



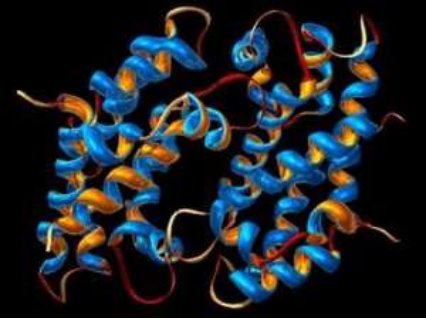
Faecal Calprotectin in County Durham – *a decade of experience*

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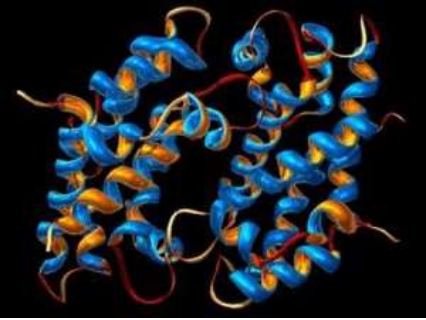
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Faecal Calprotectin (FC)

- Calprotectin is a 36kDa calcium and zinc binding protein expressed by the gene S100 calcium binding protein A8.
- Heterotrimeric structure: two S100A9 and one S100A8 subunits.
 - each subunit can bind two calcium ions and two zinc ions.
- Present in the cytosol of neutrophils and accounts for 30-40% of the cytosol.
- Has bacteriostatic and fungistatic properties, inhibits metallo-proteinases, and induces apoptosis.
- It is released extra-cellularly during neutrophil activation and during cell death, as well as during monocyte adhesion to endothelium.
- Can be detected in body fluids during inflammation.
- **During intestinal inflammation, Calprotectin is released into the gut lumen and can be quantified in faeces.**



Faecal Calprotectin (contd.)

- Faecal Calprotectin (FC) is a heat stable protein complex
 - resists enzymatic degradation
 - stable in stools for 7 days at RT
- Conventionally measured in stools by a quantitative ELISA
- Can now be measured as a “Point-of-contact” semi quantitative screening test in primary and secondary care for investigating patients with chronic diarrhoea.
- The manufacturer recommends positive stool tests (**FC levels >50µg/g**) to be referred for further investigations (e.g. imaging, endoscopy) to a Gastroenterology clinic.

Elevation of faecal calprotectin in GI Conditions

- In IBD (both UC and CD)
- Diverticulosis, NSAID intake
- Any infective colitis (for upto 3 months)
- Colorectal Cancers, large adenomas
- Calprotectin correlates very well with white cell scans and colonoscopy in IBD (sensitivity 78-100%, specificity 76-100%)
- **Meta-analysis of 13 FC studies: (cut off 50ug/g)**
 - 93% sens and 96% spec for IBS vs IBD
(van Rhee, BMJ 2010)

Testing for Faecal Calprotectin

- **Quantitative ELISA** (hospital lab based)
 - EK-CAL[®], PhiCal[®] or CalPro[®]
 - Range upto 2500ug/g
- **Point of Contact Testing:**
 - Caldetect[®] or PreventID[®]
 - Quantum Blue[®], 30-300ug/g
- **Manufacturers/Distributors:**
 - Alpha Laboratories
 - Biohit Healthcare
 - Buhlmann Laboratories
 - Calpro
 - Immundiagnostik AG
 - Preventis GmbH
 - ThermoFisher Scientific ImmunoDiagnostics Division



Examples of point of contact tests



Positive:

Calprotectin-concentration $\geq 50 \mu\text{g/g}$: Control band (C) and test band (T) are visible (s. Fig. 2a). An intestinal inflammation has been detected.

Negative:

Only the red control band (C) appears (s. Fig. 2b). The test has run correctly, no intestinal inflammation has been detected.

Invalid:

The test is invalid if no control band (C) appears, even if a test band (T) is visible (s. Fig. 2c).

