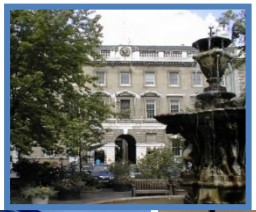
Evaluation of treatment effect in UC and CD (children)

Dr Nick Croft

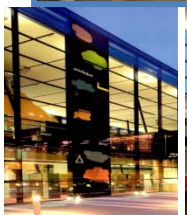
Digestive Diseases,

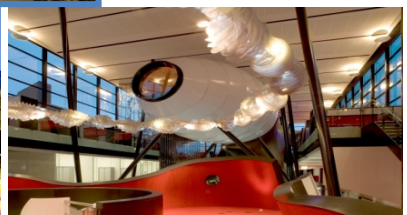
Centre for Immunobiology, Blizard Institute

& Barts Health NHS Trust



Blizard Institute





Disclosures

Dr Nick Croft has served as advisory board member, speaker or received research funding from Abbvie, Abbot, Shire, Norgine, Ferring, Johnson and & Johnson , Dr Falk, MSD, Schering Plough, GSK.

He is currently European CI for an Abbvie Humira study and local PI for a Shire study in IBD.

All funds are paid into institutional accounts.

Outline

1. Do we know what matters to patients ?

2. What are the outcome measure available now ?
   - Clinical scores
   - Endoscopy
   - Radiology
   - Biomarkers

3. Mucosal healing

4. Quality of life scores
   - IMPACTIII

What matters

1. Quick diagnosis (least invasive as possible)
2. Identify those at risk of severe disease
3. Treat (safe, easy to take) and maintain long term remission
4. Monitor accurately and as few interventions as possible
5. Prevent deterioration/complications

