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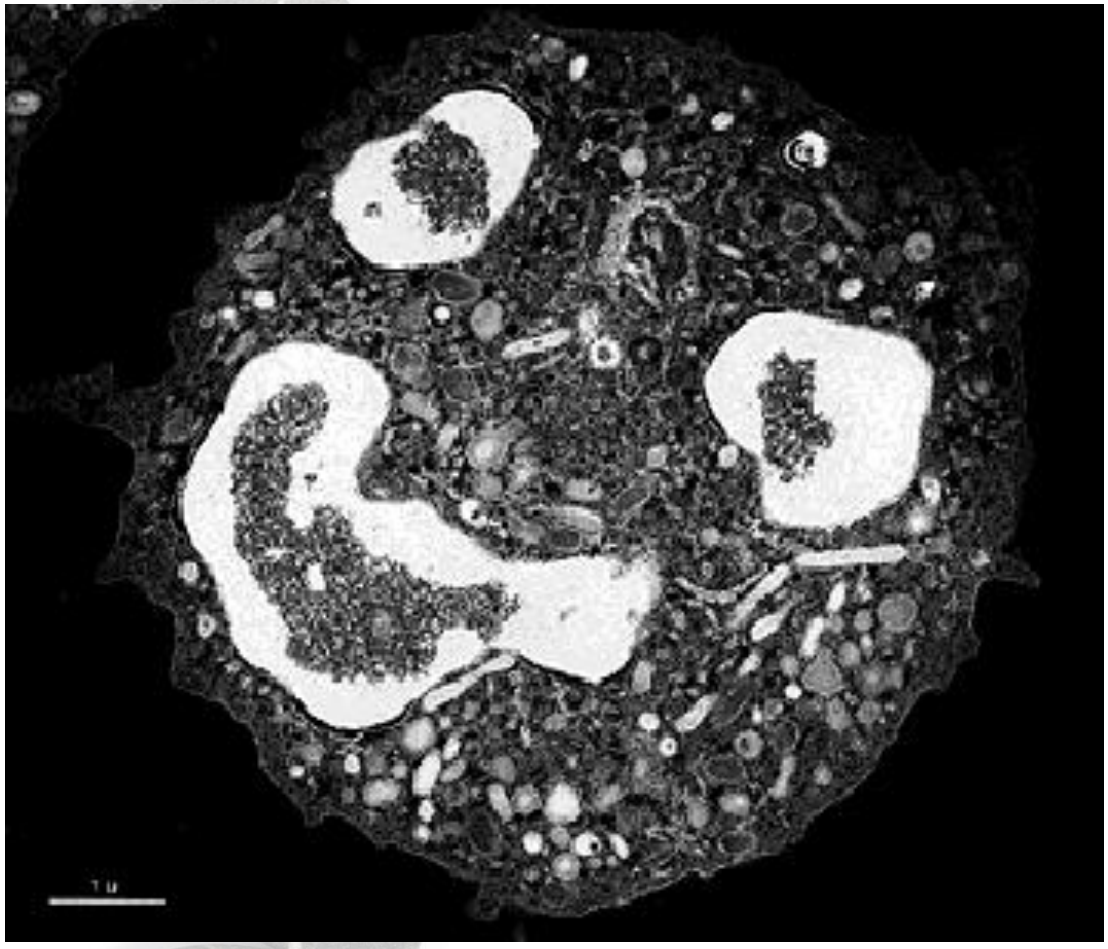
The York Faecal Calprotectin Care Pathway for use in primary care

James Turvill

NICE guidance: dg11

Faecal calprotectin (FC) testing as…an option in adults with recent onset of lower gastrointestinal symptoms for whom specialist investigations are being considered if cancer is not suspected and it is used to support a diagnosis of IBD or IBS.

(http://www.NICE.org.uk/dg11).



Faecal Calprotectin

- Crohn's disease monitoring
- IBS v IBD (NICE DG11)

How to make a biomarker work

- Get its strengths and weaknesses:
  - Is it a Troponin?
  - Is it a D-dimer?
- Optimise its sensitivity and specificity
- Understand the context in which it is used
- Make it effective for patients
  - Make it usable for clinicians
  - Develop a workable pathway
  - Safety netting

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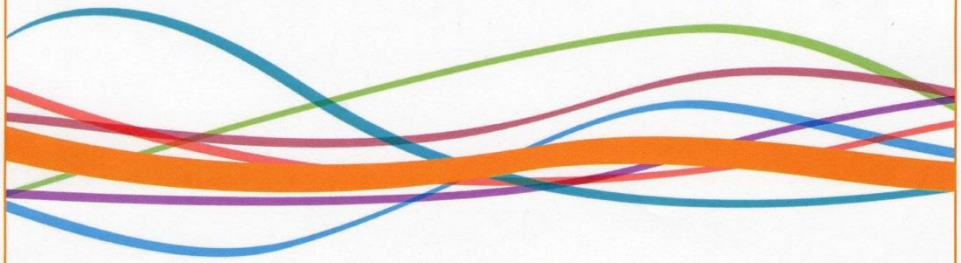
Economic report

Value of calprotectin in screening out irritable bowel syndrome

CEP09041

February 2010



Informing procurement - Encouraging innovation

NHS
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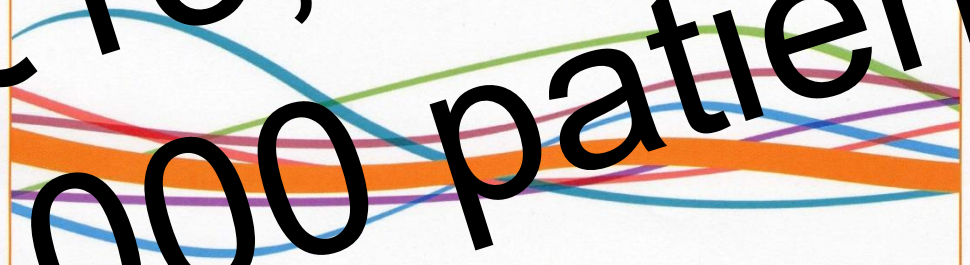

Informing procurement - Encouraging innovation

£13,463 per 1000 patients

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Economic report

Value of calprotectin in screening out irritable bowel syndrome

CEP09041

February 2010

Informing procurement - Encouraging innovation

£180,000 per 1000 patients

Unrestricted faecal calprotectin testing performs poorly in the diagnosis of inflammatory bowel disease in patients in primary care

Samantha Conroy,[1] Melissa F Hale,[1] Simon S Cross,[2] Kirsty Swallow,[3] Reena H Sidhu,[1] Ravishankar Sargur,[3] Alan J Lobo[1]

ABSTRACT

Background Faecal calprotectin (FC) measurement distinguishes patients with inflammatory bowel disease (IBD) from those with irritable bowel syndrome but evidence of its performance in primary care is limited.

Aims To assess the yield of IBD from FC testing in primary care.

Methods Retrospective review of hospital records to assess the outcome following FC testing in primary care. Investigations for all patients undergoing FC testing in a single laboratory for 6 months from 1 October 2013 to 28 February 2014 were reviewed.

Results 410 patients (162 male; median age 42; range 16–91) were included. FC>50 µg/g was considered positive (FC+). 148/410 (36.1%; median age 44 (17–91)) were FC+ (median FC 116.5 µg/g (51–1770)). 122/148 FC-positive patients (82.4%) underwent further investigation. 97 (65.5%) underwent lower gastrointestinal endoscopy (LGIE), of which 7 (7.2%) had IBD. 49/262 (18.7%) FC-negative (FC−) patients (FC ≤50 µg/g) (median age 47 (19–76)) also underwent LGIE, of whom 3 (6.1%) had IBD. IBD was diagnosed in 11/410 (2.7%; 4 ulcerative colitis, 3 Crohn's disease, 4 microscopic colitis). 8/11 were FC+ (range 67–1170) and 3 FC−. At a 50 µg/g threshold, sensitivity for detecting IBD was 72.7%, specificity 64.9%, positive predictive value (PPV) 5.41% and negative predictive value 98.9%. Increasing the threshold to 100 µg/g reduced the sensitivity of the test for detecting IBD to 54.6%.