Fig. 2a

$\geq 50 \mu\text{g/g}$



Positive

Fig. 2b

$< 50 \mu\text{g/g}$



Negative

Fig. 2c



Invalid



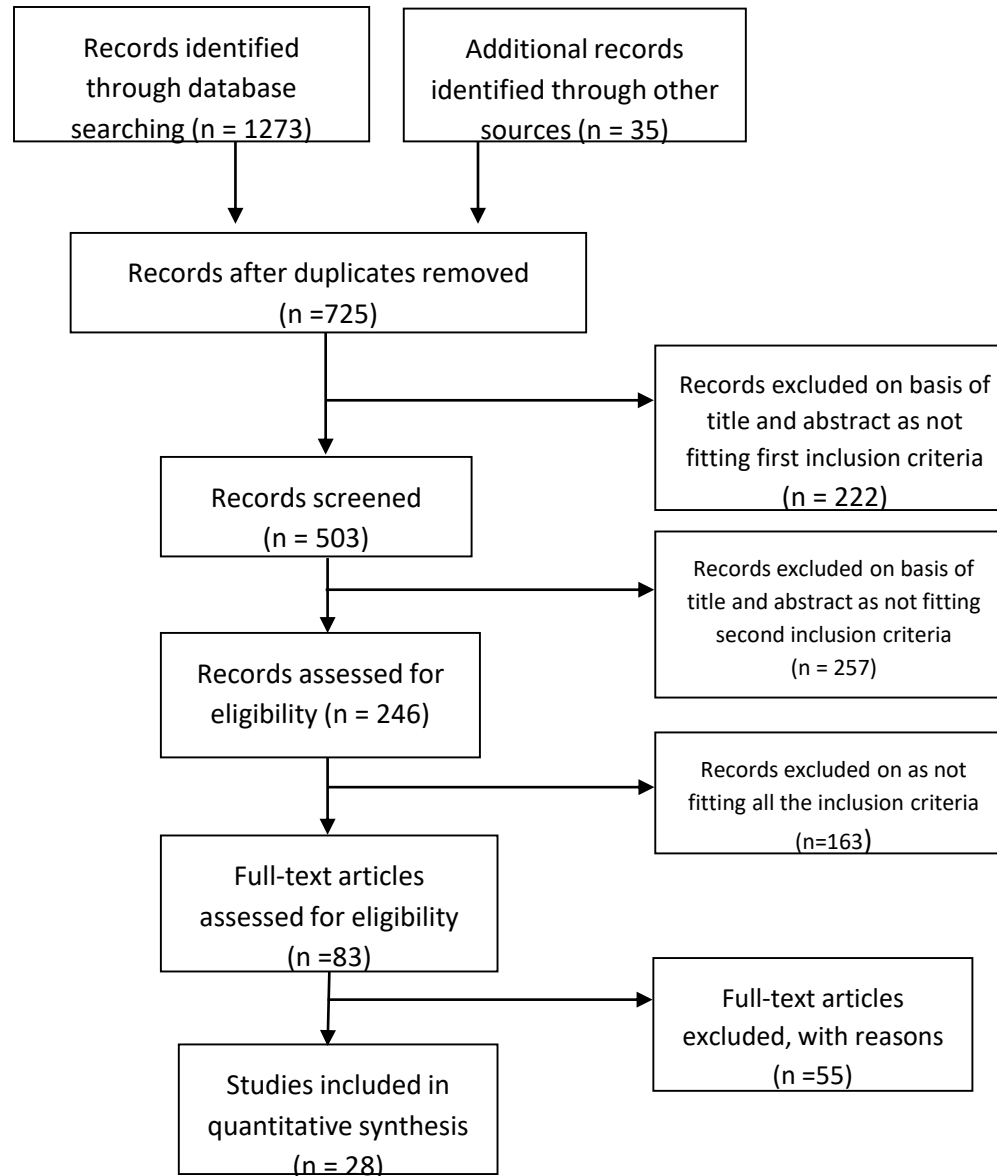
Invalid

Abb. 2 a-c: Interpretation of the test results

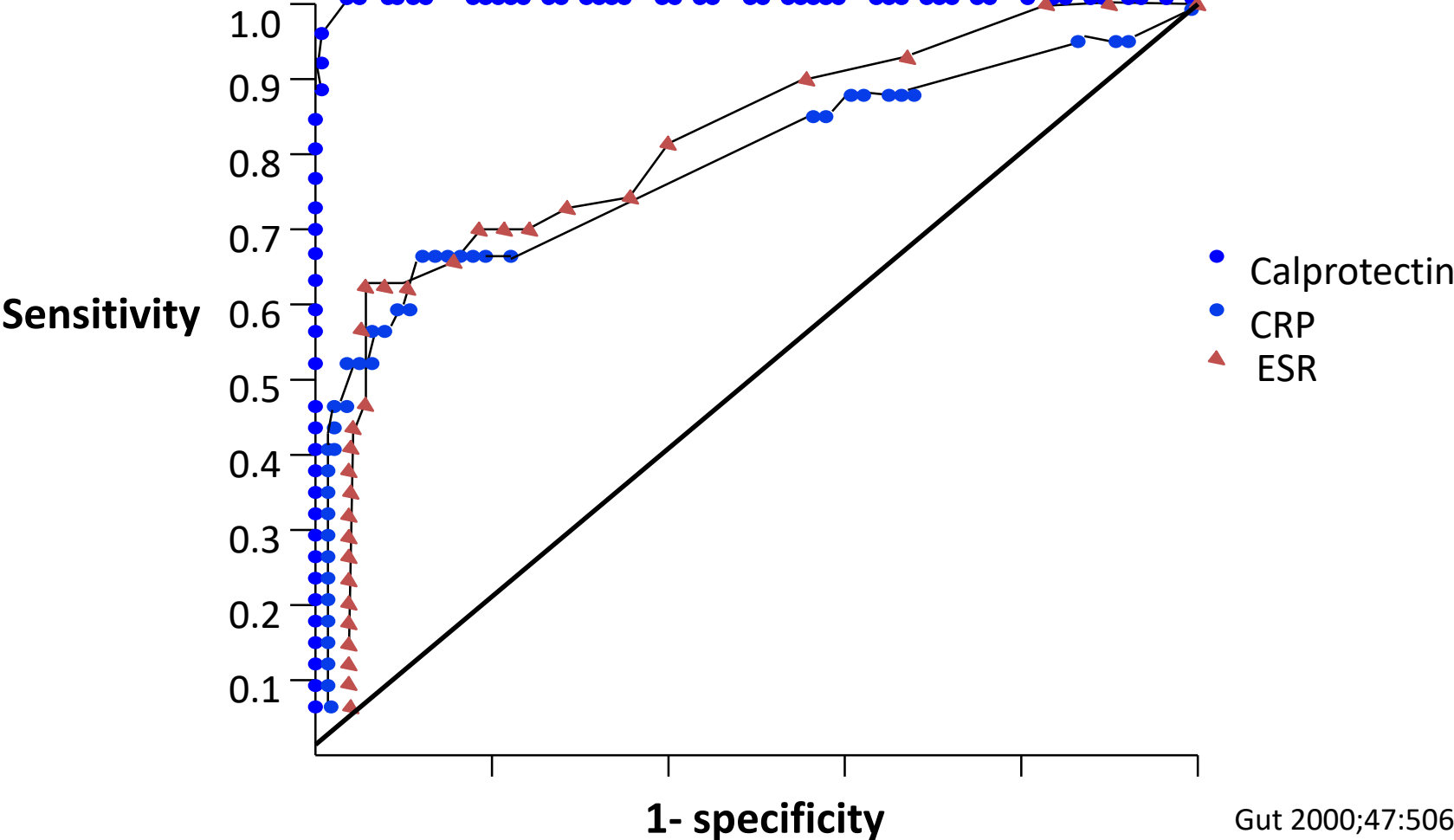
Faecal Calprotectin in differentiating IBS from IBDs

- Approx. 10% of the adult population suffer from IBS, with diarrhoea predominance, 50% consult GPs
- Symptoms of IBS mimic IBD: Crohn's and early Ulcerative colitis (without blood)
- Until recently the distinction of IBS from IBD required referral to a Gastroenterologist for colonoscopy and biopsy (cost £650)
- 11 studies in literature have reported on the ability of FC to differentiate IBS from IBS

NICE DAC - published evidence for FC



ROC analysis for Calprotectin (150 mg/L), CRP and ESR to discriminate between IBS and IBD



The Durham and Dales FC Pilot Project, 2012

Aim of the project–

- Provide a diagnosis and care pathway for patients <45 years old in primary care presenting with symptoms of abdominal pain and diarrhoea as described in NICE clinical guideline CG61 by testing for FC in practice.
- Point of care test (CalDetect®) for first line screening to differentiate between IBD and IBS
- To enable suspected IBD patients to be referred to secondary care, to reduce unnecessary referrals into secondary care for investigation and scopes
- To offer better patient experience: earlier diagnosis, and better patient experience
- Deliver cost savings to the CCG

Partnership Working with :

