Addendum from AEG

Note: When the first section of this document was initially submitted on 29th April, some material was academic in confidence and was highlighted as such. The NTAC report has now been published and the highlighting has been removed.

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1. Corrections, clarifications and updates.

Update: the systematic review by Paul Henderson and colleagues is now in press and the academic in confidence shading on pages 52 58, 59 and 61 (DAR version 4th April) can be removed or ignored.

Errata;

There were errors in Table 8. Correct version

Table 1. Evidence base for the calprotectin tests. Revisions added after Appraisal Committee meeting are highlighted in green

Name of Test	Type of test	Evidence base
Nycomed	ELISA	IBS vs. IBD: One study, El Badry 2010 IBD vs. non-IBD: 2 studies; Limberg 2000; Sidler 2008 Organic vs. IBS: none Organic vs. non-organic: none
Immundiagnostic ELISA kit	ELISA	IBS vs. IBD: 2 studies, Basumani 2013; Schroder 2007. IBD vs. non-IBD: none Organic vs. IBS: 1 study, Basumani 2013 Organic vs. non-organic: none
EK-CAL	ELISA	IBS vs. IBD: none IBD vs. non-IBD: 1 study, Damms 2008 Organic vs. IBS: none Organic vs. non-organic: 3 studies
Calprest	ELISA	IBS vs. IBD: none IBD vs. non-IBD: 5 studies: Fagerberg 2005; Diamanti 2010; Tomas 2007; Canani 2006; licata 2012 Organic vs. IBS: 1 study Organic vs. non-organic: 3 studies
CALPRO Calprotectin ELISA test (ALP)	ELISA	IBS vs. IBD: Otten 2009; Schoepfer 2008; Li 2006 IBD vs. non-IBD: Vijfer 2012; Henderson 2012 Organic vs. IBS: none Organic vs. non-organic: none
Not known	ELISA	IBS vs IBD: Bharathi 2005 IBD vs non-IBD: Ashorn 2009
Quantum Blue	POCT	IBS vs. IBD: none IBD vs. non-IBD: none Organic vs. IBS: none Organic vs. non-organic: 1 study

Prevent ID Caldetect	POCT	IBS vs. IBD: 1 study IBD vs. non-IBD: none Organic vs. IBS: none Organic vs. non-organic: 1 study
Prevista(no longer available)	POCT	IBS vs. IBD: none IBD vs. non-IBD: 1 study Organic vs. IBS: none Organic vs. non-organic: none
EliA platform	EliA	None

2. There was an error in figure 19 where Prevista should have been Prevent ID. Corrected figure (academic in confidence)

Figure 19 Organic vs non-organic bowel disease

3. Section 2.11 had a couple of errors in figures, and required clarifications. The figures have been corrected. A section on weaknesses in the assumptions made has been added. The replacement section follows.

2.11 GP assessment and referral: implications for modelling.

Adults

As noted previously, we lack published data on the use of calprotectin testing in primary care. However we have the unpublished results from the NTAC pilots, and these provide data on referral patterns by GPs in the UK (assuming that those in the North-East are representative).

The Durham Dale pilot provides data on GP referrals with no calprotectin testing, and the effect that testing would have. The data allow us to explore what might happen if calprotectin testing is made available.

The test used was the POCT Prevent ID, which divides people into 3 groups;

- Negative < 15µg/g
- Positive > 60 µg/g
- Intermediate >15 but < 60

GPs made referral decisions based on clinical assessment without knowledge of the calprotectin results. They referred those that they thought might have IBD, and managed those that they thought had IBS in primary care.

A final consultant diagnosis was made, based on calprotectin test results and clinical data, including endoscopy. The clinical data came from GP and OP data, where patients were referred, or just from GP data, when patients were not referred. Note that those diagnosed as IBS (and not referred) did not have colonoscopy so it is not possible to completely exclude false negatives. These would have IBD but appear clinically to be IBS and have negative calprotectin results. Such false negatives are unlikely given the high sensitivity (100% - see figure 3) of calprotectin in this POCT at the 15 µg/g cut-off, but not impossible. (The Durham Dale pilot could not be used in our main assessment because of the lack of a definitive reference test.)

For assessing the sensitivity and specificity of GP assessment, there are two options using the Durham Dale pilot data.

1. Use calprotectin as reference test.
2. Use final consultant diagnosis.

If we compare GP diagnosis with calprotectin levels, and assume that a positive calprotectin test implied possible IBD and an indication to refer, then we have a 2x2 table as follows

Table 2 GP diagnosis compared to calprotectin level.