What matters to patients and families

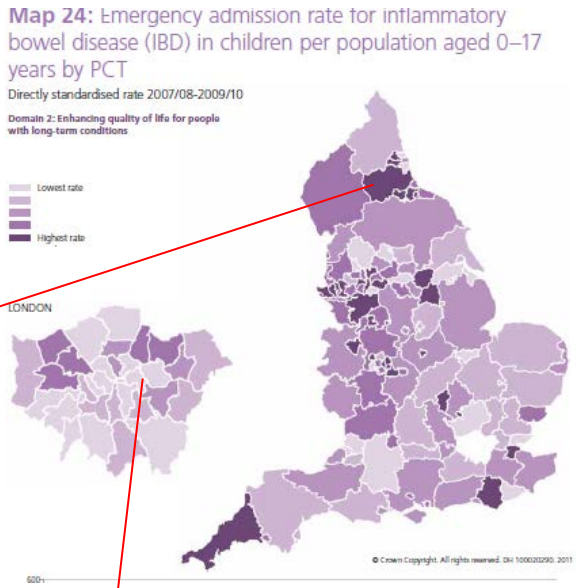
Keep well

Leading ‘normal’ lives with as little medical engagement as possible

School attendance and achievement

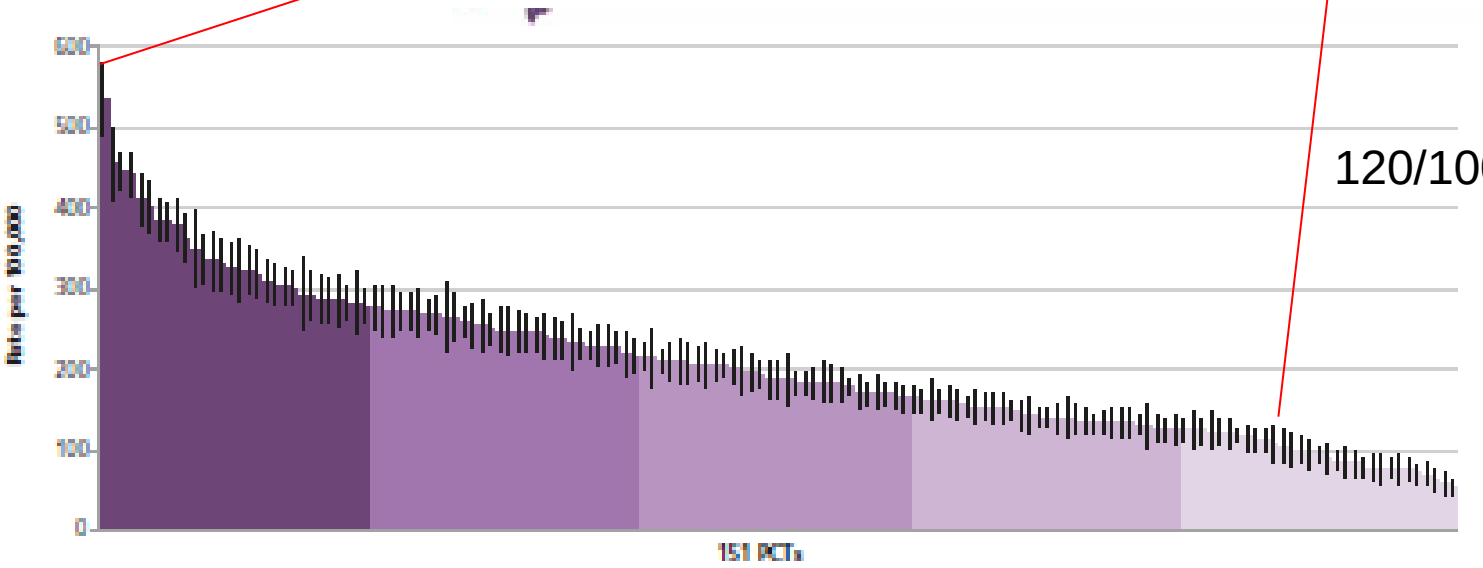
Growth/puberty

NHS Atlas of Variation: Emergency (unplanned) admission for IBD 0-17 years by local population



500/100,000

120/100,000



What matters to patients and families

Different families will want different things for their children

Trainee 1: Well child **and** colonoscopies to reassure and confirm there is mucosal healing

Vs

Trainee 2: Well child and NO interventions unless for unavoidable decision making or safety.

Well-Defined and Reliable Clinical Outcome Assessments for Pediatric Crohn Disease: A Critical Need for Drug Development

*Haihao Sun, †Elektra J. Papadopoulos, ‡Jeffrey S. Hyams, §Donna Griebel, §Jessica J. Lee, §Juli Tomaino, and §Andrew E. Mulberg

JPGN • Volume 60, Number 6, June 2015

Crohn's: Paediatric Crohn's Activity Index PCDAI - Patient and Carer input

TABLE 3. Summary of instrument development

Instrument	PCDAI	Abbreviated PCDAI	Short PCDAI	Modified PCDAI	Weighted PCDAI
Type of COA	Composite of proxy report, ClinRO, biomarkers	Composite of proxy report and ClinRO	Composite of proxy report and ClinRO	Biomarker-based outcome measure	Composite of proxy report, ClinRO, biomarkers
Source of item derivation	Experts	Experts	Experts	Experts	Experts
Qualitative interview schedule	None	None	None	Not applied	None
Interview or focus group transcript	None	None	None	Not applied	None
Items derived from the transcript	None	None	None	Not applied	None
Patient or caregiver composition used to develop content	No patient's input	No patient's input	No patient's input	No patient's input	No patient's input
	No caregiver's input	No caregiver's input	No caregiver's input	No caregiver's input	No caregiver's input
Cognitive interview transcripts to evaluate patient or caregiver's understanding	None	None	None	Not applied	None

Clin-RO = clinician-reported outcome; COA = clinical outcome assessment; PCDAI = Pediatric Crohn's Disease Activity Index.

TABLE 3. Summary of instrument development

Instrument	PCDAI	Abbreviated PCDAI	Short PCDAI	Modified PCDAI	Weighted PCDAI
Type of COA	Composite of proxy report, ClinRO, biomarkers	Composite of proxy report and ClinRO	Composite of proxy report and ClinRO	Biomarker-based outcome measure	Composite of proxy report, ClinRO, biomarkers
Source of item derivation	Experts	Experts	Experts	Experts	Experts
Qualitative interview schedule	None	None	None	Not applied	None
Interview or focus group transcript	None	None	None	Not applied	None
Items derived from the transcript	None	None	None	Not applied	None
Patient or caregiver composition used to develop content	No patient's input No caregiver's input	No patient's input No caregiver's input	No patient's input No caregiver's input	No patient's input No caregiver's input	No patient's input No caregiver's input
Cognitive interview transcripts to evaluate patient or caregiver's understanding	None	None	None	Not applied	None

Clin-RO = clinician-reported outcome; COA = clinical outcome assessment; PCDAI = Pediatric Crohn's Disease Activity Index.