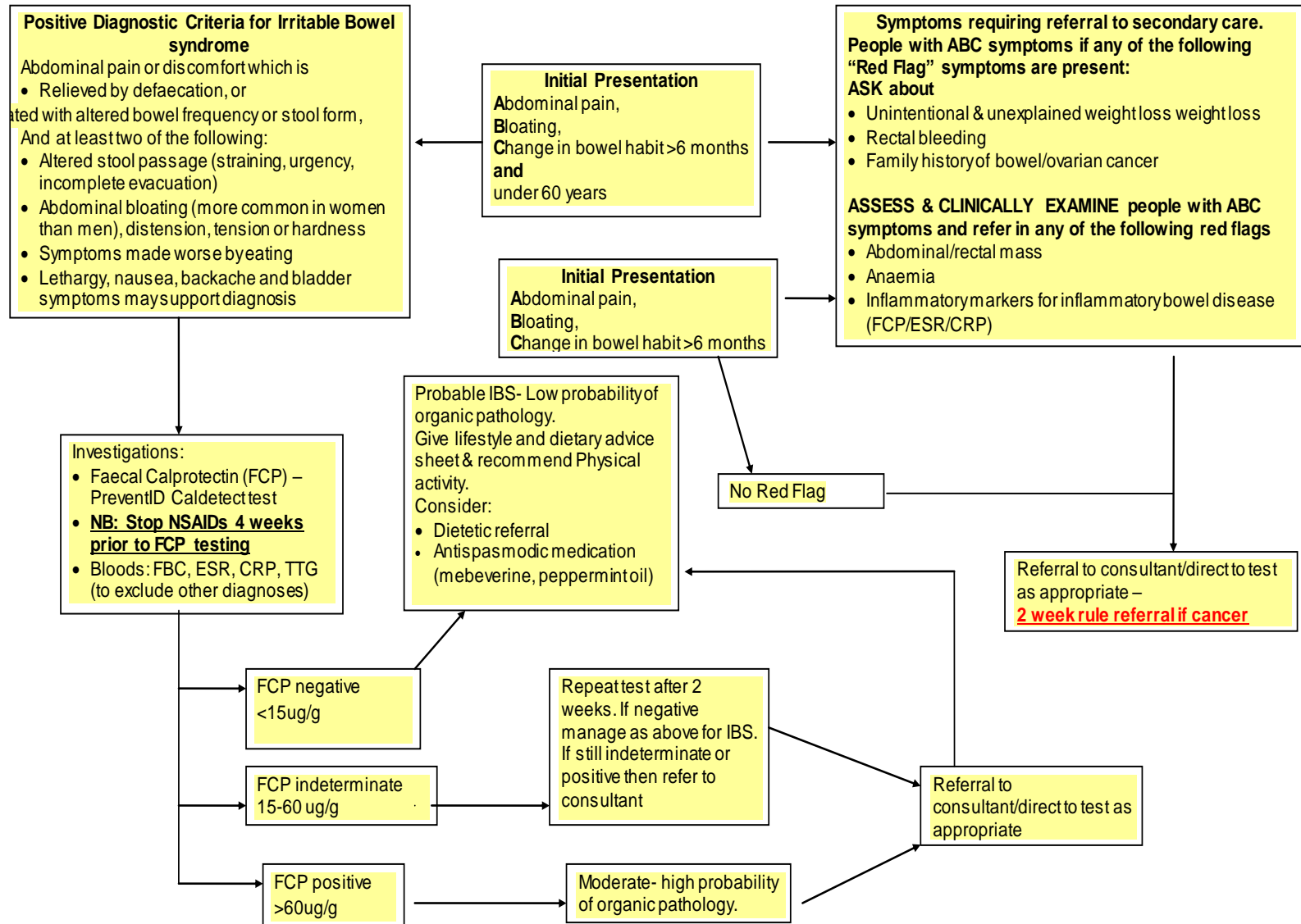
- County Durham & Darlington FT
- North East SHA
- Innovative Technologies Adoption & Procurement Programme (iTAPP)
- Darlington Pathlabs
- County Durham PCT
- Durham Dales CCG

The Faecal Calprotectin Business Case

(Durham and Dales)

- Estimated 253 direct referrals to endoscopy services per year in the Durham Dales locality for suspected IBS/IBD.
- Using the 2010/11 tariff for endoscopy services (FZ28B) of £470 the total current cost of referral calculated to be £119K.
- Use of the FC test in primary care is expected to reduce referrals by at least 75%, saving a minimum of £89k for unnecessary endoscopic examinations.
- Overall, the new pathway is expected to effect a net saving of £97k p.a. across primary and secondary care through reduced referrals, endoscopic procedures and follow up appointments.

The Durham and Dales Faecal Calprotectin Pathway



NICE Diagnostics Guidance on Faecal Calprotectin, DG11, October 2013

NICE National Institute for
Health and Care Excellence

Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel

Issued: October 2013

NICE diagnostics guidance 11
www.nice.org.uk/dg11

1 Recommendations

- 1.1 Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
- cancer is not suspected, having considered the risk factors (for example, age) described in [Referral guidelines for suspected cancer](#) (NICE clinical guideline 27), and
 - appropriate quality assurance processes and locally agreed care pathways are in place for the testing.
- 1.2 Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment, if:
- appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

NICE has accredited the process used by the Centre for Health Technology Evaluation at NICE to produce diagnostics guidance. Accreditation is valid from October 2011 to September 2017, and applies to guidance produced using the processes described in NICE's 'Diagnostics Assessment Programme manual' (published December 2011). More information on accreditation can be viewed at www.nice.org.uk/accreditation



But, are the manufacturer's cut off values clinically useful?

- Most manufacturers recommend a cut off of 50 $\mu\text{g/g}$ as positive i.e. intestinal inflammation.
- Data now suggest that values upto 100 $\mu\text{g/g}$ may be seen in patients with IBS, and values above 150 or 200 $\mu\text{g/g}$ are seen in IBD
- Most of this data is from secondary care, and may indicate a referral bias. Very little primary care data.

