NICE National Institute for Health and Care Excellence

Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel

Diagnostics Assessment Report (DAR) - Comments

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Royal College of Nursing	1.	N/A	N/A	Nurses working in this area of health were invited to submit comments to inform on the final Diagnostic Assessment Report (DAR) of the above diagnostic procedure. Feedback suggests that there are no comments to make on this document on behalf of the Royal College of Nursing at this time. Thank you for the opportunity to participate.	No response required (NRR)
Royal College of Pathologists	1.	N/A	N/A	The report appears to be well evidenced and very comprehensive and feel there is not much to add from the point of view of the RCPath. There could perhaps be more emphasis on the governance issues with performing FC testing at the point of care, but I feel this falls outside the remit of the assessment in whether FC as an entity is suitable for widespread use.	NRR
Buhlmann	1.	37		It is clear that the NICE goal here is the diagnosis around cut off 50, still it should be mentioned in the table that the EK-CAL can be run in two dilutions offering a range of 10-600 AND 30-1800 ug/g.	The NICE goal has yet to be determined.
	2.	103		Damms et al shows ROC curves for Prevista and EK CAL, we believe the difference IS significant as Prevista is below AUC 0.9 and EK CAL is a t 0.96.	NRR – Prevista no longer available.

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				Spec and Sens are also clearly better.	
	3.	106		In the Kolho paper as statement in the discussion it says: “We have demonstrated that a rapid test has comparable performance to a conventional ELISA for detecting abnormal values of FC.” It would be good to cite it that way.	NRR. We have said that POC tests are about as good as ELISA ones.
	4.	112		Next to Loitsch et al., We wonder why the study from Belgium is not mentioned, L. Claeys et al.?: Clinical comparison EK CAL vs CALPRO? (see attached poster). They should have received it	We did not receive it. No industry submissions were received by the EAG. This abstract does not appear to have led to a published paper. We looked at all abstracts if they were retrieved in our search. Meeting abstracts were included in Embase and Web of Science and we directly searched the ECCO website for new ones that may not have been included. This abstract would have been considered if a) we had received it or b) it had appeared in our searches. But it didn’’t appear.
	5.	172		All the Kings College data gathered using the EK-CAL, should be mentioned.	NRR
	6.	General		A general comment is that Whitehead is cited, basically using the content of an early NEQAS round. In later and more recent NEQAS rounds, the EK-CAL is performing “better” or “closer” to the main mean, as	NRR

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				is described here (3.8 times higher…). We believe that there shouldn't be a limited view to this.	
Thermo Fisher Scientific	1.	2	Acknowl.	The correct name of the company is "Thermo Fisher Scientific"	OK, we will correct this in final version.
	2.	2	Acknowl.	Dr Barbara Mascialino	OK, we will correct for published version. The assessment report will be published as monograph in Health Technology Assessment, possibly in the autumn. The HTA Programme will send it for anonymous peer review which will take some time. After that, we will be expected to consider the referees' comments and make any changes necessary. There are usually two rounds of editorial comment. The process often takes longer than 6 months.
	3.	17	Results	Please include to the list of "IBD versus non-IBD" studies the following article: Prell C, Nagel D, Freudenberg F, Schwarzer A, Koletzko S.Comparison of three fecal calprotectin assays in a pediatric population with suspected or proven gastrointestinal disease. Manuscript in Preparation, submission planned for Clinica Chimica Acta in June 2013.	No. We can't be expected to include manuscripts in preparation This article was never made available to us
	4.	21	How do rapid compare	We suggest stressing the fact that for rapid testing, due to higher imprecision compared to lab tests, re-testing of samples with results in the grey zone is	We are not sure this is entirely correct. We would expect a borderline lab result to be tested too. This applies to people with

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			to lab tests?	sometimes recommended, while this does not happen in laboratory test. Therefore, re-testing has an impact on the total costs using rapid tests. This does not occur with lab tests.	levels in the 50ug/g to 150ug/g (or even to 200ug/g)
	5.	36	1.4.2	POC tests have a higher imprecision than lab tests, making them less reliable. Manufacturers recommend re-testing samples around the cut-off, which creates extra costs.	NRR
	6.	36	1.4.2	We suggest adding FEIA to the list of laboratory testing methods.	OK, will add in published version for completeness.
	7.	37	Table 2	Name of Test: EliA Calprotectin Type of Test: FEIA (fluoroenzyme immunoassay) Manufacturer: Thermo Fisher Scientific (manufactured by Phadia AB, Sweden) Notes: Quantitative fluorescence enzyme immunoassay (FEIA) test. Uses monoclonal antibodies. Recommended cut-off 50 mg/kg. Measuring range 15 - 3000mg/kg. EliA Calprotectin is a fully automated test, said by the manufacturer to reduce technician workload, time and cost.	NRR