Conclusions FC testing in primary care has low sensitivity and specificity with poor PPV for diagnosing IBD. Its use needs to be directed to those with a higher pretest probability of disease. Local services and laboratories should advise general practitioners accordingly.

Interpretation of Faecal Calprotectin results

Participants were asked to provide a free text interpretation for each specimen based upon a combination of the result they obtained and the clinical scenario below.

A 40 year-old woman visited her Family Doctor. The details on the request form were:- Alternating diarrhoea and constipation for 3 months. ?IBS .

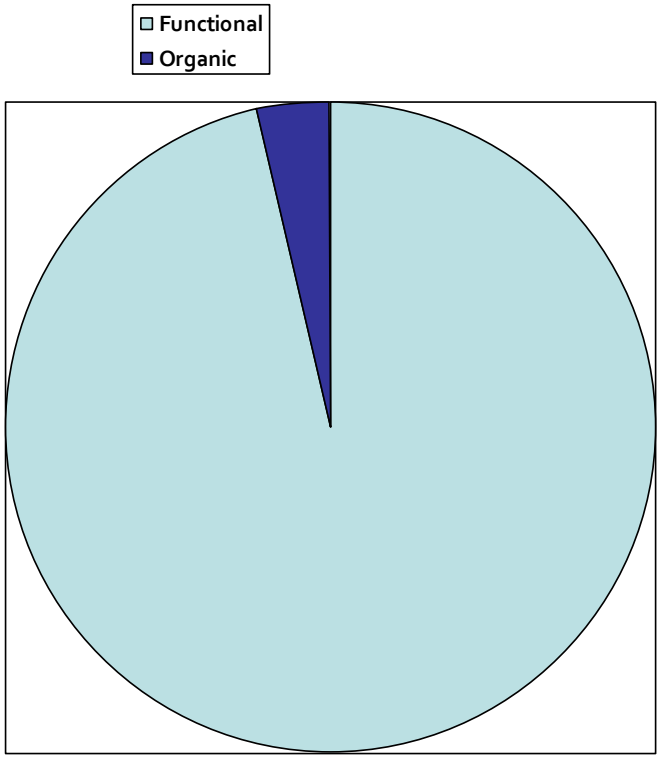
Specimen 160A

Kit	Result	Interpretation	Comment
Accusay [2AY]	97.3	P	
Accusay [2AY]	105	P	
Accusay [2AY]	107.960	P	
Accusay [2AY]	112	E	A Faecal Calprotectin (FCP) result of <100 ug/l is of doubtful clinical significance. FCP 100 - 200 ug/l should be repeated and the patient referred if the value is similar or higher. FCP >200 ug/l suggests inflammatory bowel disease or an infective colitis. Raised FCP can also occur in patients on NSAIDS or with bleeding in the gut (including patients with cancer). Patients with a raised FCP should be referred promptly to Gastroenterology for further assessment.
Accusay [2AY]	138.7	P	Positive
Buhlmann [2BU]	78	N	Inflammatory bowel disease unlikely.
Buhlmann [2BU]	78.7	P	
Buhlmann [2BU]	107	P	
Buhlmann [2BU]	109.152	P	
Buhlmann [2BU]	115	P	Results <200ug/g are rarely associated with significant pathology. Please see GG&C guidelines for advice and secondary care referral. www.nhsggc.org.uk/media/236675/ggc_fc_guidelines_dec_2015.doc
Buhlmann [2BU]	117	P	Calprotectin >100: Please repeat within 2 weeks
Buhlmann [2BU]	123	P	
Buhlmann [2BU]	142	P	
Buhlmann [2BU]	153	E	Evidence of moderate GI inflammation. IBD not excluded but consider other causes eg NSAIDS, diverticular disease.
Buhlmann [2BU]	158	E	Borderline faecal calprotectin. In patients without alarm symptoms or a pre-existing diagnosis of IBD repeat the sample. Ensure NSAIDs and PPIs have been withheld for 4-6 weeks. Exclude alternative causes of mildly elevated calprotectin such as coeliac disease, diverticulitis and gut infections. If repeat calprotectin is persistently raised gastroenterology referral will be indicated.
Buhlmann [2BU]	169.7	E	Evidence of moderate GI inflammation. IBD not excluded, but consider other causes e.g. NSAIDS, diverticular disease etc.
Buhlmann [2BU]	177	P	Borderline faecal calprotectin. In patients without alarm symptoms or a pre-existing diagnosis of IBD, repeat sample. Ensure NSAIDs and PPIs have been withheld for 4-6 weeks. Exclude alternative causes of mildly elevated calprotectin such as coeliac disease, diverticulitis and gut infections. If repeat calprotectin is persistently raised, a gastroenterology referral will be indicated
Buhlmann [2BU]	180.6	P	>50ug/g Refer to Gastroenterology
Buhlmann [2BU]	192.6	P	
Buhlmann [2BU]	200		Elevated level suggests intestinal inflammation. Suggest refer to Gastroenterology for further investigations. N.B levels may be raised in colorectal neoplasia, GI infections, GI bleeding and NSAID use. Interpret results in the clinical context
Buhlmann [2BU]	214	P	Faecal calprotectin suggests gasto-intestinal inflammation. Possible causes include inflammatory bowel disease, infection, polyps, neoplasia and NSAID use. If the patient has previously been diagnosed with IBD, then result may be consistent with active disease. If not previously diagnosed with IBD, further investigation should be considered to establish the aetiology.
Buhlmann [2BU]	243	P	
Buhlmann [2BU]	252	P	Faecal calprotectin results greater than 150 ug/g, suggest referral to a Consultant Gastroenterologist.
Buhlmann [2BU]	253	P	Raised calprotectin >200ug/g suggests GI inflammation.
Buhlmann [2BU]	320	P	Significant intestinal inflammation. If over 150ug/g on one occasion or over 50ug/g on two occasions 6 weeks apart and not on NSAID. Then suggest referral to gastroenterology
Buhlmann [2BU]	321	P	Faecal calprotectin raised (>250ug/g), suggestive of GI inflammation. Suggest immediate referral to gastroenterology.
Buhlmann [2BU]	338	P	Calprotectin values >200 ug/g are indicative of active organic disease with inflammation of the G.I tract. Suggest specialist referral for further investigation.
Buhlmann [2BU]	345	P	Significant intestinal inflammation detected.Possible causes include:IBD,GI infection,polyps,GI bleeding,neoplasia and NSAIDs.Suggest refer to Gastroenterology. NOTE: No NSAIDS 4 weeks prior to testing. Not to be used for cases of suspected bowel cancer (NICE DG11 and NICE CG12)
Buhlmann [2BU]	365	P	Result of FC >150 ug/g : please refer to Gastroenterology for further investigation of the cause of this raised result.
Buhlmann [2BU]	>600	P	
Buhlmann fCAL turbo [4BU]	77	E	

Published at 11:36 on Friday 12 January 2018

High negative predictive value of a normal faecal calprotectin

Bile salt malabsorption
Giardiasis
Microscopic colitis
Diverticulitis
Crohn's disease
Coeliac disease
Chronic pancreatitis
Thyrotoxicosis
Small bowel bacterial overgrowth
Lactose intolerance
Sorbitol induced diarrhoea