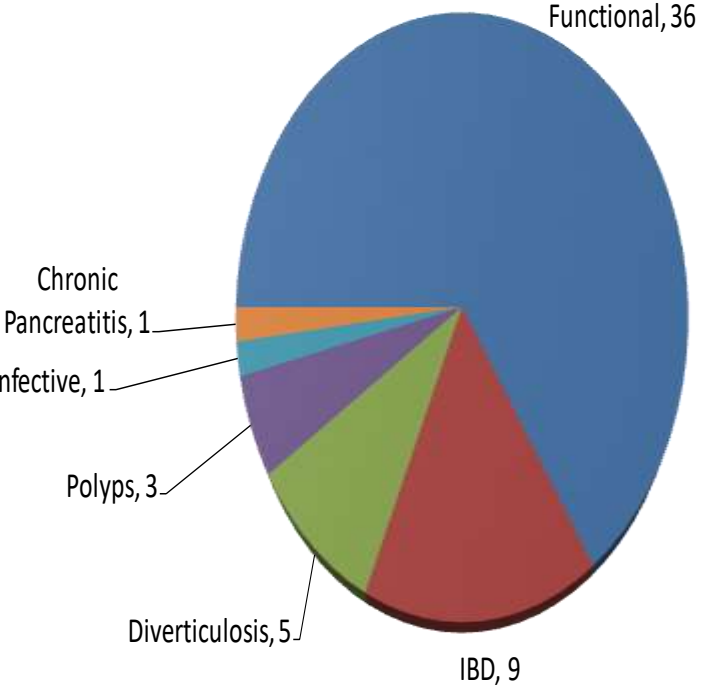
Post implementation audit of secondary care FC testing

- 122 FC test results done in primary and secondary care during a 3 month period from October to December 2011 on patients who presented with chronic diarrhoea without pre-existing Inflammatory Bowel Disease (IBD).
- Primary outcome :
 - To record the final diagnosis of patients with positive tests (FC levels $>50\mu\text{g/g}$) and negative tests (FC levels $\leq 50\mu\text{g/g}$)
- Secondary outcome:
 - To correlate FC levels to diagnosis.

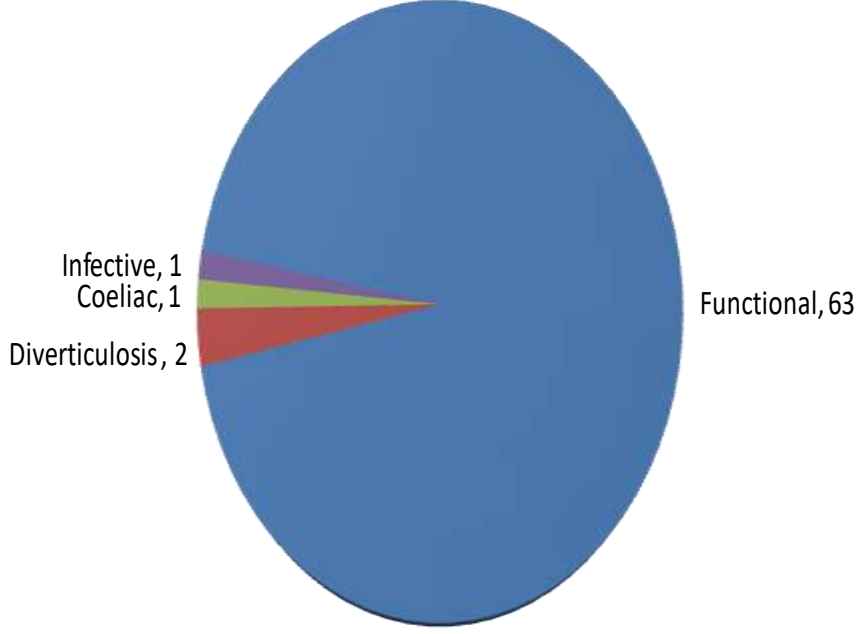
Results

- Of 122 FC tests:
 - 45% (n=55) positive vs. 55% (n=67) negative.
 - 19 of the 55 (35%) FC positive patients had a positive diagnosis (IBD=9, Diverticulosis=5, Colonic Polyps=3, Infective colitis=1 and Chronic Pancreatitis=1)
 - Remaining 36 pts (65%) had functional bowel disorder after investigations.
- Of the 67 patients tested negative:
 - 94% (n=63) had functional bowel disorder with only 6% (n=4) with an organic condition (Diverticulosis=2, Coeliac=1, Infective=1), **none of them IBD.**