	FC +ve	FC –ve	Total
GP IBD	28	4	32
GP IBS	6 (4 high, 2 indet.)	79	85
	34	83	117

So for GP diagnosis compared to the Prevent ID test, Se 28/34 = 82% and Sp 79/83 = 95% where "positive" = a positive FC test. If we exclude the two indeterminates (who would be re-tested, rather than referred), sensitivity is 88%. Of the 83 diagnosed as IBS by GPs, only 4 had high calprotectin, a 5% error rate giving NPV of 95%. Note that the four are not false negative in the sense of being missed IBD, but in the sense of being "false non-referrals". Not all would have IBD, because the

Prevent ID test does not have a 100% Se and Sp compared to colonoscopy. So without FC testing, GPs would not refer four of 32 patients with high calprotectin

Given that the above comparison is of GP versus calprotectin, the final consultant diagnosis is more useful for our purposes, and the next table compares the GP diagnosis (without knowledge of calprotectin result) and the consultant diagnosis (with knowledge of calprotectin result and of endoscopy where performed. Note that far more patients (33) had endoscopy than were found to have IBD.)

Table 3 GP diagnosis compared to final consultant diagnosis

	Consultant IBD	Consultant IBS	Total
GP IBD	7	22	29
GP IBS	0	82	82
	7	104	111

Numbers are slightly less than in the previous table because some patients do not appear to have been followed up. No data are given in the YHEC report on the presumed diagnosis or calprotectin results in five missing cases. The sixth was found to have cancer.

These results show that the GPs referred all those diagnosed as IBD, giving a "whole pathway" sensitivity of 100% (if we assume there were no false negative IBDs as discussed above.) "Whole pathway" combines GP assessment, calprotectin testing and consultant opinion based on clinical data that included endoscopy (mainly colonoscopy but some flexible sigmoidoscopies).

However this is achieved at a specificity of 79% for GP assessment without calprotectin testing. Without calprotectin testing, GPs refer a group of whom around 25% have IBD (7 of 29) and 75% have IBS. The PPV of GP assessment (without calprotectin) compared to consultant diagnosis (with calprotectin and endoscopy) was 24% and NPV was 100%. This matches results from routine care that over 60% of colonoscopies in young people are normal.

This implies that if GPs had access to calprotectin testing, they might be able to reduce referrals by a considerable amount – about three-quarters. The Durham Dale data suggest that GPs refer about a quarter of patients presenting to them with gastrointestinal symptoms that could be due to IBS or IBD. The number of patients is quite small, but that proportion is similar to the figure of 29% reported in the BSG guideline on IBS, which increases confidence in the pilot data.[99]
The prevalence of IBD in the whole population was 6.3 % (SE 2.3%), but amongst those referred, it was almost 25% (6.3 of 25%.

In the pilot, a GP decision to refer set a patient on a pathway that could lead to colonoscopy and possible other invasive investigations. This decision would not be taken lightly. However, if faecal calprotectin testing is introduced, we might expect that GPs would consider testing in a wider patient group then they would consider for referral. They refer only about 25% of those that present to them with these symptoms. We can create a scenario analysis, assuming that if calprotectin testing becomes available, GPs will test twice as many as they would have referred in the absence of faecal calprotectin testing.

We also note from the Durham pilot that if GPs thought that a patient had IBS, they were right at least 95% of the time because only 5% of those they thought had IBS had high calprotectin and needed referred. (NPV 95%).These "false non-referrals" could theoretically include some with IBD. . In our scenario analysis, we assume that all patients with IBD will be in the larger group (50% of all patients with symptoms, so 222 patients) that will have calprotectin testing. If we assume that 50% of patients with symptoms will be tested with calprotectin by GPs, we get figures as shown in table 36. All of the 6.25% of patients with IBD are tested, and assuming the POCT sensitivity of 100%, no patients with IBD would be missed.

If we used an ELISA test, with a sensitivity of 93% (from meta-analysis, we would miss 0.44%, or 0.49 patients in the numbers in this group.

The extra group are those regarded by the GP as less likely to have IBD than the 25% (because the GP didn't refer them), and GP is really doing the test to confirm IBS. . The false positive rate amongst the additional 25% tested, will therefore be much less than in the 25% referred. One option is to assume that there will be no new false positives.

So figures change, with 222 being tested compared to 111 being referred (out of a total of 444 with symptoms) to;

Table 36 Expected numbers if 50% of presenting patients are tested with FC.