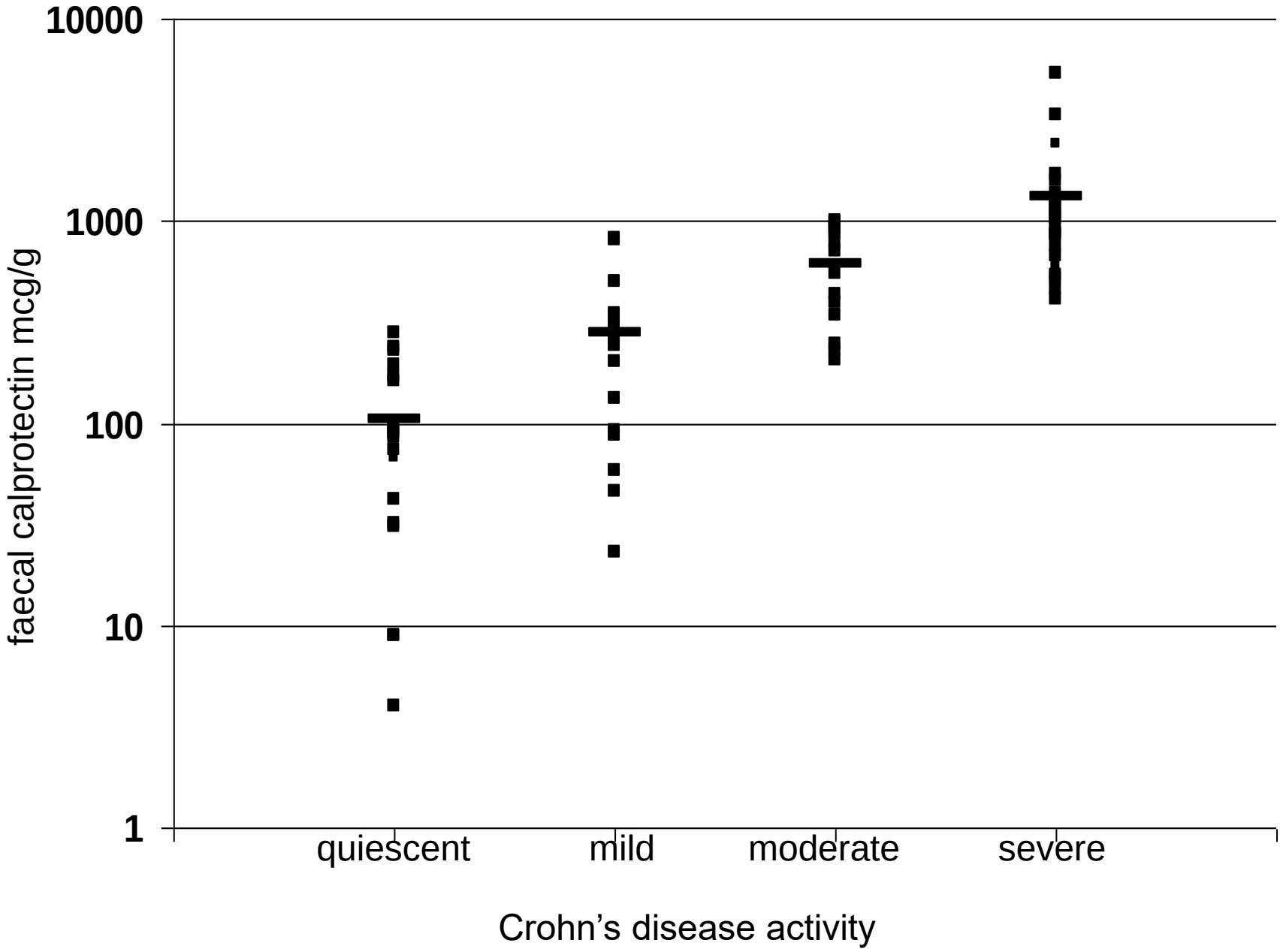
NPV 96.4%
n=500 secondary care referrals

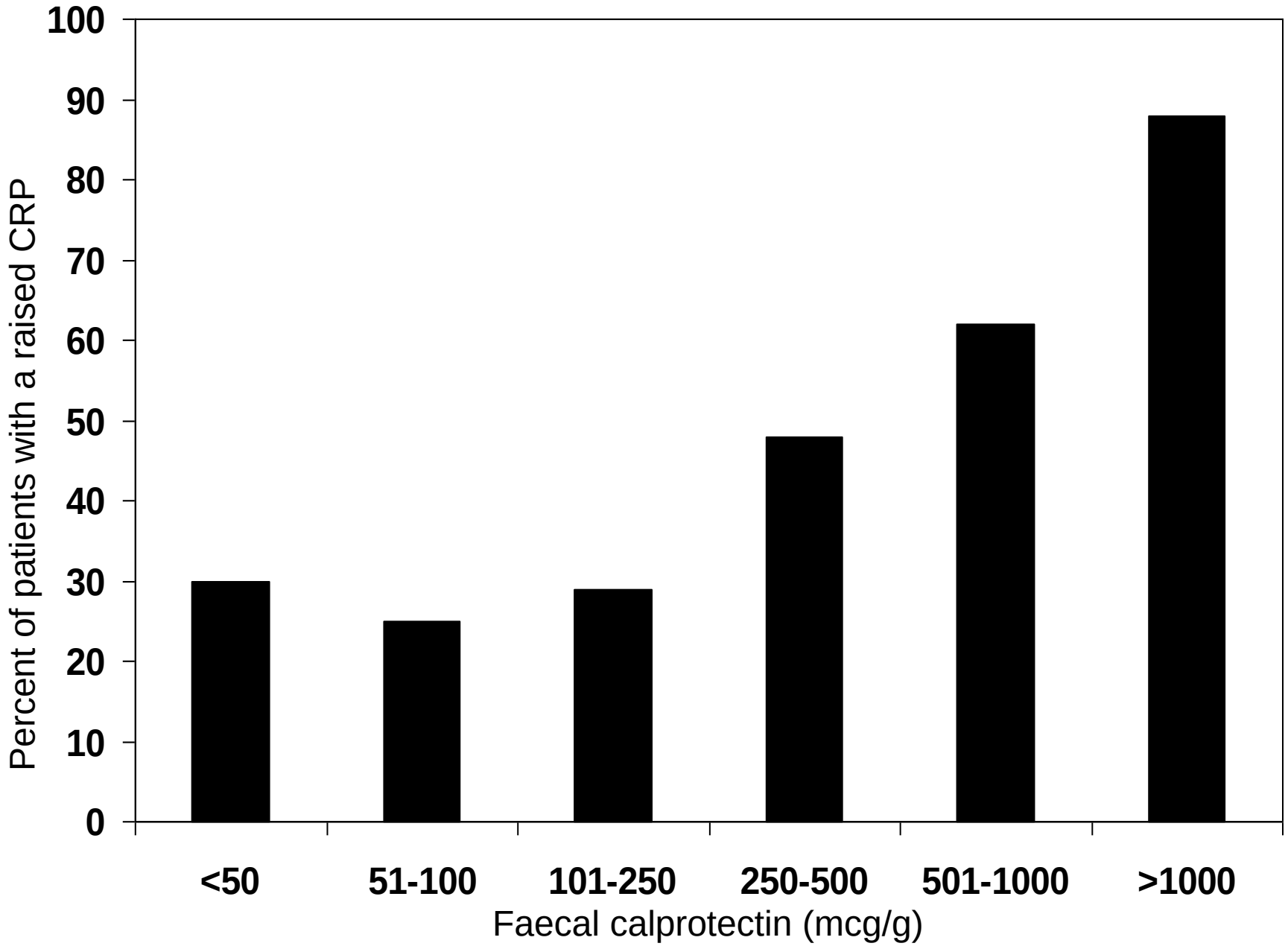
But what does a raised faecal calprotectin mean?