Positive FC results



Negative FC Results



Predictive values

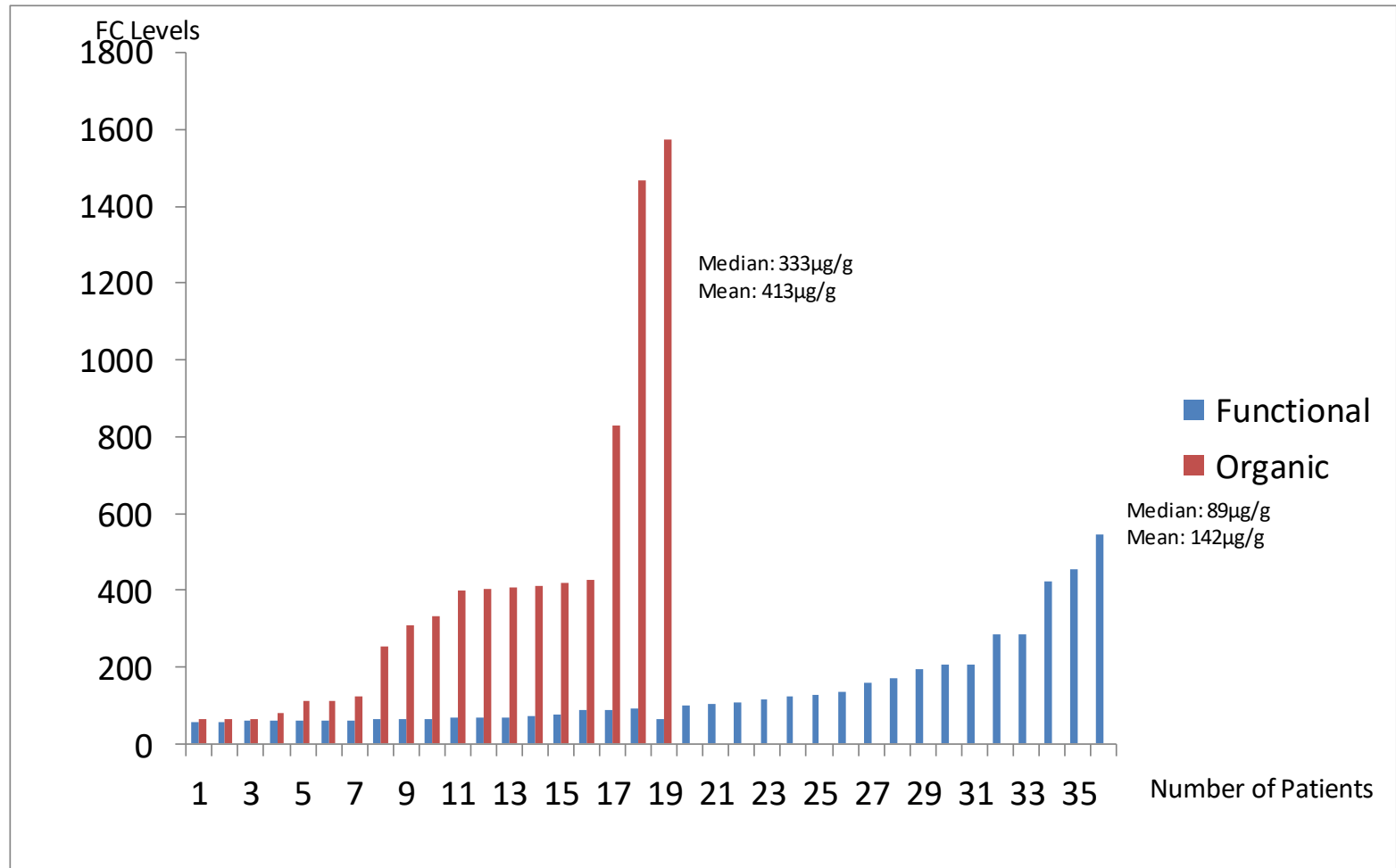
- Positive Predictive Value of 35%
- Negative predictive value of 94% for organic causes of chronic diarrhoea.