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	8.	41	1.5 Stat Methods	The meta-analysis was conducted by pooling the lab ELISAs and the POCT separately; based on the evidence provided in the Prell et al article (that will be submitted in June 2013, outline and related plots in attachment), the performance of ELISA and FEIA methods is in agreement. Therefore, we kindly ask to repeat the meta-analysis pooling lab data from ELISA and FEIA.	NRR. We have not seen the unsubmitted Prell article nor any published studies on the Elia method.
	9.	63	Table 8	Name of Test: EliA Calprotectin Type of Test: FEIA Evidence Base: IBD vs. non-IBD (Prell et al. Manuscript in Preparation, submission planned for Clinica Chimica Acta in June 2013)	NRR. Prell paper not available to EAG.
	10.	68-71		Figures 3 – 4 – 5 – 6 – 7 are missing (maybe because unpublished material)	Yes, academic in confidence.
	11.	77-78		Figures 9 – 10 – 11 are missing (maybe because unpublished material)	Yes, academic in confidence data in figures
	12.	79	2.7	Please include to the list of studies the following article: Prell C, Nagel D, Freudenberg F, Schwarzer A, Koletzko S.Comparison of three fecal calprotectin assays in a pediatric population with suspected or proven gastrointestinal disease. Manuscript in Preparation, submission planned for Clinica Chimica	Cannot be included.

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				Acta in June 2013.	
	13.	82	Table 17	Study: Prell et al, 2013 (to be submitted), outline attached Number of patients: 197 Recruits: 130 patients with newly diagnosed IBD and 67 patients with non-inflammatory functional bowel diseases Setting: Hospital, Germany Aim: performance comparison between one FEIA and two ELISA products in unselected pediatric patients Reference test: PhiCal (Calpro AS, Norway) Exclusions: Children below 2 years old	NRR. We did not receive this paper until 29th April, far too late for inclusion. From the outline, it is doubtful if it would meet our inclusion criteria, which required a group of newly presenting children with symptoms that could be IBD or not. Group 1 in this study is a mixture of old and new patients, and it is not clear whether there is a comparison group with new symptoms but who did not have IBD.
	14.	83	Table 19	Study: Prell et al, 2013 (to be submitted), outline attached Cut-off value: 50 PPV : 91.4 NPV : 94.8 PLR: 5.43	NRR

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				NLR : 0.03 Accuracy: excellent (AUC 0.979) Disease prevalence: 66 % in the cohort tested	
	15.	102	2.10	Please include to the list the following reference: Prell C, Nagel D, Freudenberg F, Schwarzer A, Koletzko S.Comparison of three fecal calprotectin assays in a pediatric population with suspected or proven gastrointestinal disease. Manuscript in preparation, submission planned for Clinica Chimica Acta in June 2013. The study compares the performance of EliA Calprotectin (FEIA), PhiCal (ELISA), and EK-Cal (ELISA). See outline and plots attached.	Not admissable since we have never seen it
	16.	119		At the time of the ECHE abstract submission, our collaboration with Prof Larsson at Uppsala University had not formally started yet. As we have a very nice collaboration with him, we would appreciate if you could add the following reference to a poster presentation that took place at The Nordic Conference of Evidence Based Medicine on February 5th-6th 2013 in Linköping, Sweden. The content of this poster is identical to the ECHE one, simply the authors differ. Attached are both the ECHE and the new poster, for you to check. The reference is:	NRR. The Linkoping poster does not add anything new.

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				B. Mascialino, L-L Hermansson, A. Larsson, "Comparison of the IBD pre-endoscopic screening F-Calprotectin test versus serologic markers in the United Kingdom – a cost-effectiveness study"	
	17.	133		In the very last line, there are two dots at the end of the sentence.	OK, will correct in published version.
	18.	179	Ongoing research	We suggest including in the list that a variety of factors may affect F-Calprotectin test result. Research is still ongoing in this field.	Fair point but some specific examples would have been useful. We have noted some uncertainty around the effect of NSAIDs.
	19.	179		"Some patients…" The sentence should end with a full stop.	OK.
	20.	180	Conclusions	"Relative cost will be more important in choice of test." In relation to this concept, in the conclusions or somewhere else in the text, we suggest adding: "Consideration should also be given to the method chosen to perform the F-Calprotectin test in the laboratory: recent technological improvements allow testing of hundreds of samples (up to 300) per working day minimising the operator time. Thanks to this, further significant savings on labour / operator costs are foreseen."	NRR. We have suggested to NICE that technologies will be developing and that new tests and new packages will continue to emerge, and that costs will change.
	21.	182	References	Please include the following reference: Prell C, Nagel D, Freudenberg F, Schwarzer A,	No. We have never seen this manuscript.