- 30% of referrals with raised FC have IBS
  mean: 164.2
- Third of FC become normal when repeated
  initial mean: 251
- Raised FC results in extensive intestinal investigation
  - 75% colonoscopy or barium enema
  - 58% small bowel studies
  - 12.5% capsule endoscopy

- 20% UC FC<200 45% Crohn's FC<200

Frontline Gastroenterol doi:10.1136/flgastro-2011-100011


10000
1000
100
10
1
faecal calprotectin mcg/g
quiescent
mild
moderate
severe
Crohn's disease activity


100
90
80
70
60
50
40
30
20
10
0
Percent of patients with a raised CRP
<50
51-100
101-250
250-500
501-1000
>1000
Faecal calprotectin (mcg/g)

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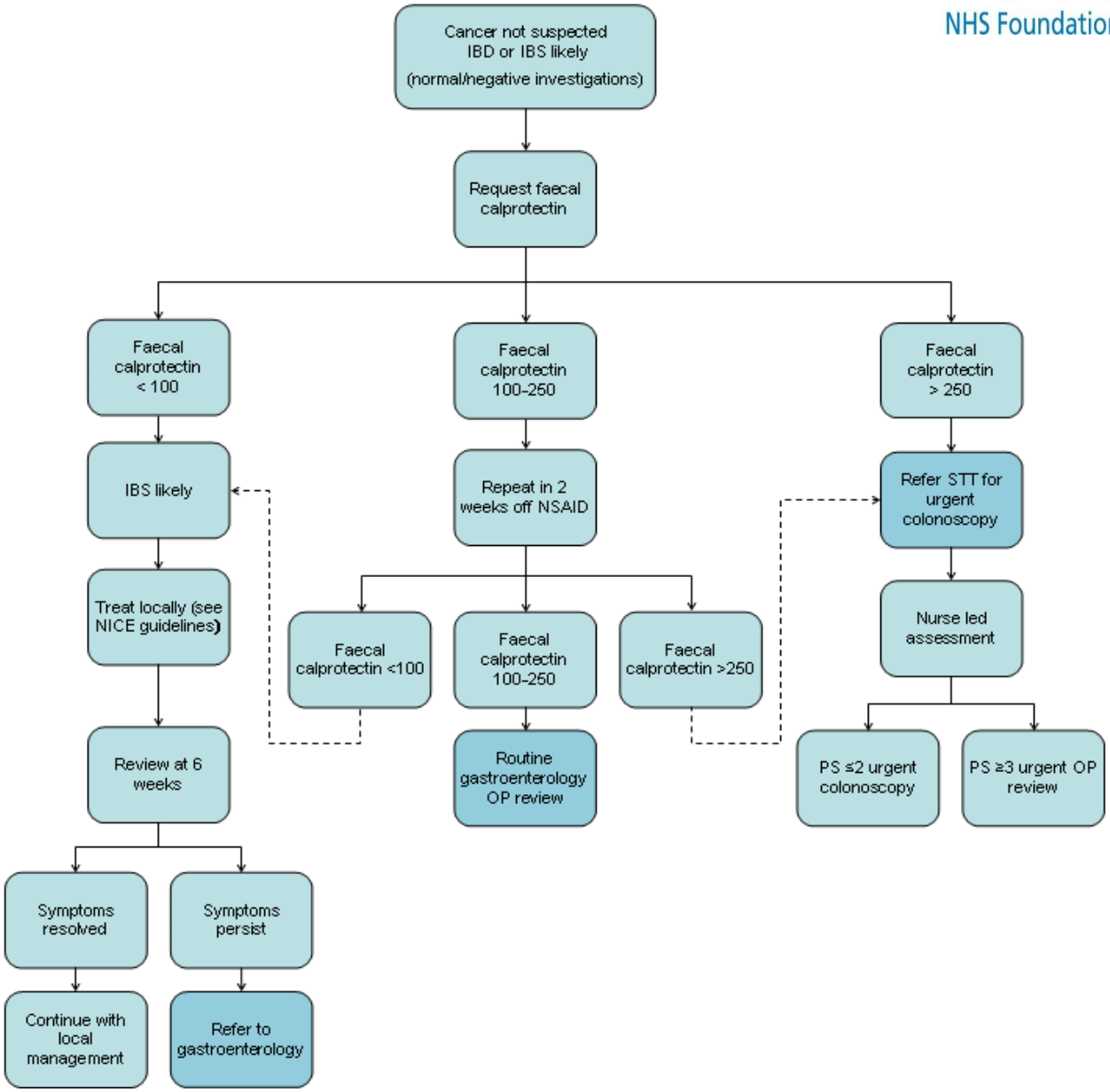

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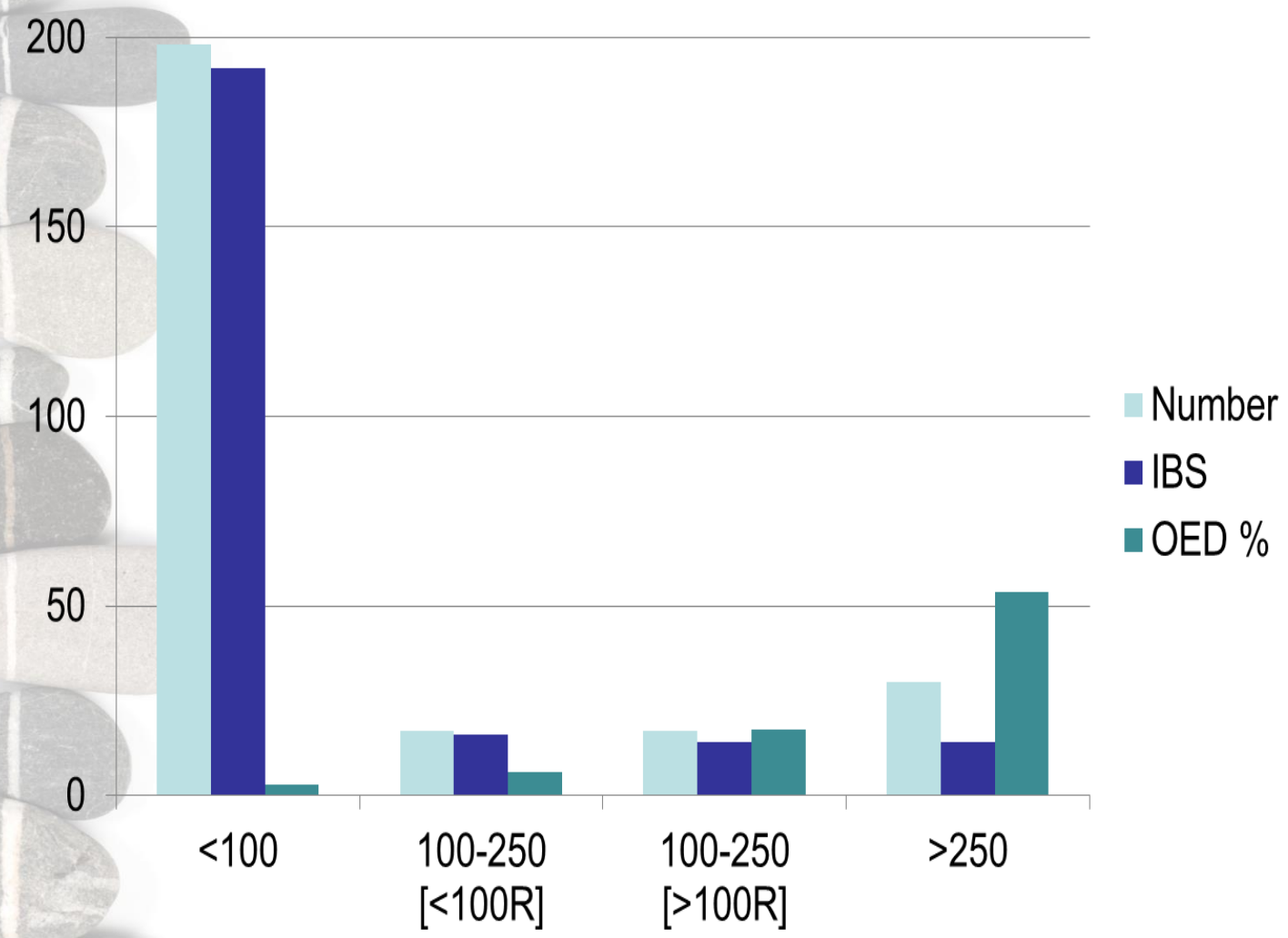
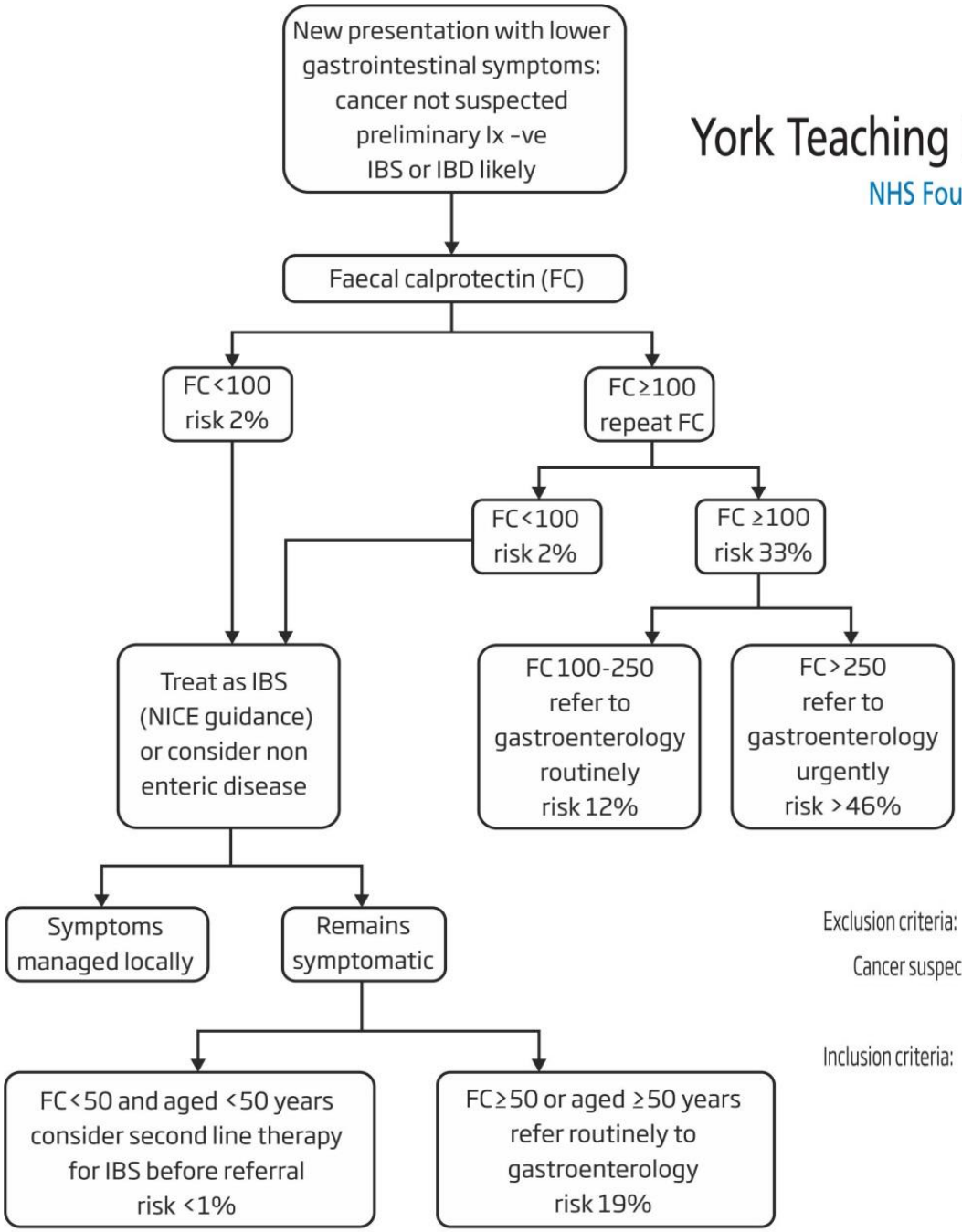
Primary Care Pilot:
Distribution of FC and Outcomes