Patient or caregiver composition used to develop content

No patient's input

No caregiver's input

The Paediatric UC Activity Index (PUCAI)

Derivation

Large Delphi group
Multivariate analysis from 157 prospectively enrolled children

Validation

48 children undergoing colonoscopy
Two other independent cohorts (MSH and registry)
Prediction validity

ITEM	POINTS
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only in < 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
>8	15
5. Nocturnal bowel movement (any diarrhea episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
SUM OF PUCAI (0-85)	

Turner et al; Gastroenterology 2007;133:423-432

TUMMY index, a newly derived patient reported outcome (PRO) for pediatric ulcerative colitis

Liron Marcovitch[1,2], Anat Nissan[2], David Mack[3], Tony Otley[4], Seamus Hussey[5], Mike Kappelman[6], Beth Mclean[6], Nick Croft[7], Farah Barakat[7], Anne Griffiths[8], Dan Turner[1,2].

- Stage 1 completed

  - Derived from caregivers and patients
  - Qualitative interviews, 35 patients
  - Good caregiver and patient correlation,
  - Items scored out of 5
    - **Abdominal pain** (4)
    - **Rectal bleeding** (3.5)
    - **Stool frequency** (2.8)
    - **Stool consistency** (2.8)
    - **General well-being (**2.8)
    - **Urgency** (1.8)
    - **Nocturnal stools** (1.7)

  Lack of appetite (1) and **weight loss** (0.6)