	IBD	IBS	
GP + FC IBD	7	22	
GP + FC IBS	0	193	
	7	215	222

The prevalence of IBD in the tested group is half that in the referred group – about 12.5% (the 6.25% with IBD are now in the 50%). Since all those with IBD are tested, there are no false negatives if we

assume sensitivity of calprotectin testing to be 100% . Specificity is 90%. If we assumed that there would be more false positives, specificity would be 80% if we double the false positives to 44 and 85% if we increased them to 33.

If the calprotectin test was the average ELISA with Se 93% and Sp 94%, the figures in the above table would change to;

Table 36b

	IBD	IBS	
GP + FC IBD	6.51	13.19	
GP + FC IBS	0.49	201.51	
	7	215	222

Only 9% would be referred due to the greater Sp of ELISA, but 0.49 patients would be missed.
If we assume that only patients with raised calprotectin are referred, and that calprotectin is 100% sensitive for detecting newly presenting (and hence active) IBD, then with calprotectin testing, GPs will refer about 9% (20/222) compared to the 25% referred when they have no calprotectin testing available – a drop of around two-thirds. However, not all the calprotectin false positives would be referred if GPs, aware of the imperfect specificity of the test, used clinical judgement and a repeat test with the more specific (94%) ELISA test before referral. That would reduce number referred to about 20 (approx. 7TPs and 13 FPs) or 9% - a drop of over 60%

So for modelling purposes, using the Prevent ID test , we can use a prevalence of IBD of 6.3% , and in the absence of faecal calprotectin testing, a sensitivity of GP referral of IBD of 100%, and 79% specificity.

Using the North European data from Shivananda et al[24], we would expect in this adult group, a ratio of UC to CD of 3:2. (Incidence of UC 12.9 in 15-44 age group, based on 539 cases; of CD 8.7, based on 365 cases.).

Note that there are some weaknesses in the above arguments;

1. The 50% is a rather arbitrary assumption. We have reasonably assumed that more patients with symptoms would have calprotectin testing than were referred when testing was not available, but we cannot say if 50% is correct. Given that GPs are good at diagnosing IBS, we would not expect 100% to be tested.
2. Our base case assumption is that doubling the number tested would not increase the number of false positives. Since the extra 25% tested would have less severe symptoms than the first

25% (referred), it seems reasonable to rule out a doubling of false positives. However assuming no increase may be too optimistic

3. The 100% sensitivity for the POCT test is based on only one study with not very large numbers, and needs to be replicated in a larger study. The mean ELISA Se was 93%. However, GPs would not simply rely on the test results alone, knowing that sensitivity was not perfect, and some of the false negatives on ELISA testing might be referred on clinical nous.

Children

Modelling requires different assumptions in children. Based on the recent UK study by Henderson et al, 48% of referred cases (91/190) had IBD.[25] The ratio of CD to UC is much higher – 2.3:1. The potential reduction in colonoscopies is therefore greater.

2. Economic erratum (submitted 20th May).

EAG Economics: Erratum to PSA for the primary care modelling

An error within the EAG report of the 4th of April 2013 was identified by committee members. This relates to the PSA for the primary care modelling where the central estimates of the cost elements were out of line with those of the deterministic analysis. Running a PSA for the primary care modelling over 5,000 iterations revises these estimates, with them now being in line with the deterministic estimates. None of the conclusions of the report are affected by this amendment. It requires the introductory text to table 50, table 50 and figure 25 to be revised as below.

Introductory text to table 50, table 50 and figure 25

The central estimates and cost effectiveness acceptability frontiers (CEAFs) from the probabilistic modelling run over 5,000 iterations are as follows. Within this, it should be borne in mind that the prevalence of IBD is also treated as being probabilistic within the PSA.