Primary Care Pilot

FC <50	FC 50-100	FC >100
58% of patients	30% of patients	12% of patients
3% risk of disease	3% risk of disease	33% risk of disease

	NPV %	PPV %
FC care pathway	97	40
FC <50mcg/g	98	20



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Exclusion criteria:

Cancer suspected (NICE guideline NG12. https://www.nice.org.uk/guidance/ng12)

Inclusion criteria:

- Adult 18-60 years
- New lower gastrointestinal symptoms
- Normal or negative initial workup (FBC, U&E, Cr, TFT,CRP, Ca, coeliac screen) Stool culture / C. difficile screen as appropriate.

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Using the Care Pathway

- Patients aged 18-60 years
- Presentation with lower gastrointestinal symptoms
  - change of bowel habit
  - abdominal pain
  - abdominal bloat
- Investigate as you judge to be clinically appropriate:
  - FBC, biochemistry, C-reactive protein
  - Thyroid function test, coeliac screen
  - Stool culture, *C difficile*

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IBS or IBD is suspected
Diagnostic uncertainty
Cancer is not suspected
Request a faecal calprotectin

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FC<100mcg/g

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- IBS 98% likely
- Reassure and treat as IBS

  or
- Consider non-GI diagnosis (uro-gynaecological)
- Review at 6 weeks

- If still symptomatic
  - FC <50 and aged <50years
    - trial second line IBS therapy initially
    - if unsuccessful refer routinely to gastroenterology
  - FC ≥50 or aged ≥50years
    - refer routinely to gastroenterology

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FC ≥100mcg/g

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- Repeat
- FC<100
  - treat as likely IBS
- FC 100-250
  - refer routinely to gastroenterology
- FC>250
  - urgent gastroenterology referral for straight to test colonoscopy

YFCCP roll out

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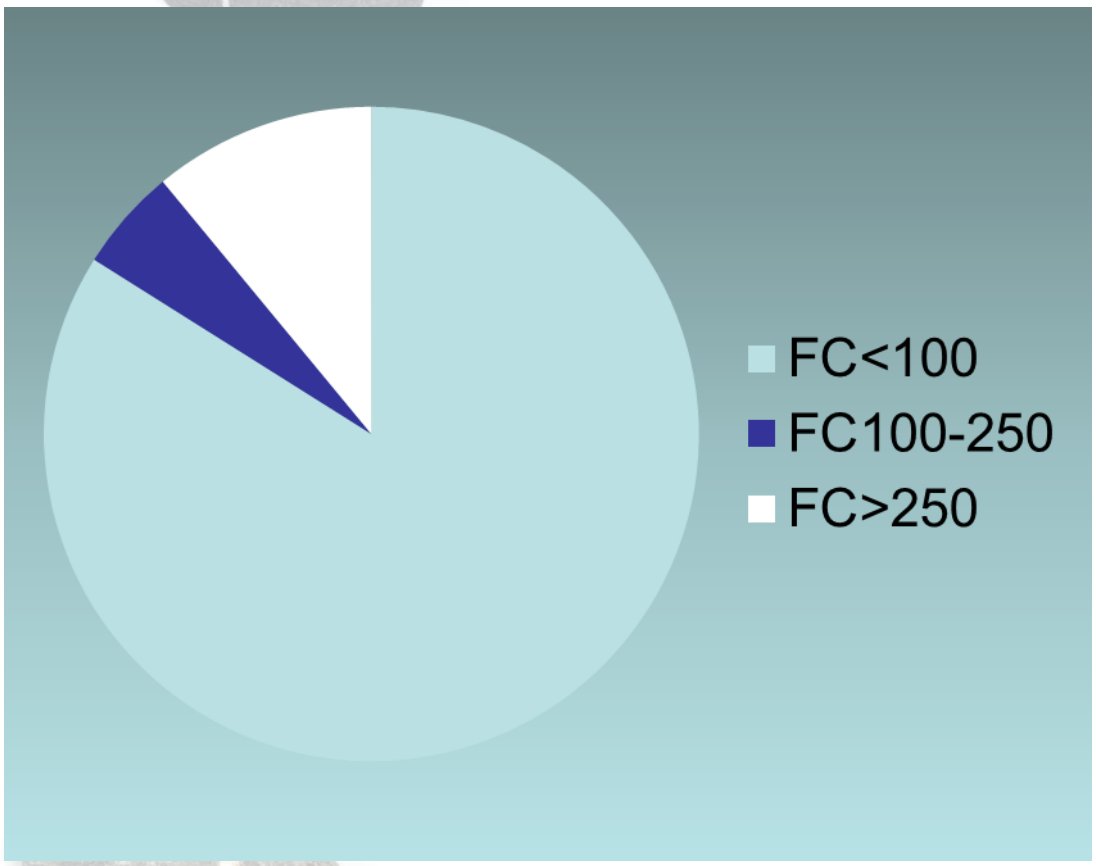

