NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 23 March 2017

THEME: Evidence for RIDASCREEN assays

Comment number	Name and organisation	Section number	Comment	NICE response
1	R-Biopharm Rhone Limited	4.3	Clinical effectiveness of RIDASCREEN Haemoglobin (Hb) and Haemoglobin / Haptoglobin (Hb/Hp) complex assays is supplied in the attached 3 publications – 2009, Haug et al; 2010, Brenner et al; 2013, Brenner for inclusion in to the DAP DCD.	Thank you for your comment which the committee considered. The publications were reviewed by the external assessment group who confirmed that all 3 publications were identified by the literature searches conducted to inform their systematic review. They were excluded because they were conducted in screening populations and do not report data for the population defined in the scope for this assessment.
2	R-Biopharm Rhone Limited	Table 4	Diagnostic accuracy for sensitivity and specificity derived from published data is provided in the attached product brochure.	Thank you for your comment which the committee considered. The product leaflet was reviewed by the external assessment group who confirmed that it did not provide sufficient information to determine whether the data reported are applicable to the decision problem for this assessment.
3	R-Biopharm Rhone Limited	5.3	Please review to include information from the 3 attached publications as stated in comment 1 above.	Thank you for your comment which the committee considered.

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				The publications were reviewed by the external assessment group who confirmed that all 3 publications were identified by the literature searches conducted to inform their systematic review. They were excluded because they were conducted in screening populations and do not report data for the population defined in the scope for this assessment. Therefore no changes to the diagnostics guidance were needed.
4	R-Biopharm Rhone Limited	Additional information	Additional information provided by the RIDASCREEN Gastroenterology Product Manager in e-mail exchange on the 13th of October with Professor Longson.	Thank you for your comment which the committee considered. The committee noted the additional technical information provided and decided that no changes to the diagnostics guidance were needed.

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THEME: Cost-effectiveness of RIDASCREEN assays

Comment number	Name and organisation	Section number	Comment	NICE response
5	R-Biopharm Rhone Limited	4.27	The price for both the RIDASCREEN Hb and RIDASCREEN Hb/Hp assays is £188 for a 96 well EIA kit. Considering 4 standards in duplicate and 2 controls this gives a cost per patient sample of £2.19. Additional cost of a sample preparation device if required is £0.84 per patient.	Thank you for your comment which the committee considered. The committee noted that because of insufficient clinical data on the population defined in the scope for the assessment, this technology could not be included in the cost effectiveness modelling.
6	R-Biopharm Rhone Limited	Tables 5 and 6	Prices given in comment 5 above can now be used to give consideration to the RIDASCREEN Hb and RIDASCREEN Hb/Hp assays	Thank you for your comment which the committee considered. The committee noted that because of insufficient clinical data on the population defined in the scope for the assessment, this technology could not be included in the cost effectiveness modelling.
7	R-Biopharm Rhone Limited	4.31; 4.32; 4.33	Consideration needs to be given to RIDASCREEN Hb and RIDASCREEN Hb/Hp assays in light of prices given in comment 5 above.	Thank you for your comment which the committee considered. The committee noted that because of insufficient clinical data on the population defined in the scope for the assessment, this technology could not be included in the cost effectiveness modelling.

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THEME: Equivalence of technologies and test threshold

Comment number	Name and organisation	Section number	Comment	NICE response
8	NHS Professional	General	To our awareness there are 4 quantitative FIT analysers currently available on the market (OC-Prime/ Sensor, HM-JACK, Sentinel FOB-gold, Alfresa NS-prime). Based on analytical evaluations carried out at the Southern bowel cancer screening Hub and Guildford Medical Evaluation Centre (GMEC), all these analysers have acceptable analytical performance so are fit for purpose. It is however important to be aware that the absolute value of results obtained on each analyser will be different since there is no standardisation of FIT immunoassays. We have unpublished data that demonstrates this variation and the bias of results obtained on the analysers in relation to each other. In view of the above, consideration needs to be given to the absolute value of 10ug/g that is currently being proposed in the Diagnostic Guideline.	Thank you for your comment which the committee considered. The NS Prime assay was not included in the scope for this assessment because expert advice received during scoping indicated that the test was not being marketed in the NHS. The committee acknowledged that further work needs to be done by the companies and the laboratory medicine community to ensure standardisation of the results provided by the technologies. The committee decided to change section 1.2 of the diagnostics guidance and include a research recommendation on assay variability (section 6.3).

