail from Callum Fraser, Honorary Consultant Clinical Biochemist, NHS Tayside, to Marie Westwood, Project lead, KSR Ltd, 19/07/2016). This is mentioned at the bottom of Table 31. |
| Cancer Research UK | 63 | 112 | 4.2.5 | Restated that sensitivity and specificity of colonoscopy for detection of CRC is 100% - this is not supported by the evidence. | See response to comment 60 |
| Cancer Research UK | 64 | 112 | 4.2.5 | Model assumes that "…only those with a negative test result, and whose symptoms do not persist, do not receive a colonoscopy/CTC." – This assumes that 100% of patients take up the offer of the colonoscopy/CTC – is there any available information on drop-out rates for symptomatic patients? | Four of the studies included in our systematic review reported numbers of study participants not undergoing colonoscopy; these data were for the whole study population (both those with positive and those with negative FIT results); estimates were 1%, 1.5%, 3% and 4.5%. Only one study reported information about the number of participants with a positive FIT result who did not have colonoscopy; 2/202 (1%). |
| Cancer Research UK | 65 | 113 | 4.2.5 | It is assumed that reduction in quality of life from adverse events, including bleeding and bowel perforation following colonoscopy are "negligible within a life-time", and thus does not seem to consider long-term complications such as hernia, bowel | The model does not consider reduction in quality of life associated with adverse events. This is mentioned on page 106 of the diagnostic assessment report: |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | obstruction and bleeding, the placement of a permanent stoma, or wound-related complications. | "No evidence was found on the effects of bleeding and perforation on quality of life. Thus, in line with the cost effectiveness analysis performed in NG12, our diagnostic model did not include dis-utilities for adverse events." |
| Cancer Research UK | 66 | 152 | 5.2.2 | Model assumes that all patients with a positive FIT/gFOBT and all patients in the 'no FIT/gFOBT' arm receive a colonoscopy – an acknowledged simplification as a consultation with gastroenterologist would in practice form part of the triage and only a proportion of patients would actually be referred on to colonoscopy. Could this proportion be instead estimated using the Diagnostic Imaging Dataset and/or Hospital Episode Statistics, if expert opinion is not thought robust enough? Otherwise the risk is that the costs of the 'no FIT/gFOBT' arm are over estimated. | This issue was considered and is acknowledged as a limitation in the discussion section of our report.<br><br>The model structure used follows a similar approach to that used in NG12 in that it assumes that all patients with a positive FOB test and all patients in the 'no FOB testing' arm receive colonoscopy. This is clearly a simplification, however, the alternative would involve trying to estimate the proportion of patients that the gastroenterologist would refer for colonoscopy without the FOB test information (this proportion would apply to the 'no FOB testing' arm). We would also need to estimate the effect that the positive FOB test result has on the gastroenterologist's probability of requesting colonoscopy (numbers referred from the FOB test +ve pathway). Additionally, we would then have to estimate probability of |

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | colonoscopy at every point downstream where a patient, not initially receiving colonoscopy, could be re-referred to secondary care. This would mean asking clinicians for a large number of estimates and they would essentially be giving estimates of their own performance (the accuracy of their referral decisions); high risk of bias and high levels of uncertainty seem likely and over estimates could result in any effects of FIT triage being obscured. Overall, it seems likely that the effect of the gastroenterologist (on reducing the overall number of colonoscopies) would be similar in the FOB arm to that in the no FOB testing arm, but the time to colonoscopy/delay may differ. On balance we therefore chose to include referral to a gastroenterologist (and associated costs) in the model structure, but not to attempt to model the effects of this referral on colonoscopy rates. |
| Cancer Research UK | 67 | 152 | 5.2.2 | FIT positive patients without CRC could benefit from referral to secondary care/colonoscopy for diagnosis of other conditions –this is not currently captured in the model, but could this be estimated from available data? It is not stated whether expert opinion was sought on this. | This assessment is focused on CRC; other differential diagnoses are outside scope and are therefore not included in the model.<br><br>The systematic review component of the assessment includes estimates of the proportions of people without CRC who |