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				Koletzko S.Comparison of three fecal calprotectin assays in a pediatric population with suspected or proven gastrointestinal disease. Manuscript in preparation, submission planned for Clinica Chimica Acta in June 2013.	
	22.	189	References	In reference 106, the correct name of the second author is: "L.-L. Hermansson"	Apologies – we will correct this for published version.
	23.	211	App. 3	We suggest to use the following text instead: EliA Calprotectin (details based on correspondence with manufacturer) EliA Calprotectin is a fully automated CE-marked calprotectin stool test, manufactured by the Immuno Diagnostics Division of Thermo Fisher Scientific [manufactured by Phadia AB, Sweden]. The test was formally launched in December 2011, and is being currently used across 7 sites in the UK. The test is a fully quantitative test which gives results in mg/kg. Four different types of instruments are available namely Phadia 100, 250, 2500 and 5000. They all vary in size and capacity and are designed to meet the requirement of different laboratories. The most commonly used platform in the UK are Phadia 250 and Phadia 100. The test is run as a single test and does not need to be repeated, an advantage over other ELISA tests. The platform is fully automated.	At this late stage, it may be inappropriate to add this level of detail from manufacturers, but we will add the cost details to the final version, while making it clear that costs may change. Note that in section 1.4.2, table 2, we did quote the manufacturer as saying that this method would reduce costs.

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				The Phadia solution can be added to the existing Phadia systems without the need for further readers and plate washers. The fully automated system reduces laboratory technician workload, time and cost. Based on internal data, the estimate per 100 tests is: - ELISA- 3-4 hour technician time at £20 per hour - EliA Calprotectin (Phadia 250) 45mins technician time at £20 per hour This means labour costs equal to: - per 100 ELISAs = £60, or £6 per test - per 100 EliA Calprotectin = £15, or £1.50 per test	
	24.	211	App. 3	Please add to this section the following reference: http://www.phadia.com/en/Laboratory/Autoimmunity/Autoimmunity-Products/Connective-Tissue-Diseases21/Celiac-Disease-Other-Gastrointestinal-Diseases/#Fecal Calprotectin	No.
	25.	211	App. 3	Please delete from the current text the sentence: "No details, such as CE mark, were available from the NICE scoping documents."	Accepted, and we will delete this sentence.
	26.	213-214		The pages are empty.	They are not empty in our version. They have quality assessment tables.

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	27.	215-216		Figures 27 – 28 are missing.	Yes, because academic in confidence
	28.	217 - 218		Figures 29 and 30 would benefit from a slightly longer caption.	Fair point and we will expand caption for published version.
	29.	237 - 238		Please add to the model the accuracy of EliA Calprotectin (FEIA) test, based on the outline of the article by Prell et al that will be submitted in June 2013.	No.
Calpro	1.	37	Table 2	The product “CalproLab Calprotectin ELISA” is not on the list even if it is part of this program and mentioned in this review. This ELISA is quantitative using monoclonal coat and polyclonal conjugate, cut-off at 50 mg/kg, measuring range 25-2500 mg/kg.	To be checked.
	2.	105	*Burri* 2013 publ. All page	Testing has been conducted as early as 2005, even if it has not been published before 2013. The PhiCal Test is *not* identical to the FDA approved version, but actually an *older version* of the Calpro Calprotectin ELISA (art. CAL0100). Cut-off values/ROC curves based on results from testing patients with many different conditions/diseases, not everybody that relevant. As an example only 10 patients out of 405 had Chron’s. The results summarized in table 1 in this paper are	We have noted that tests change not infrequently, going through different “editions”. We could only go on the detail given in the paper

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				very difficult to understand since it lacks sufficient explanations and units. As an example it looks like the values for adenomatous polyps is higher than in Chron's measured with EK-CAL which is quite surprising. Dubious conclusion that monoclonal is better than polyclonal based on comparing only one monoclonal and one polyclonal based test.	We did say "slightly better".
	3.	111	Publication from *Labaere et.al.*	Assays from different manufactures do correlate, but have poor agreement even if everybody uses the same cut-off value. We will draw your attention to the calprotectin test program organized by Equalis, a Swedish organization for quality assessment for clinical laboratory investigations. They have had this program since 2010 and clearly demonstrated large differences in measuring levels between assays, and for some manufacturers, changing calibration. This has in general not been properly communicated. As an example, please find the latest Equalis report attached.	The Equalis report was published on 6th April, after submission deadline for the assessment report. It is copyright and may not be quoted without permission. But it has interesting data that NICE will no doubt take note of.
	4.	208	All appendix	CalproLab Calprotectin ELISA is not included, se comment no. 1.	To be checked.