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THEME: Study heterogeneity

Comment number	Name and organisation	Section number	Comment	NICE response
9	MAST Group	General	We are missing a trick with this publication. Quantitative FIT assays produce a numerical result. The WEO expert working party went to the trouble of authenticating the µg/g units to enable direct comparison. Why don't we use it? Clearly if you used the HM Jack in the Mowat cohort – it would also miss cancers at 10µg/g. Likewise if you used the OC Sensor in the Godber paper – where all the cancers are huge bleeders, the sensitivity would be 100%. I'm very conscious that the patients are different – Mowat requested a FIT test of all patients that GP's were considering for referral. Godber only collected samples from patients that were referred (based on the severity of other symptoms presumably) – by default those of most concern. Looking at the range of haemoglobin levels across pathologies in both cohorts – they are clearly very different.	Thank you for your comment which the committee considered. The committee opted to recommend a threshold using the internationally accepted reporting units (micrograms of haemoglobin per gram of faeces). The committee noted that direct comparison between the assays had not been feasible in the analysis because no studies were found which reported comparative data, but heard from experts that there was thought to be variability between the technologies. It heard from the external assessment group that the proportion of patients with rectal bleeding was higher in the Mowat study (34.2%) than the Godber study (15.2%), and that it is not possible to directly compare the OC Sensor and HM JACKarc with the available data from these studies. The committee noted that a range of scenario analyses had been done by the external

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			By summarising the outcomes in simple terms of sensitivity without making the patient background much clearer, you are in effect directly comparing the statistical performance and this is wrong. The issue is then amplified in the model of 1000 patients and compounded in the financial assessment.	assessment group to examine the impact of diagnostic accuracy on cost effectiveness. The committee decided to amend the diagnostics guidance to encourage companies to work towards standardisation of results (see section 1.2 of the guidance) and to encourage further research to investigate variability between the assays (see section 6.3 of the guidance).
10	MAST Group	4.6	In the analysis of the OC Sensor – the performance of the McDonald paper has not been included. Only that of Mowat and Rodriguez-Alonso are included. Given that Mowat or Rodriquez-Alonso did not use the same patient cohorts as Godber – it is not a fair comparison to use when it comes to statements about sensitivity and missed cancers in the financial calculations.	Thank you for your comment which the committee considered. The committee heard from the external assessment group that data from Mowat et al. (2015) and Rodriguez-Alonso et al. (2015) were used to illustrate diagnostic outcomes when colorectal cancer and advanced neoplasia was the target condition because they were the only studies reporting data for this endpoint. A summary estimate derived from 4 studies, including McDonald et al. (2012) was used to model the cost effectiveness of the OC sensor

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				assay (see table 1 and table 4 in the diagnostics guidance). The committee decided that no changes to the diagnostics guidance were needed.

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THEME: False negative results

Comment number	Name and organisation	Section number	Comment	NICE response
11	NHS Professional	General	The evidence that is available demonstrates that with a cut-off of 10ug/g both the HM-Jack and OC-sensor analysers will miss some cancers. This should be made clear in the guidelines.	Thank you for your comment which the committee considered. The committee noted its previous conclusion that using a threshold of 10 micrograms haemoglobin per gram of faeces gave sufficient sensitivity to reliably rule-out colorectal cancer in primary care in a low risk symptomatic population (see section 5.5 of the diagnostics guidance). Further it heard from the external assessment group that the economic modelling took account of the 95% confidence intervals associated with the summary estimates in the probabilistic sensitivity analyses, which captures the impact of false negative results (see table 4 in the diagnostics guidance). However, the committee wished to highlight the need for healthcare professionals to consider that the tests will be associated with false negative results and chose to amend section 5.14 of the guidance to emphasise the need for safety netting where false negative results are suspected.

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THEME: False negative results

Comment number	Name and organisation	Section number	Comment	NICE response
12	Cancer Research UK	3.1	We welcome the recognition of false-negatives as an issue and the need for safety netting. It is very important that patients with false-negative results, in case of persisting symptoms, would be immediately referred to secondary care.	Thank you for your comment which the committee considered.
13	MAST Group	4.10	The document states that two publications (Godber 2016 & Thomas 2016) reported data for CRC using the HM Jack. Clearly the Thomas paper shows a lower sensitivity of 91.3% at 7 g/g cut off. At 10µg/g this sensitivity could be even lower because the cut off is raised. Why is this data ignored when it comes to the statement of 100 sensitivity for CRC and even worse not accommodated in the assumption model of 1000 patients in table 3 – and the resulting financial calculations where it assumes no cancers will be missed. Which is simply not the case as users will tell you.	Thank you for your comment which the committee considered. The committee heard from the external assessment group that the economic modelling took account of the 95% confidence intervals associated with the summary estimates in the probabilistic sensitivity analysis and therefore takes account of false negative results (see table 4 in the diagnostics guidance). Diagnostic accuracy estimates were also varied in sensitivity analyses (see sections 4.34 to 4.37 of the diagnostics guidance). The committee decided that no changes to the guidance were needed.