Table 4. Primary care: Probabilistic modelling central estimates

	Base case	
	QALYs	Costs
GP	6.2319	£3,295
POCT	6.2327	£3,212
ELISA	6.2325	£3,213

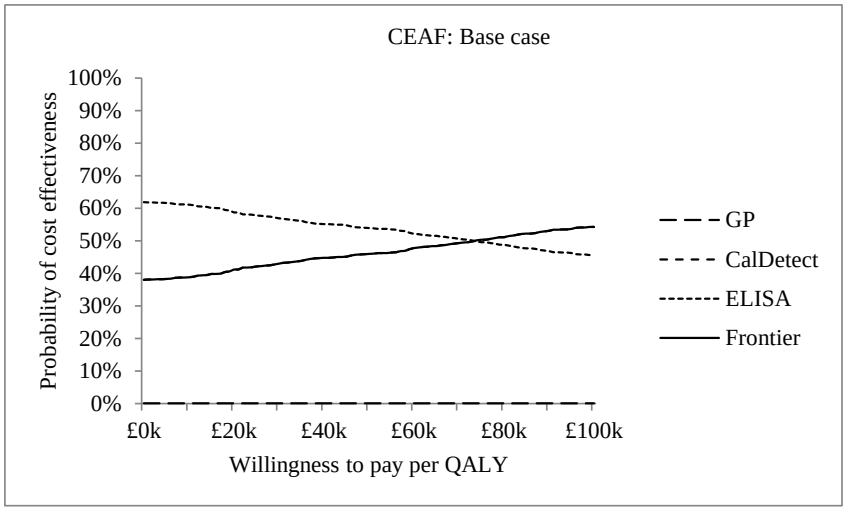

Figure 1. CEAFs: Primary care: Base Case

3. Table of tests.

Manufacturer	Test	Platform
Buhlmann	EK-CAL calprotectin ELISA test *Referred to as the 'EK-CAL' test in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: 10-600µg/g
Buhlmann	EK-CAL calprotectin ELISA test *Referred to as the 'EK-CAL' test in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: 30-1800µg/g
Buhlmann	LF-CAL25 Quantum Blue calprotectin test *Referred to as the 'Quantum Blue' test in table 2 of the diagnostics assessment report*	Rapid test - Immunoassay designed for the quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. Range: 30-300µg/g
Buhlmann	LF-CHR 25 Quantum Blue calprotectin test *Referred to as the 'Quantum Blue' test in table 2 of the diagnostics assessment report*	Rapid test - Immunoassay designed for the quantitative determination of FC in combination with the BÜHLMANN Quantum Blue® Reader. Range: 100 - 1800µg/g

Manufacturer	Test	Platform
Calpro	CALPRO CALPROTECTIN ELISA TEST (ALP) – formerly known as the Phical test CAL0100 *Referred to as the 'CALPRO Calprotectin ELISA test (ALP)' in table 2 of the diagnostics assessment report* *Table 2 of the diagnostics assessment report also refers to the 'Phical ELISA kit' test which is believed to be the same test as the 'CALPRO Calprotectin ELISA test (ALP)'. Therefore, studies of the 'Phical ELISA kit' test are also summarised here*	ELISA – quantitative Range: up to 1250mg/kg
Calpro	CALPROLAB CALPROTECTIN ELISA (ALP) – formerly known as the Phical test CALP0170 *Referred to as the 'CALPRO Calprotectin ELISA test (ALP)' in table 2 of the diagnostics assessment report*	ELISA – quantitative Range: up to 2500mg/kg

Manufacturer	Test	Platform
Eurospital	Calprest *Referred to as the 'Calprest' test in table 2 of the diagnostics assessment report*	ELISA – quantitative
Eurospital	CalFast *This test is not referred to in table 2 of the diagnostics assessment report*	Rapid test - Quantitative determination of FC in combination with a dedicated reader
Immundiagnostik	ELISA (K6927) *Referred to as the 'PhiCal Calprotectin ELISA kit' in table 2 of the diagnostics assessment report*	ELISA – quantitative
Thermo Fisher Scientific	EliA Calprotectin *Referred to as the 'EliA platform)' in table 2 of the diagnostics assessment report*	EliA – quantitative In contrast to ELISA, EliA measures the presence of target antibodies by fluorescence signal detection.

Manufacturer	**Test**	**Platform**
Preventis (sister company to Immundiagnostik)	KST11005 CalDetect Calprotectin Rapid test (version 1 - Caldetect) *Referred to as the 'Prevent ID Caldetect' test in table 2 of the diagnostics assessment report*	POCT – immunochromatographic rapid test. A semi-quantitative test with 3 lines corresponding to: Calprotectin "negative", Calprotectin ≤ 15µg/g, Calprotectin 15-60µg/g and Calprotectin > 60µg/g stool
Preventis (sister company to Immundiagnostik)	CalDetect Calprotectin Rapid test (version 3 – CalScreen) *This test is not referred to in table 2 of the diagnostics assessment report*	POCT – immunochromatographic rapid test. A yes-no test with only 1 Test-Line corresponding to the cut-off value of 50µg/g stool (no inflammation = <50µg/g and inflammation present = ≥50µg/g)