CICRA Family Day Survey 2014

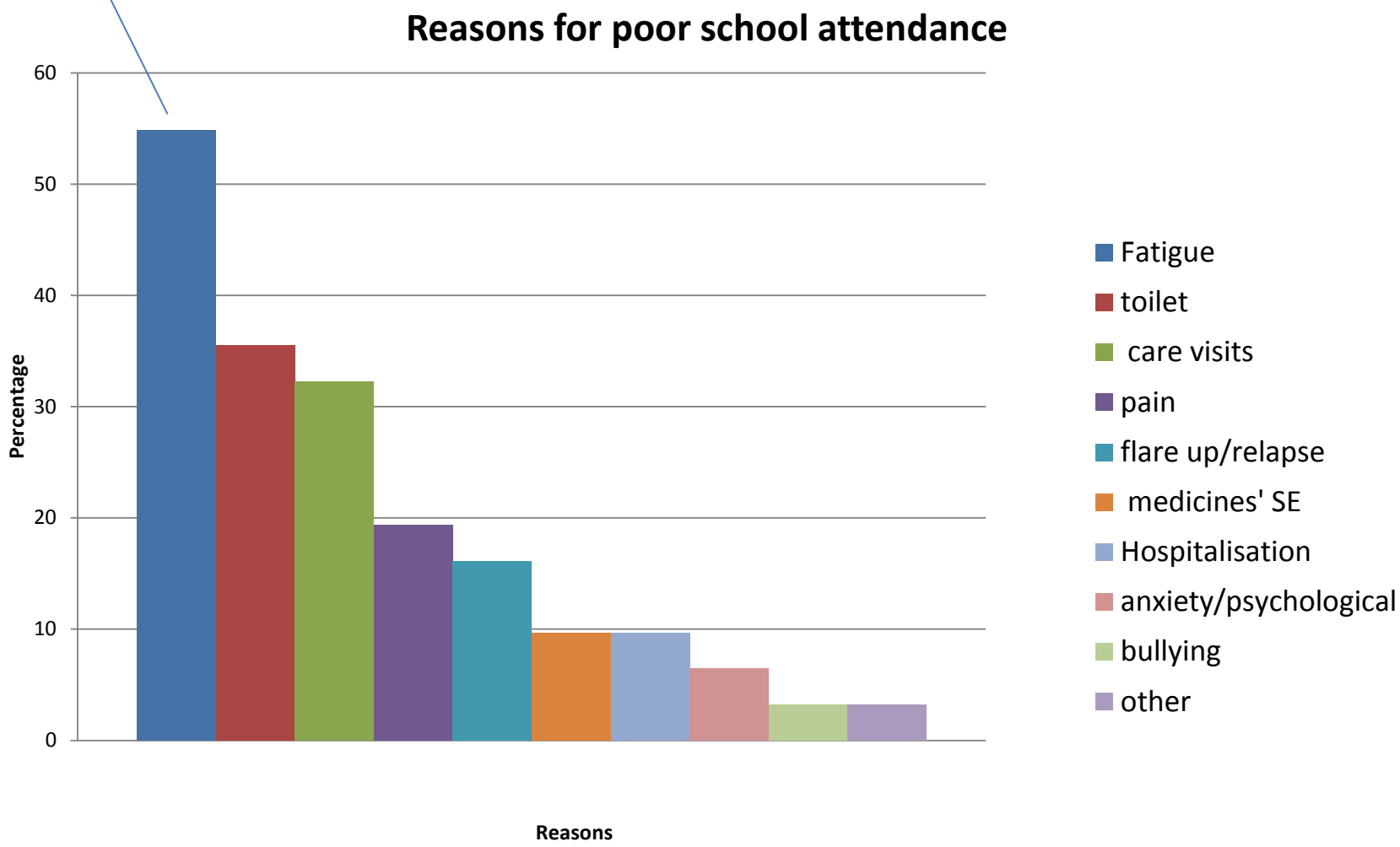
41 families; Effect of IBD on education

- 72 % concerned about their child's education
- 62% affected school attendance
- 39 % .. affected school performance.

Blizard Institute

Free text response:

Fatigue was the major reason given for reduced school attendance (and is not in any score)



Growth and Puberty

A minority of patients have growth failure at some point (25%)

Important secondary outcome measure in maintenance studies

What are the outcome measures available now ?

Ideal measure: Assessing Disease

Table 1 Performance and qualities of an ideal marker

Performance	Qualities
▶ Simple	Be disease specific: identify individuals at risk for IBD and differentiate IBD from non-IBD
▶ Easy to perform	Able to objectively measure disease activity
▶ Not or minimally invasive	Able to predict the disease course (relapse or recurrence)
▶ Cheap	Able to monitor the effect of treatment
▶ Rapid	Have a prognostic value in assessing morbidity/mortality
▶ Reproducible between labs and individuals	

IBD, inflammatory bowel disease.

RECENT ADVANCES IN CLINICAL PRACTICE

LABORATORY MARKERS IN IBD: USEFUL, MAGIC, OR UNNECESSARY TOYS?

S Vermeire, G Van Assche, P Rutgeerts

Gut 2006;55:426–431. doi: 10.1136/gut.2005.069476

1. Clinical Score:
   - UC
     - Physicians Global Assessment
     - PUCAI (UC)
     - PRO-PUCAI - TUMMY
     - Adult scores MAYO /SCCI/Lichtiger etc
   - Crohn's
     - PGA
     - PCDAI x 5 (PCDAI, shPCDAI, wPCDAI, abrPCDAI (Crohn's)
     - Adult scores (CDAI (adult), HBI (adult))

2. Endoscopy and histology:
   - OGD and Colonoscopy
   - Capsule endoscopy

4. Radiology:
    - MRE
    - USS
    - Barium

5. Blood or stool biomarkers:
    - Faecal Calprotectin
    - CRP, ESR, Albumin

6. Quality of life scores:
    - IMPACTIII

Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee

Frank M Ruemmele,[1,2,3] Jeffrey S Hyams,[4] Anthony Otley,[5] Anne Griffiths,[6] Kaija-Leena Kolho,[7] Jorge Amil Dias,[8] Arie Levine,[9] Johanna C Escher,[10] Jan Taminiau,[11] Gabor Veres,[12] Jean-Frederic Colombel,[13] Séverine Vermeire,[14] David C Wilson,[15] Dan Turner[16]

Working groups
Literature search
Modified Delphi process

Resulted in 21 statements with > 80 % agreement

2. Disease activity scores (weighted Paediatric Crohn's Disease Activity Index (wPCDAI) or Paediatric Ulcerative Colitis Activity Index (PUCAI)) can be considered as primary end points in studies that test therapies already shown to induce MH (in adults) and if they do not represent a new drug category (93% agreement)

3. Design of clinical trials based on disease activity scores as primary outcome measures should include evaluation of endoscopic MH as a co-primary or secondary outcome measure in a subpopulation of patients (83% agreement)

PUCAI

- 17+ studies in different scenarios
  - Good discriminative validity (mild/mod/severe)
  - Good responsiveness (improvement or deterioration)
  - Reliable (inter observer / test-retest) ~90%
- Used routinely in clinical practice across the world and guiding management

Crohn’s disease

Crohn's Disease: 11-item PCDAI (0-100)

- 3 History (1 week recall)
  - Stool frequency + blood
  - abdominal pain
  - wellbeing
- 5 Examination
  - Perirectal, extraintestinal manifestation, weight, height velocity (over 9-12 months), abdominal examination
- 3 Labs
  - Hematocrit, ESR, albumin

J Pediatr Gastroenterol Nutr. 2005 Oct;41(4):416-21.