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THEME: False negative results

Comment number	Name and organisation	Section number	Comment	NICE response
14	MAST Group	General	We have the tools, we should be using the information that comes out appropriately. I'm concerned for two reasons: 1) Nice have gone to a lot of hassle to try and answer these questions after the NG12 was received last year. It would be a shame for those who read the report to pick out the clear inconstancies and for the publication to tarnished. 2) Worse still would be those that don't read the document (and have to read the researchers publications to understand the true differences in patient cohorts) in its entirety and leave with the impression that either FIT has a 100% sensitivity.	Thank you for your comment which the committee considered. The committee noted its previous conclusion that using a threshold of 10 micrograms haemoglobin per gram of faeces gave sufficient sensitivity to reliably rule-out colorectal cancer in primary care in a low risk symptomatic population (see section 5.5 of the diagnostics guidance). Further it heard from the external assessment group that the economic modelling took account of the 95% confidence intervals associated with the summary estimates in the probabilistic sensitivity analyses and therefore takes account of false negative results (see table 4 in the diagnostics guidance). However, the committee wished to highlight the need for healthcare professionals to consider that the tests will have some false negative results, and chose to amend section 5.14 of the diagnostics guidance to emphasise the need for

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				safety netting where false negative results are suspected.

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THEME: Management recommendations

Comment number	Name and organisation	Section number	Comment	NICE response
15	Institute of Biomedical Science	2	The introduction of automated tests for faecal haemoglobin provide an opportunity to improve the accuracy and quality of information used by clinicians to manage people with suspected cancer.	Thank you for your comment which the committee considered.
16	Institute of Biomedical Science	2	There is growing evidence that using faecal haemoglobin can aid the triage patients to appropriate care pathways across a number of clinical settings.	Thank you for your comment which the committee considered.
17	Institute of Biomedical Science	2.5	It is important the test is used send patients to the correct care pathway, not deny them colonoscopy.	Thank you for your comment which the committee considered. Section 5.14 of the diagnostics guidance includes the committee's consideration of using safety netting to ensure that people who may have had a false negative result receive appropriate follow-up.
18	Institute of Biomedical Science	5.15	There is growing evidence that faecal haemoglobin could be used in 'risk scores' further enhancing the usefulness of this test in triaging patients for endoscopy.	Thank you for your comment which the committee considered. Section 5.15 of the diagnostics guidance includes the committee's considerations on the use of risk scores, which include faecal haemoglobin levels, to assess people who have symptoms which may

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THEME: Management recommendations

Comment number	Name and organisation	Section number	Comment	NICE response
				be associated with colorectal cancer. The committee wished to encourage further research to develop these scores and further refine the use of faecal immunochemical tests in primary care (see section 6.2 of the diagnostics guidance).
19	NHS Professional	General	The limited evidence that is available does indicate that FIT has the potential to triage symptomatic patients. However, the evidence base is still very limited at this stage with no evidence, to our awareness, demonstrating whether FIT introduction does actually decrease referral to colonoscopy. There is a risk that by offering GP's an additional test there will be an increase in testing leading to an increase in referrals.	Thank you for your committee which the committee considered. The committee noted that the impact of faecal immunochemical tests on colonoscopy capacity may vary across England, and that there was uncertainty surrounding this at present. The committee wished to encourage commissioning groups adopting the faecal immunochemical tests to audit their outcomes and monitor the associated resource use (see section 6.1 of the diagnostics guidance).

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THEME: Further research

Comment number	Name and organisation	Section number	Comment	NICE response
20	Cancer Research UK	2.5	We recommend further research should be conducted on the quantity of people who were not before, but would now 'under the new guidelines' be eligible for the investigation via FIT.	Thank you for your comment which the committee considered. Section 6.1 of the diagnostics guidance notes that this work is already ongoing, and encourages commissioning groups who adopt the faecal immunochemical tests to audit their outcomes and monitor associated resource use.
21	Cancer Research UK	5.3	We welcome the auditing point. This will be helpful to establish the clinical effectiveness of the FOB Gold test. Auditing will also be valuable to assess the risk of missing cases.	Thank you for your comment which the committee considered. Section 6.1 of the diagnostics guidance encourages commissioning groups who adopt the faecal immunochemical tests to audit their outcomes and monitor associated resource use.
22	Cancer Research UK	6	We welcome further work from NHSE and PHE to research optimal FIT thresholds/algorithms. This research will also be relevant for the use of FIT in the bowel screening programme.	Thank you for your comment which the committee considered.