	Organic	Functional
FC positive	19	36
FC negative	4	63

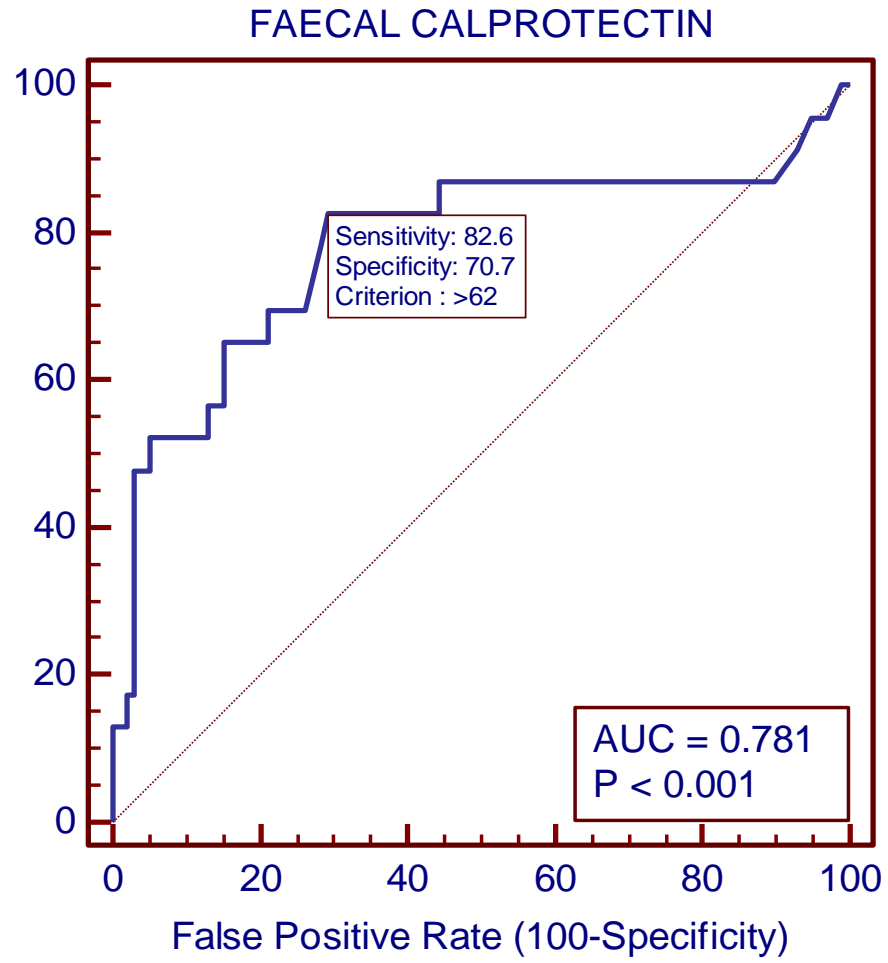
Organic vs. functional disease

- FC values of those tested positive with organic conditions ranged from 63 - 1573 $\mu\text{g/g}$, mean = 413 $\mu\text{g/g}$.
- FC levels of those tested positive with functional bowel disorder ranged from 55 - 547 $\mu\text{g/g}$, mean = 142 $\mu\text{g/g}$

FC range in patients tested positive



ROC Curve



Outcome of the audit

- The current manufacturer's cut-off at $>50\mu\text{g/g}$ does not demonstrate a high pick up rate for organic bowel conditions
- Our data suggests a higher cut-off should be used, e.g.
 - At $50\mu\text{g/g}$, sens 98%, spec 74%.
 - At $100\mu\text{g/g}$, sens 94%, spec 82%
- Further studies to determine the true cut offs for a positive diagnosis arrived after investigations correlated to FC values are needed to help decision making.

Distribution of FC at Rotherham

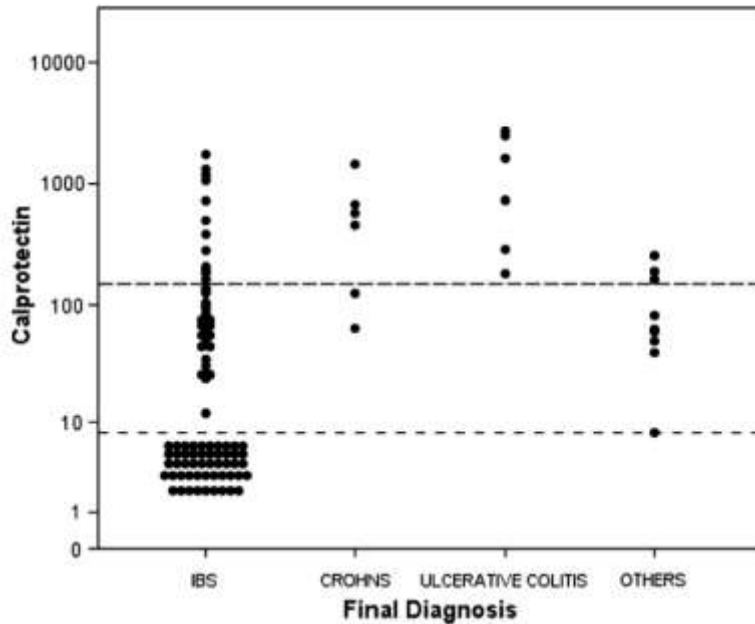
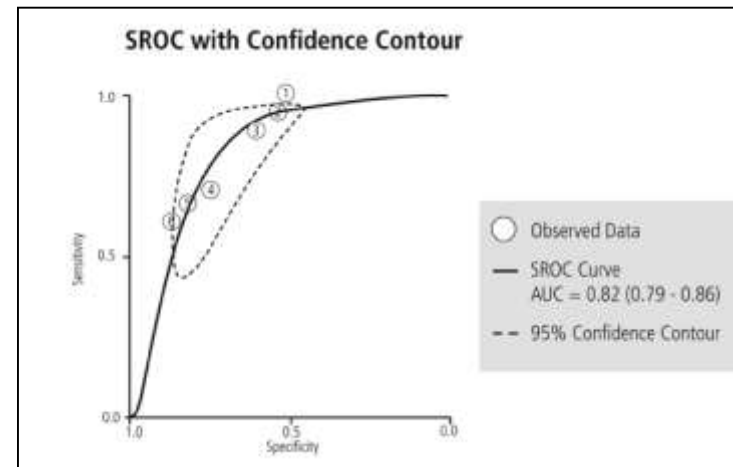


Figure 1 Individual patients' FCP ($\mu\text{g/g}$) values ($n=119$). IBS $n=98$, Crohn's disease $n=6$, UC $n=6$. 'Others' $n=9$ (note that the 5th value from the top represents two patients). 'Others'=other organic diseases (FCP value). Two microscopic colitis (8, 50). One bacterial colitis (190). One infective (257). Four adenoma (40, 60, 63, 163). One adenocarcinoma (82).