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	5.	209	Bottom	"One limitation of the test is that repeated freeze-thaw cycles of the specimen may affect the accuracy of the test results". Comment: this is meant as a general precaution relevant for all calprotectin tests, the same is true for establishing diagnosis on a single result. We believe these precautions are relevant for all calprotectin assays and not special for this assay.	NRR
Immundiagnostik	1.			Generally: Terminology • It is not clear to us what was marked in black. We are especially interested in what is hidden in pages 113-115 because here our Prevent ID-Test is discussed. • One should generally rather speak – if comparisons are performed –about relative clinical sensitivity and relative clinical specificity because the reference standard or disease were mostly not the same	Sorry, this had confidential data from the NTAC pilots that we were told to keep confidential till publication.
	2.	37	Table 2	Please correct the spelling: Immu**n**diagnostik AG (Ben**s**heim, Germany)	OK
	3.	37	Table 2	Please change 50 mg/kg to 50 µg/g	OK

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	4.	37	Table 2	PreventID Caldetect: Please add **µg/g** to the description of the 3 bands.	OK
	5.	37	Table 2	The EliA-Test is characterized as being **fully automated**. However, the extraction procedure very likely will not be automated and will be off-line from their analyser system	NRR.
	6.	40	7	??? mg/L ➔ µg/ml ….by multiplying by a factor of five…"	NRR. The reasoning is in the references we gave to explain why factor of 5 used. From van Roon 2007: In 2000, a new assay for FC became widely available, which was five times as sensitive as the original assay and measured FC in micrograms per gram rather than milligrams per liter (8). A number of authors have asserted that results obtained with the old assay method may be directly compared with results obtained by the new method through simply multiplying the former by a factor of five (8, 16, 17). In order to verify this, the manufacturers (Calpro AS, Oslo, Norway) were contacted directly, who confirmed that results could be translated in the manner described above. To allow inclusion of all studies in the common analysis, we therefore applied a factor of five to FC values obtained from

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					studies that used the original assay. From vanRheenen 2010 – legend -under table 2: PhiCal (Calprest) is a commercial enzyme linked immunosorbent assay (CALPRO AS, Oslo, Norway). Roseth is an in house enzyme linked immunosorbent assay (results obtained with Roseth can be compared with those obtained with Phical by multiplying former by a factor of 5.
	7.	86	Last section	Term: precision better: clinical precision?	
	8.	101	1	There have been conflicting results regarding whether Calprotectin is raised in celiac disease. Last sentence should list coeliac disease after the diverticulosis as well	Not sure. Coeliac disease was not considered in this review, but one of our expert advisors commented that calprotectin was usually slightly raised in coeliac disease.
	9.	178	4	What are IBD antibodies?	Error – to be deleted.
	10.	208	Last section	**Please substitute the first sentence with:** The assay can measure levels up to 2100 µg/g. Only very high samples (> 2100 µg/g) need to be further diluted.	As noted in this section, the very high levels are not relevant. However we are happy to make the change in the published version.
Crohn's and Colitis UK	1.	170		We welcome the finding that '*Calprotectin could be very useful for GPs as a way of confirming a clinical diagnosis of IBS*' and that delays in diagnosis of IBD	NRR

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				will be reduced, particularly in children	
	2.	174		We welcome any further work to examine the effectiveness of treatment for those with "f*ew or no symptoms, but on-going inflammation, in whom the anti-TNFs are not recommended" as revealed by calprotectin"*	NRR, because outwith our remit. NICE may wish to take note of this when considering the need to review the TA guidance on infliximab.
Alpha Laboratories	1.	21/170		On Page 21 under cut-off it is stated that: "The same cut-off should be used in primary and secondary care – 50µg/g for ELISA tests". However, on Pg 170 under Discussions it then states: "It is not a perfect test because some patients with IBS have raised calprotectin levels, but false negative IBD is unusual if we use the cut-off of 50µg/g (for ELISA tests) and 15µg/g (for Prevent ID POCT) recommended by the manufacturers" Could you clarify which cut-off level you are suggesting should be used both in primary and secondary care, please?	The same cut-offs should be used in primary and secondary care, as appropriate for the test being used, and taking into account the manufacturers' recommendations. So different cut-offs for Prevent ID and ELISAs NRR