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | would have a positive FIT and subsequently be diagnosed with other conditions at colonoscopy. This information has been included in the assessment in order to provide the committee with some information about the potential incidental benefits of using FIT in people with 'low risk' symptoms of CRC. |
| MAST Group Ltd | 68 | 4, 19,67 | Summary, Sec 1 Sec 3 | The Summary estimates of sensitivity.<br>The document states a comparative cut off of 10ug/g. At this cut off it states a sensitivity estimate of the OC-Sensor of 92.1%. Primarily because of the data from the Mowat paper. This paper is representative of real life and includes symptomatic patients that by both excluded and meet the NG12 criteria for a 14 day referral.<br>As a result of its inclusion of all symptomatic patients, there were the non-challenging patients that are significant 'bleeders' and would likely have been the ones included in NG12, and the challenging patients that were not significant 'bleeders'. These are the few CRC cases with a value below 10µg/g.<br>Fair enough, the true use of FIT will miss some cancers in this setting.<br><br>In contrast the quoted sensitivity estimates for the HM Jackarc (based on only 1 publication) is quoted in the summary and on page 19 as 100%. While correct, | We believe that the issue of the applicability of the studies included in our systematic review to the population defined by the scope is fully considered in our report.<br><br>At a number of points in the report (e.g. sections 3.2.2 and 5.2.1) we note that no study reported data specific to the population defined by the scope (i.e. people with 'low risk' symptoms as described in NG12). We also note that the Mowat study was the only study to be conducted in primary care, with GPs ordering FIT before referral.<br>For further clarification, the table in Appendix 2a records the proportions of patients, in each study, presenting with individual symptoms (where these data were available. It is interesting to note that the proportion of patients reported as presenting with rectal bleeding was higher in the Mowat study |

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | based on this single paper – its not a fair comparison.<br><br>The Godber data set is not identical to the Mowat cohort and represents a much more refined (along the lines of NG12) patient set. As a result it does not include the challenging patients mentioned above. All of the CRC cases found were very significant bleeders and would be well within the range of both the OC Sensor and HM Jackarc – in which case they would both be 100% sensitive.<br><br>By contrast, if you pitch the HM-JACKarc in the Mowat data set, it's a reasonable assumption that the same results would be obtained. The HM-jack would miss the low cancers because they are all below the manufacturers stated cut off of 10µg/g.<br><br>I believe to present the HM-Jackarc as a 100% sensitivity could be risky given that clearly it will miss some cancers (as has happened since publication) when pitched against the challenging patients (as indeed would the OC Sensor).<br><br>I believe this statement also presents a commercial bias. This is a very big document and I would suggest that it's unlikely to be read in its entirety by the majority of prospective users. If you assume that most | (34.2%) than the Godber study (15.2%). |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | would only read the summary, this does not give a representative picture. | |
| MAST Group Ltd | 69 | Page 67 | 3 | Further to the above comment, here on page 67 it states an HM-Jack sensitivity of 91.3% at 10µg/g. Since this is the minimum stated cut off value and the comparator point between the assays, this is the data that should be presented in the summary pages – not 100%. Remembering that the data classified as 'any detectible blood' or below the minimum cut off value is interesting, it cannot be used in real life. So should be represented as such in this document. | This is a typographical error in the main text (pg.) 67). The sensitivity value of 100% is, in fact, the correct value for the 10µg/g threshold. We thank the stakeholder for noting this and will correct the error ahead of publication. |
| MAST Group Ltd | 70 | Page 104 | 4 | Since there is no support data for the FOB gold with which to make ICER and QUALY assessment and they have not provided sufficient breakdown of prices to directly compare against the HM Jack and the OC Sensor. I see no value in mentioning the price of the FOB gold table 33. It would appear artificially low and therefore could be misleading for prospective customers that have nothing else in the document to support FOB-Gold. This should be excluded as well. | We have chosen to include the limited data available for FOB gold in order to provide the committee with the fullest possible information. All limitations are clearly described and it is for the committee to decide whether these data are sufficient to support any recommendation. |