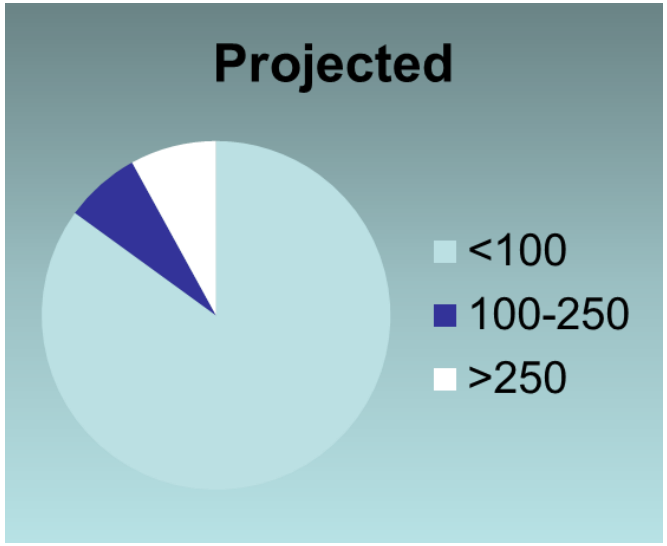

YFCCP evaluation

- 6 month outcomes on 1000 patients
- median age: 38 [27-48]
- 63% female
- 7% prevalence of IBD (organic enteric disease)
- 53% FC > 100 normalise on repeat
- compliance 85%
- NPV: 99% (98-100); PPV: 50% (42-59)
- Sens: 94% [85-98]; spec: 92% [90-94]
- non-pathway (FC<50): NPV 99% PPV 16%
- comparator:
  - retrospective evaluation of the NPV and PPV of FC usage (cut off 50mcg/g)
  - 280 patients Scarborough and Ryedale CCG in the six months before the pathway went live
  - NPV of 100% but a PPV of 13%

YFCCP
economic evaluation

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YHEC

- Health economic evaluation with YHEC
- Outcome data compared against historic standard care, predicted outcomes from FC usage and outcomes from this implementation using standard cut off (per 1000 pts)

	Intervention	No FC (ESR + CRP)	Incremental
Total costs	£308,954	£416,839	-£107,885
Correctly diagnosed IBS cases	849	677	172
Correctly diagnosed IBD cases	66	25	41
Unnecessary colonoscopies (i.e. false +ves)	79	251	-172

	Intervention	Standard cut-off	Incremental
Total costs	£308,954	£467,820	-£158,866
Correctly diagnosed IBS cases	849	562	287
Correctly diagnosed IBD cases	66	68	-1
Unnecessary colonoscopies (i.e. false +ves)	79	366	-287

YFCCP
Sensitivity analysis

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YHEC

- Prevalence of IBD

  varied the range from 0% to 20% (YFCCP CI 6.5% - 10%)

  YFCCP is cost saving with health benefits across all outcomes except at a prevalence of 0%

- GP Adherence

  varied GP adherence with the intervention arm between 0-100%

  as soon as we reach 1% the YFCCP is cost saving with better health benefits.

- Effectiveness

  varied sensitivity and specificity between 50% and 100%

  YFCCP is dominant at all levels of specificity above 75%

  YFCCP is more effective at diagnosing IBD at a sensitivity & specificity > 70%

YFCCP implementation portfolio

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- Engagement with stakeholders
  - CCG, primary care, secondary care, laboratory medicine
- Business cases
- Patient management system templates
  - SystmOne
  - EMIS
- Training package and youtube video
- Compliance
  - referral vetting, laboratory guidance, 2ww
- Patient information leaflet
- GP information leaflet
- Local arrangements: OA colonoscopy

Acknowledgements

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YFCCP

Outstanding challenges

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YHEC

- When to repeat a raised FC?
  - 2-6weeks?
- What about a very high FC?
  - maybe VERY high
- Assay variability
- FIT

Buhlmann versus immundiagnostik

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UK NEQAS for Faecal Markers of Inflammation | Laboratory :

Distribution : **160** Date : 10-Sep-2017 | Page 6 of 19

Analyte : Calprotectin (ug/g)

		160A			160B			160C		
	n	Mean	SD	CV(%)	Mean	SD	CV(%)	Mean	SD	CV(%)
All methods [ALTM]	93	136	74	54.6	34.4	18.6	54.2	180	83	46.4
ELISA	78	133	75	56.6	32.8	19.0	57.8	170	82	48.3
Accusay [2AY]	5	108	7	6.4	22.9	1.3	5.5	110	8	7.0
Buhlmann [2BU]	24	194	101	51.9	45.7	17.5	38.4	248	76	30.8
Calpro (ALP) [2CP]	4	174			27.0			154		
Diasorin [2IN]	4	102			16.0			104		
Immundiagnostik (K6927)	7	175	50	28.3	53.3	9.2	17.3	206	36	17.7
Inova [2IF]	1	309			27.0			183		
Orgentec Alegria [2OC1]	5	78.7	20.1	25.5	14.6	6.7	45.9	144	117	81.5
Thermo EliA Calpro 2 [2KO2]	17	96.5	42.9	44.4	21.2	8.7	41.0	151	74	48.6
Thermo EliA [2KO]	11	75.1	22.7	30.2				111	25	22.4
Lateral flow	6	124	67	53.8	46.0	13.7	29.8	209	65	31.1
Quantum Blue [3BU]	6	124	67	53.8	46.0	13.7	29.8	209	65	31.1
Immuno turbidimetric	8	157	41	26.4	39.8	9.2	23.2	241	45	18.7
Buhlmann fCAL turbo [4BU]	8	157	41	26.4	39.8	9.2	23.2	241	45	18.7
Chemiluminescence	2	300			11.0			251		
Inova QUANTA Flash [9IF]	2	300			11.0			251		
non-numeric results	20									

FC and risk of IBD (Buhlmann)

Faecal Calprotectin (mcg/g)	IBS	IBD	risk of IBD (%)
<25	413	2	0.5
25-49	321	5	1.5
50-74	176	4	2.2
75-99	88	3	3.5
100-124	15	3	16.7
125-149	8	3	25
150-174	4	3	42.9
175-199	4	1	20
200-224	3	9	75
225-249	7	5	41.7
250-300	11	2	14.5
300-399	12	6	33.3
400-499	5	5	50
500-600	8	4	33.3
>600	26	41	61.2

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FIT NICE DG30:

FIT for low risk patients

- NICE guidance DG30 states the OC Sensor, HM-JACKarc and FOB Gold quantitative faecal immunochemical tests (FIT) are recommended for adoption in primary care to guide referral for suspected colorectal cancer in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in NICE's guideline on suspected cancer (recommendations 1.3.1 to 1.3.3).

FIT NICE DG30:

FIT for low risk patients

- How does it fit with FC?