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THEME: Implementation

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23	Institute of Biomedical Science	3, 4.6	The guidelines present analytical solutions and a suggested cut-off. This will contribute to a uniform approach to delivery, however timescales for implementation have to be considered to ensure equal opportunity to access the new technology across geographical areas.	Thank you for your comment which the committee considered.
24	Institute of Biomedical Science	5.16	A solution to the issue of access to tests for faecal haemoglobin would be for regional centres to take on faecal haemoglobin testing for defined areas, eg following the screening hub model – five in England, one in Wales, one Northern Ireland and one in Scotland.	Thank you for your comment which the committee considered.
25	Cancer Research UK	1	We welcome this guidance from NICE. We believe the guidance will help to reduce confusion by promoting clarity and consistency in commissioning intentions and practice. More consistent use of the Faecal Immunochemical Test (FIT) for people who have symptoms which are 'low risk but not no risk' will be a positive addition to our efforts to diagnose cancer earlier, as they may otherwise miss out on a diagnostic test. If the publication of this guidance can be accelerated before April 2017 (as currently	Thank you for your comment which the committee considered.

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THEME: Implementation

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			timetabled) this would be useful as we understand that some CCGs would like to commission FIT in the next financial year.	
26	Cancer Research UK	5.9	If fully adopted in the service, this NICE guideline will enable laboratories to be commissioned to deliver the test, thereby allowing primary care access. NICE's implementation team could have a role in disseminating the guidance and ensuring it is widely used. We recommend that the NICE implementation team (working with NHS England and devolved nations health services) explore the barriers to the use of symptomatic Faecal Immunochemical Testing (FIT) and any variations at the local level. Information on access to FIT across England, Wales and Northern Ireland is needed as at the moment it seems to be used in only a few locations in the UK. This implementation work should also aim to reduce inappropriate variation between tests produced by different manufacturers, as further understanding can be gained about the different tests and the thresholds that could be used.	Thank you for your comment which the committee considered. NICE diagnostics guidance recommendations cover the NHS in England. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

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27	Cancer Research UK	6	We recommend guidance should include information on the logistics and processes for use of the FIT in primary care. For example, will the sample for testing be given to the GP on the day of consultation, or will the patient be referred elsewhere? For instance, in Mowat's study patients were asked to collect their sample from a single faeces and return the sample immediately to the GP surgery. In Godber's study participants were instructed to post their sample back to the Department of Biochemistry and in Rodriguez-Alonso's study, patients were instructed to store the sample in a fridge and submit within 7 days. There is an evidence gap about which pathway should be used, but current best practice (as suggested below) should be included in the guidance. This should also include defined turnaround time for how long GPs should wait for results. Patients currently return their faecal samples to their GP surgery, where it is then sent onto labs for analysis. To allow for the swift introduction of FIT for symptomatic patients, continuing to use this process would be the least disruptive. However, we	Thank you for your comment which the committee considered. The committee noted that there were various models of testing that could be implemented, but that this may depend on systems that are already in place at a local level for other laboratory tests such as faecal calprotectin. NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

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			recommend further research is needed to explore attrition from the diagnostic process, as the additional step of returning the sample to the GP might mean that patients do not return their tests. In the UK-based studies we have looked at, in Godber's study (which involved one sample, directly posted) the return rate was 507 out of 909 invitees, whereas in Mowat's study the return level was 1043 out of 2173 (although this required two samples). Currently uptake has not been compared between different pathway arrangements.	
28	Cancer Research UK	5.16	As well as information for people who have recently taken part in screening, the committee should also consider how to provide patients with sufficient information when they are invited for screening and have recently used FIT for symptomatic testing. Although FIT used for screening would have a different threshold, we would not want to undermine future participation in screening.	Thank you for your comment which the committee considered. The committee decided to change section 5.16 of the diagnostics guidance to highlight that consideration needs to be given to providing information to people who have had a symptomatic test and who are subsequently invited to take part in the bowel cancer screening programme.

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THEME: General

Comment number	Name and organisation	Section number	Comment	NICE response
29	Institute of Biomedical Science	2	The NICE guidelines will be important in offering guidance on how to use faecal haemoglobin in clinical settings other than screening for colorectal cancer.	Thank you for your comment which the committee considered.
30	Institute of Biomedical Science	2.5	If used appropriately the guidelines will provide an opportunity to standardise practice in the management of patients with suspected cancer.	Thank you for your comment which the committee considered.
31	Sysmex UK Ltd	General	I do not wish to make any comments in regard to the diagnostic consultation document at present.	Thank you for your comment which the committee considered.
32	Alpha Labs		We have no comments regarding the draft recommendations based on the data provided.	Thank you for your comment which the committee considered.