| MAST Group Ltd | 71 | Page 67 | 3 | Expanding into the 1000 hypothetical patients discussion. Again it assumes that the HM Jack will not miss any cancers at 10µg/g based in the Godber data. I propose that if used on the same patient cohort – neither would the OC Sensor. | Please see response to comment 68 |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| MAST Group Ltd | 72 | Page 82 onwards | 4 | The majority of the statistics in the section may need to be reworked. It's based on the assumption that the HM Jack base case has 100% sensitivity. As stated above at the minimum of 10ug/g cut off has a sensitivity of 91.3% – therefore the 100% assumption is invalid and cannot be used in real-life as its below the cut off stated by the manufacturer. | Please see responses to comments 68 and 69 |
| MAST Group Ltd | 73 | Page 30 | Table 4 | Please amend the cut off values for all the OC Sensor platforms to 10µg/g (50ng/ml). as supported by the IFU. | We assume that the stakeholder is referring to Table 1: Overview of Quantitative Faecal Immunochemical Tests (information supplied to NICE by test manufacturers), on page 30. The correction will be made ahead of publication. |
| MAST Group Ltd | 74 | Page 25 | 2 | The documents states that NG12 recommends the use of Guaiac testing – no it doesn't. It simply states testing for occult blood in faeces. | Please see response to comment 9 |
| MAST Group Ltd | 75 | Page 33 | 2.4.2 | States that following a positive test for occult blood in faeces, patients are usually offered colonoscopy in 14 days. I would question the 'usually' in the statement as most laboratories can no longer offer an FOBT of any sort. | Opinion only – no response required |
| British Society of Gastroenterology | 76 | | | The model parameters may not reflect the way FIT will be used in primary care if NICE makes a recommendation based on this report<br><br>a) The model assesses FIT "as a triage test for people presenting, in primary care settings, with lower abdominal symptoms, who are at | The specific issues raised are discussed in the report. The wording of any potential recommendations is a matter for the committee. Implementation issues are considered elsewhere in NICE. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | low risk for CRC according to the criteria defined in NG12, *and for whom a referral for secondary care investigation for possible CRC is being considered*" (my italics).<br>At present, GPs understand that referral to secondary care may involve invasive investigations. Their threshold for considering referral is adjusted accordingly.<br>FIT offers a much less invasive "triage" test with high exclusion value for CRC. It is likely, therefore, that it will be used in patients where the GPs index of suspicion for cancer is far lower than the index of suspicion required to consider referral for colonoscopy.<br>The studies included in the report comprised patients in whom the decision to refer to secondary care had already been made or who were tested in secondary care after referral.<br>How can NICE ensure that the use of FIT will be restricted to these groups in practice?<br><br>b) We have no information about how a recommendation concerning FIT would be implemented in primary care.<br><br>The report is clear that there are no studies available that examine utility of FIT in the low- | |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | risk population described by NG12.<br>The recommendation for FOBt in low risk patients is widely ignored because gFOBt is seen as an unreliable test.<br>If FIT is regarded as a more useful exclusion test it may be more widely adopted.<br>The model assumes that all patients tested with FIT would otherwise be referred to gastroenterology clinics and then undergo colonoscopy. I am not sure this is valid.<br>I contend that if FIT is recommended by NICE it will be used to test many more patients than are presently “considered for referral” to secondary care. This will generate a high number of false-positive patients who will need colonoscopy. This will offset the savings achieved by referrals avoided. It will also create a significant burden for endoscopy services.<br><br>c) The cost effectiveness calculation is sensitive to the CRC prevalence in the population. If FIT is used for a wider population than the studies (or NG12 estimates) assume, the prevalence may be lower than that used in the base-case model.<br>d) The model implicitly assumes FIT will be used only in patients over 40 years old. | |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | NG12 allows FOBt without any age restriction for patients with change in bowel habit or iron deficiency anaemia.<br><br>The studies discussed in the report generally included older patients. As I understand it, the CRC prevalence of 1.5% used in NG12 was also based on a population in the age range of 40 to 59.<br>The danger is that, if FIT is promoted as a useful exclusion test, it will be adopted for younger patients (i.e. those <40 years). The prevalence of CRC for this young cohort is presumably much lower than estimates used in this model.<br>It might be assumed that GPs would restrict testing to patients >40 years. I know from experience however that when NICE includes non-age-restricted symptoms in their recommendations this leads to inappropriate referrals. For example, I see women in their 30s referred for upper endoscopy under the 2 week rule with globus pharyngeus (interpreted as “dysphagia”). | |