FC in suspected colorectal cancer

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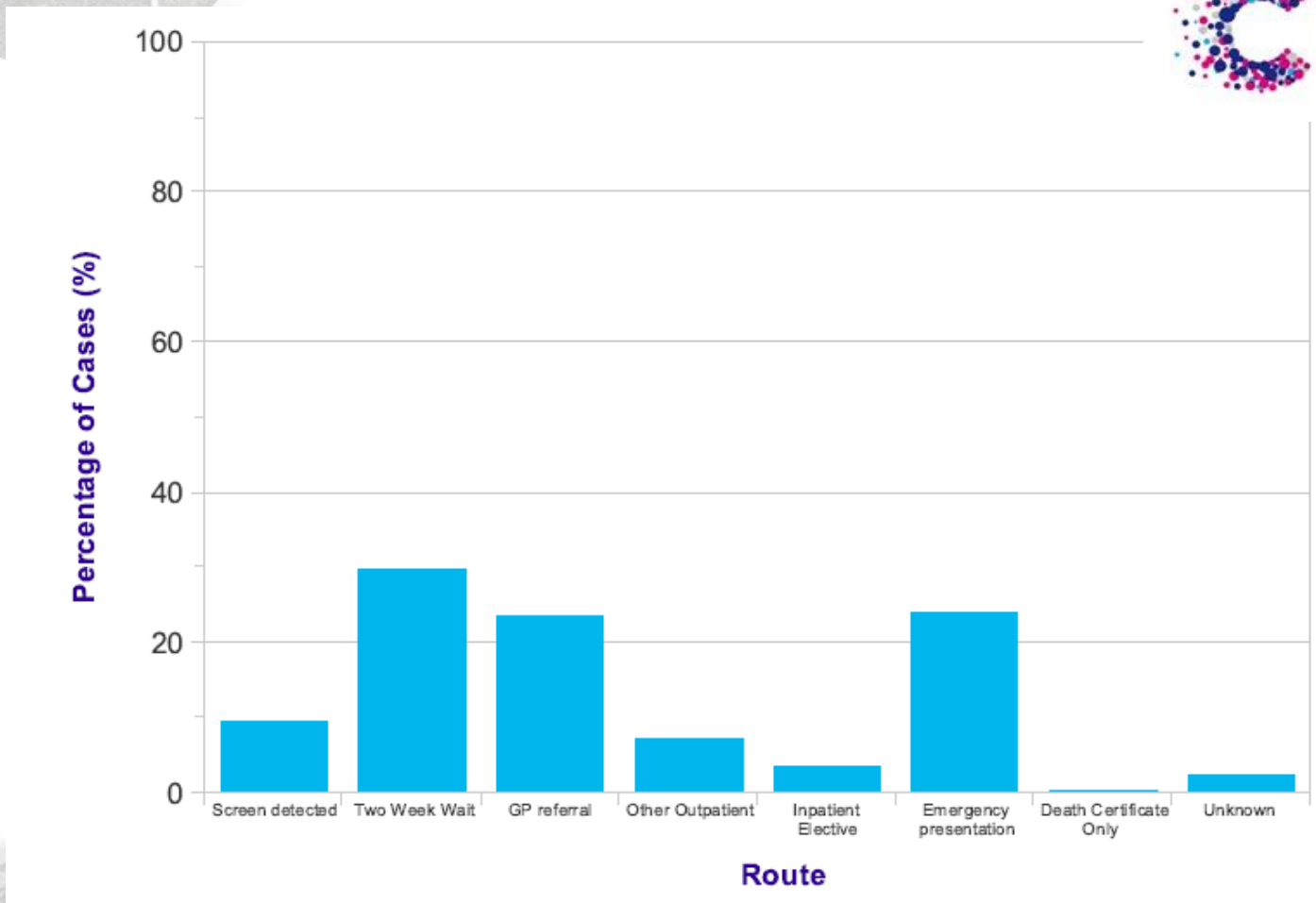
Diagnostic accuracy of faecal calprotectin for neoplasia and organic enteric disease					
	Median	NPV	PPV	Sensitivity	Specificity
Neoplasia					
• **cancer**	227 (94.5-496)	98.6 (95.7-99.6)	8.7 (6.3-11.9)	92.7 (79-98)	35.2 (31.5-39.2)
• **cancer and polyps**	189.5 (88-494)	97.2 (93.8-98.9)	15.6 (12.4-19.4)	91.9 (82.6-96.7)	36.4 (32.5-40.5)
Organic enteric disease					
	232 (79-580)	89.4 (84.3-93)	32.7 (28.4-37.4)	86.1 (79.7-90.8)	39.8 (35.4-44.3)

FIT NICE DG30:

FIT for low risk patients



FIT NICE DG30:

FIT for low risk patients

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CANCER RESEARCH UK

FIT NICE DG30:

FIT for low risk patients

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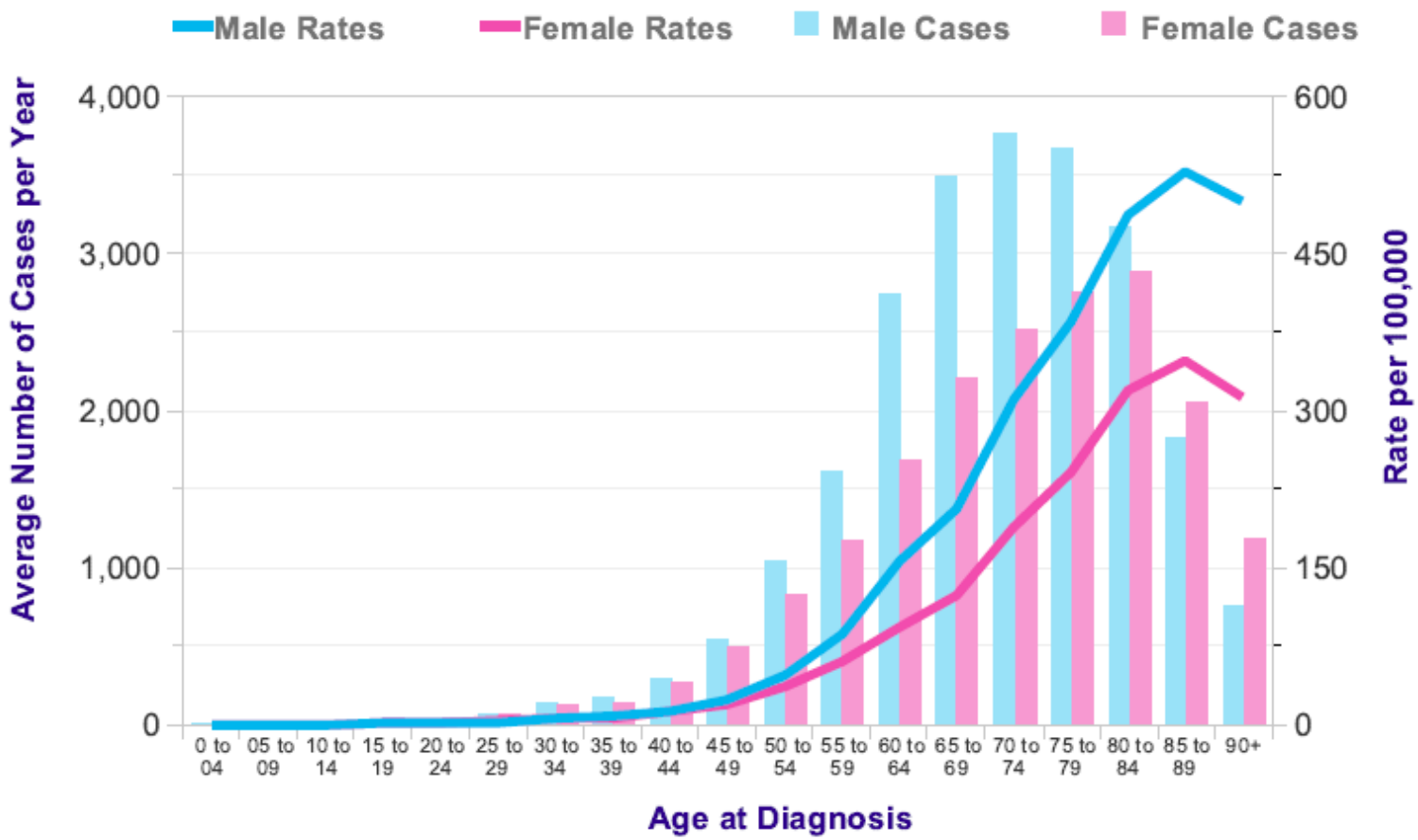

FIT v FC:

1229 patients <60y fulfilling DG30 criteria applied to YFCCP

	Age range (yrs)	Sensitivity (CI)	Specificity (CI)	NPV (CI)	PPV (CI)
CRC					
FIT≥10mcg/g*		89.3	79.1	99.5	14.2
FC ≤100mcg/g	50-59	50	83	99	5
	40-49	N/A	N/A	N/A	N/A
	30-39	100	89	100	3
	18-29	N/A	N/A	N/A	N/A
CRC, polyps & IBD					
FIT≥10mcg/g*		68.6	83.6	94.4	39.8
FC ≤100mcg/g	50-59	65	85	98	21
	40-49	89	90	99	33
	30-39	100	92	100	31
	18-29	100	89	100	47