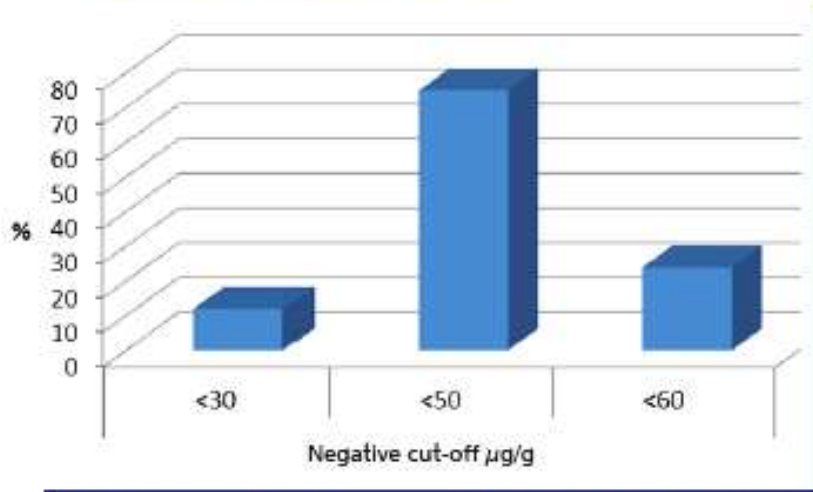
Table 2 Detecting inflammation: a comparison of CRP and FCP against histology, the reference 'gold standard'

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP cut-off				
10	44	87	38	89
20	28	95	50	88
30	22	97	57	87
FCP cut-off ($\mu\text{g/g}$)				
8	100	51	30	100
25	95	53	30	98
50	90	60	33	97
75	71	74	37	92
100	68	82	44	92
150	61	86	52	91

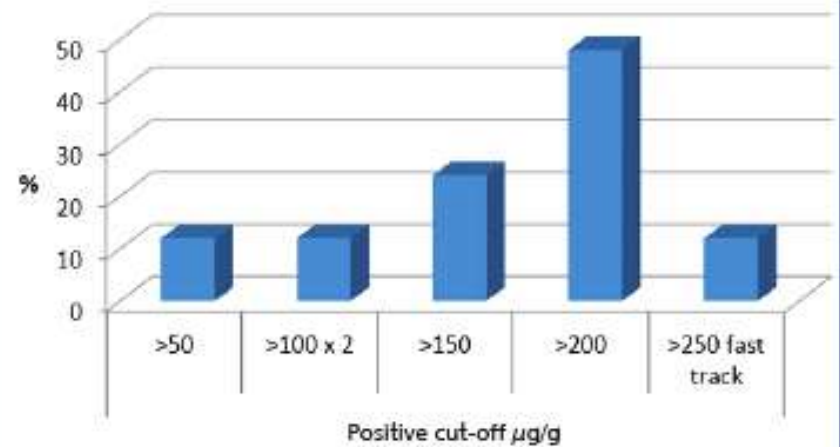


A survey of laboratories around the country

What cut-off value do you use?



<50µg/g was the overwhelming negative cut off value that was reported to be in use, with 75% of laboratories using this.



The majority of labs were also using >200µg/g as their Positive cut off value.

The state of play at County Durham in 2017

- 5645 GP requests for FCP
- 1129 secondary care requestes (predominantly from Gastroenterologists)
- GP median calprotectin: 31ug/g (4-3000)
- Secondary care median Calprotectin: 86ug/g (4-3000)
- Mean turn around time for all samples = 6.6days

Going beyond IBS- FC and IBD Monitoring

- For control of inflammation and disease Rx monitoring: $FC < 200\mu\text{g/g}$
- FC correlates better with Endoscopic Score for CD ($r=0.75$) than CRP ($r=0.53$), WCC ($r=0.42$) and CDAI ($r=0.38$)

Schoepfer et al AJG 2010

- $FC > 250\mu\text{g/g}$ correlates with large ulcerations in the gut in CD and UC, sens 60.4%, spec 79.5%
- FC may predict relapse of CD at a cut off of $>200\mu\text{g/g}$, with a time to relapse of approx. 6 months before clinical relapse
- **How often should FC be monitored in IBD: ? 3 monthly**

D'Haens IBD 2012



Thank you for your attention