| British Society of | 77 | | | Service implication of an elevation in referral priority | Please see previous response (comment 76) |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| Gastroenterology | | | | a) Even if FIT is used only for those patients who would otherwise be referred to a gastroenterology clinic, the committee must remember that FIT positive patients would be referred under the 2-week rule, whereas previously they would have been referred as routine (given their low-risk status).<br><br>For every 1000 patients tested in primary care at the 10 µg Hb/g faeces threshold, about 250 extra urgent colonoscopies will have to be accommodated. I concede that the potential cancer yield from this is high, but shifting these patients to 2-week rule status will have a significant impact on endoscopy units' ability to meet the target for other NICE "high-risk" symptomatic patients.<br><br>b) I accept the argument that other significant colonoscopy findings in FIT positive patients will mitigate the impact of the relatively high false positive rate. However, there are cheaper and less demanding methods to diagnose many such conditions, such as flexible sigmoidoscopy – and there is rarely a need for these conditions to be diagnosed with 2-week rule priority. | |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | | |
| British Society of Gastroenterology | 78 | | | The clinical experts' estimates for the proportion of patients with a negative faecal occult blood test result in whom symptoms will persist and who will eventually receive a colonoscopy/CTC varied widely. Only 2 out of the 5 experts who returned the questionnaire felt able to answer this question (I was not one of them). I believe that this reflects a lack of clarity about the sort of patients who are likely to be tested by FIT in primary care. The NG12 recommendation to offer FOBt to patients under 60 with changes in their bowel habit is too all-encompassing. | Comment about the validity of NG12 – no response from EAG needed |
| British Society of Gastroenterology | 79 | | | CT colonography vs colonoscopy<br><br>a) The report quotes Logan 2012 as justification for the assumption that most FIT positive patients will undergo colonoscopy. However, this publication is about the NHS Bowel Screening Programme in which colonoscopy is, by protocol, the primary imaging modality offered. CT colonography is permitted in the Programme only for those patients who are medically unfit to have colonoscopy or in whom colonoscopy is impossible.<br>b) CT colonography is being used increasingly for | The assumption most FIT positive patients undergo colonoscopy rather than CT colonography was also based on expert opinion form the survey and discussions at the scoping meeting.<br><br>a) Logan is used for the scenario where we assume that all patients undergo colonoscopy (and no CTC) but for the base case we used the estimate given by the experts.<br>b) Comment only – no response needed<br>c) The model does not incorporate this. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | investigation of 2-week rule patients referred from primary care because of pressures on colonoscopy waiting lists.<br>c) Patients who have a cancer (or significant polyp) detected on CT colonography will need a subsequent colonoscopy for histological confirmation in nearly every case. I am not sure if the model incorporated this fact in the cost analysis. | The options are either colonoscopy or CTC and both are assumed to be equally effective based on the discussion during the scoping meeting. |
| British Society of Gastroenterology | 80 | 159 | | "all colonoscopy findings buy ICD-10 code" in second paragraph. | This error will be corrected ahead of publication |
| British Society for Gastroenterology | 81 | | | Much of the work on which FIT referral algorithms are based has been undertaken in secondary care. BSG believe that further research on this matter, particularly in primary care, should be undertaken. Funders should prioritise research in this area. | Comment for discussion by the committee |