* Mowat C, et al. Gut 2015;0:1–7. doi:10.1136/gutjnl-2015-309579

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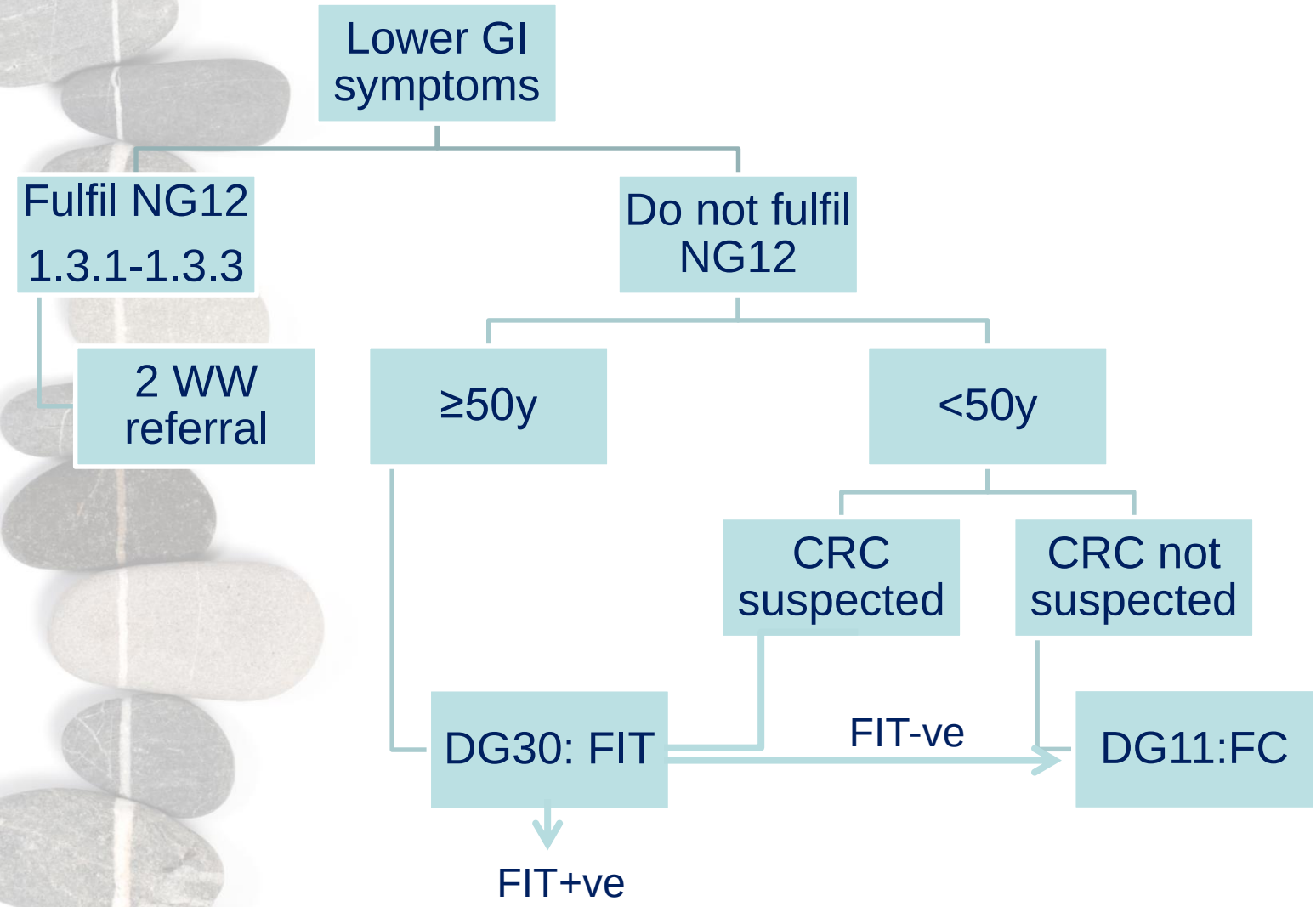
NICE DG30 and DG11:

The future FIT/FC pathway



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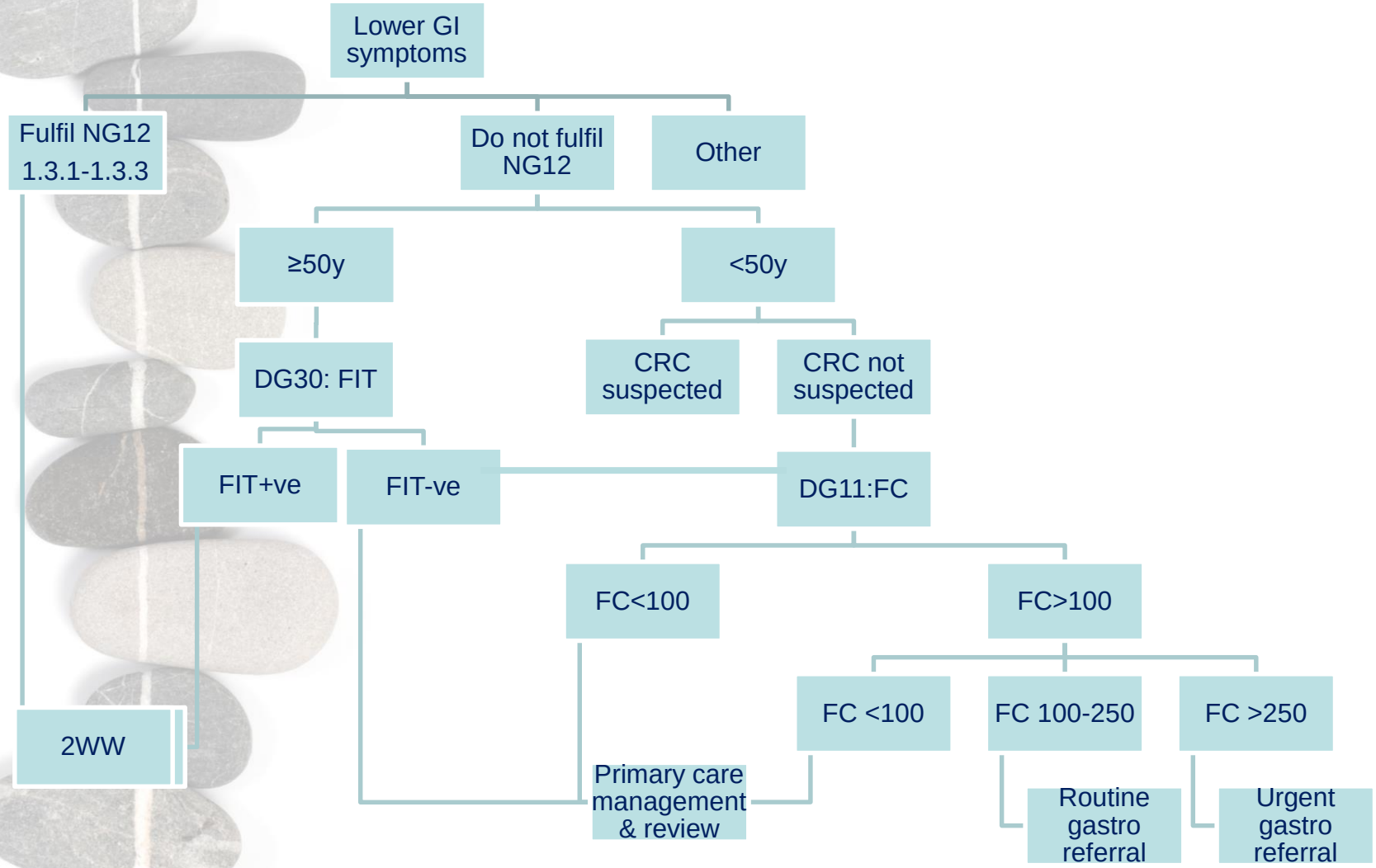
NICE DG30 and DG11:

The future FIT/FC pathway



Future pathway for all

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