| Sysmex UK Ltd | 82 | | | We note that the included publications for other FIT systems aren't clearly focused on patients from primary care, but just on symptomatic patients.<br><br>Therefore, we consider that the submitted study by Dr. Augè - Personal Communication from Philippa Pinn Sysmex UK Ltd - in regard to FOB Gold should be considered on the same level and thus fully included | The difference between the FOB study and others included in the review lies in the description of the included participants, rather than in the study setting. Other studies provide a clear statement that participants were symptomatic and/or a description of presenting symptoms. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | in the evaluation. | The draft article, which was provided AiC by Sysmex, did not report any details of presenting symptoms. The study was described as a [redacted] After seeking clarification, through NICE, the company stated that participants were symptomatic, but no further details were supplied. The study was provided without details of authorship.<br><br>This lack of information is reflected in our assessment |
| Sysmex UK Ltd | 83 | | | We would appreciate feedback from the committee in regard to what is missing in Dr. Augè data that may prevent its inclusion since it is very similar to the publication featured for the HM Jack system.<br><br>Will it be a requirement that the 'Confidential' cloak be removed in order for the study to be fully considered? Please consider that, in case that we need to clarify some aspects of the study with him, we need some time to contact/visit him hence we will exercise the right to notify NICE that we will submit additional data within the scope of the Report | AiC status will not affect consideration of these data by the committee (AiC data are made available to the committee, but not to other stakeholders or the general public. We do not agree that the data provided are similar to that for HM-Jack, for the reasons outlined above and because the majority of the data were analysed on a per. sample rather than a per. patient basis. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| Sysmex UK Ltd | 84 | | | We would like to ask why FOB Gold is not fully considered for the economical evaluation.<br><br>We are available to provide as soon as possible detailed costs for FOB Gold system. | FOB Gold is not included in the base-case economic analysis due to the limitations described above, as well as the lack of costs data.<br><br>Detailed costs were requested by NICE and were not provided.<br><br>In any case, two additional scenarios were explored where the FOB Gold was included as an intervention in the economic analysis (see e.g. Table 45, accuracy scenarios IV and V). |
| Sysmex UK Ltd | 85 | | | The comparison of every FIT system is rather difficult considering the differences in cut-off values for each FIT; this because every company refers to their own “in house” standard material as there is no international reference material.<br><br>In the Augè study we have submitted, there is a variety of cut off levels examined (40, 120,200,400) with respective Sensitivity and Specificity values, PPV and NPV. And also evaluation of performances using the 117 ng/mL cut-off (20 µg/g) that corresponds to 100 ng/mL of OC Sensor.<br><br>We would like to represent the “positivity rate” for consideration as suggested in the recent study by Dr. | We acknowledge the differences between FIT assays. For this reason our systematic review does not attempt to make comparisons of test performance between assays; each assay is assessed individually.<br><br>There are a number of methodological problems with the Augè study (see comments above) and these are reflected in our report.<br><br>The study cited was conducted in a screening population and is therefore not applicable to this assessment. |

**Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care**

**Diagnostics Assessment Report (DAR) - Comments**

| Stakeholder | Comment no. | Page no. | Section no. | Comment | EAG Response |
|---|---|---|---|---|---|
| | | | | Grobbee (A randomized comparison of two faecal immunochemical tests in population-based colorectal cancer screening. Gut 2016): These findings imply that future studies should compare FIT brands on positivity rate rather than on faecal Hb concentration and in reliability at analysis? | We do not believe that it is appropriate to assess diagnostic tests in terms of their "positivity rate", as this takes no account of the numbers of false positive results that occur. |
| Sysmex UK Ltd | 86 | | | One Italian Hospital will present a poster with data of sensitivity and specificity at different cut-offs and comparison vs. OC Sensor Diana at the UEG Week in Vienna, using samples from the routine (symptomatic patients).<br><br>Data from this study will be available immediately after the presentation at the congress (Oct 17th). Is it possible to evaluate their inclusion afterwards? | This is a decision for NICE.<br><br>If details of the presentation are supplied on the 17th October, we can read it and provide verbal comment for the committee. There is insufficient time to provide a formal written response or to include any relevant data in the report. |