Mathematical weighting of the PCDAI

n=437 children with CD

Item	β-Coefficient[1]	t	P value	Frequency of endorsement
Abdominal pain	.209	4.532	<0.001	159 (36%)
Stool frequency	.146	3.938	<0.001	65 (15%)
General well-being	.268	5.916	<0.001	100 (23%)
Abdominal examination	.060	1.576	0.116	19 (4%)
Perirectal disease	.152	4.490	<0.001	24 (6%)
EIM	.106	3.028	0.003	5 (1%)
Hematocrit	.033	0.858	0.391	35 (8%)
ESR	.153	3.909	<0.001	92 (21%)
Albumin	.194	5.063	<0.001	84 (19%)
Height velocity	-.047	-1.419	0.157	94 (22%)
Weight	.116	2.982	0.003	61 (14%)

R^2 remained unchanged after excluding the three non-significant items (0.604 to 0.601)

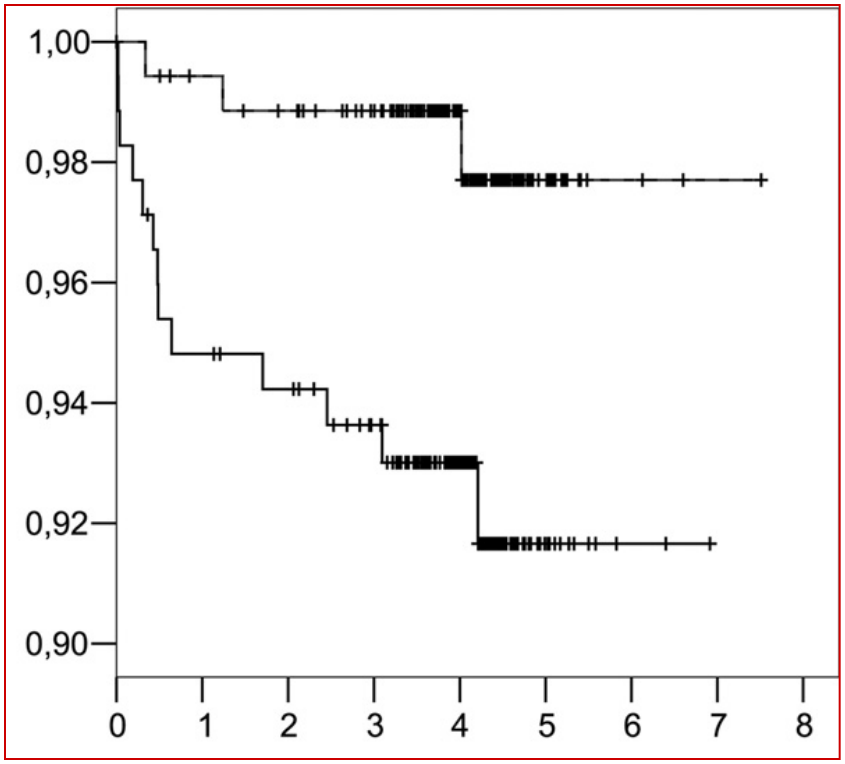
Turner et al. Inflamm Bowel Dis 2012;18(1):55-62

Mucosal Healing

2. MH is best evaluated by ileocolonoscopy showing disappearance of mucosal ulcerations based on the Simple Endoscopic Score for Crohn's Disease (SES-CD)<3 evaluated by central reading (92% agreement)

2. MH is best evaluated by colonoscopy showing disappearance of mucosal ulcerations based on a MAYO score of 0 evaluated by central reading (100% agreement)

The emerging importance of identifying deep remission in UC



Frøslie et al. Gastroenterology 2007;133:412–422

Enteral feeds (EEN) vs steroids in acute Crohn's

EEN:

Berni Canani 2006

Better mucosal healing

More prolonged remission

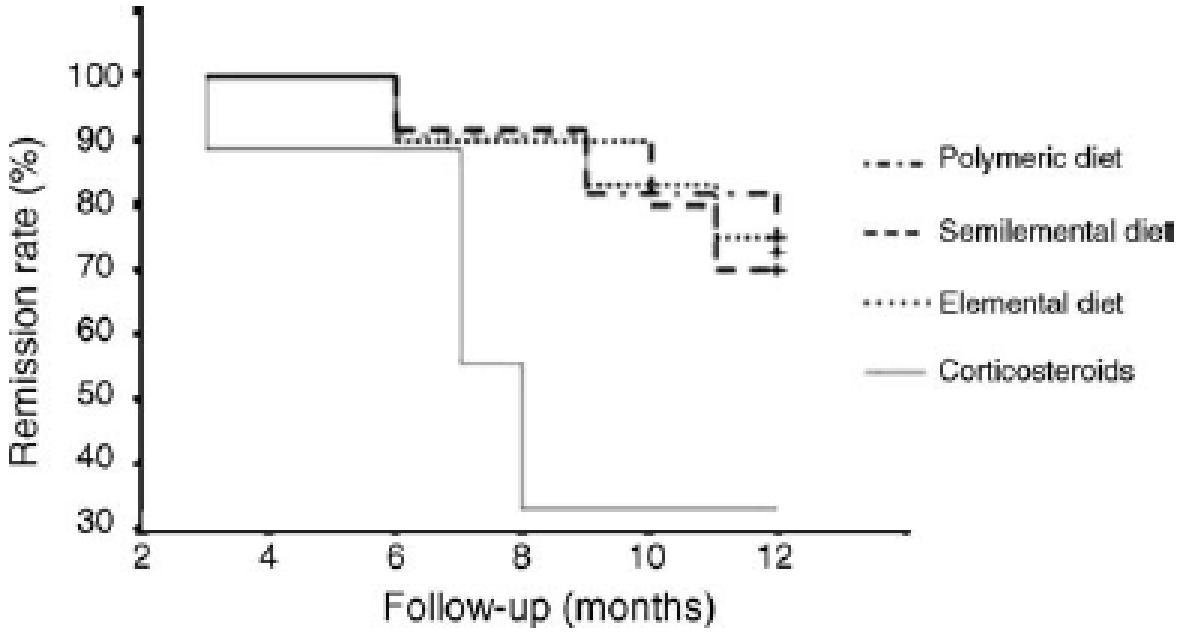
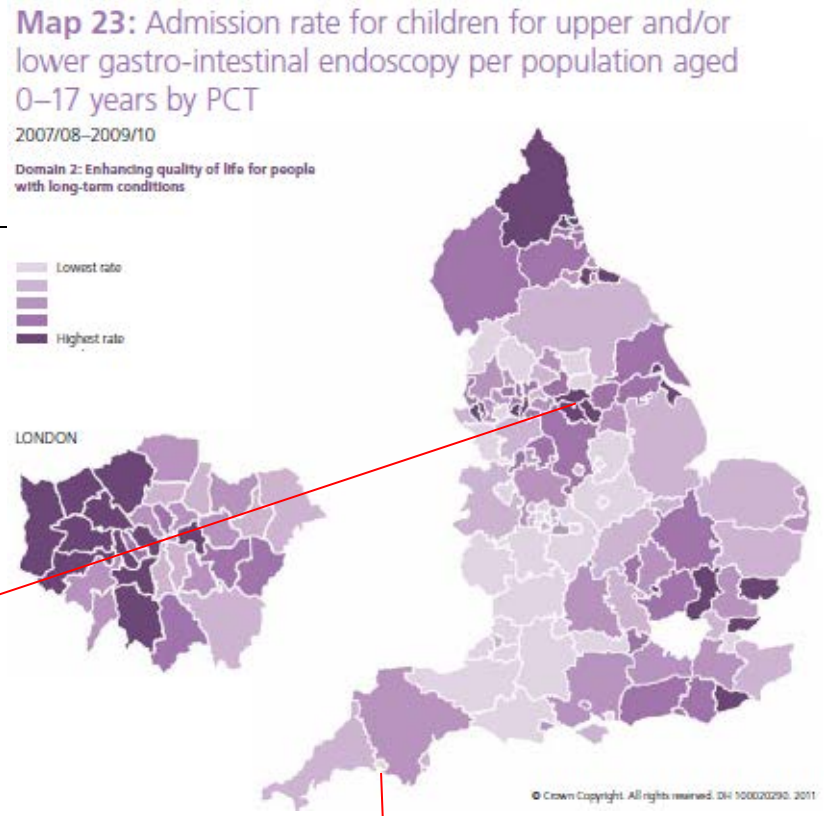


Fig. 2. Kaplan–Meyer curve showing a more prolonged clinical remission during the 12 months of follow up induced by NT compared to Cs in children with active CD.

Problems with endoscopy

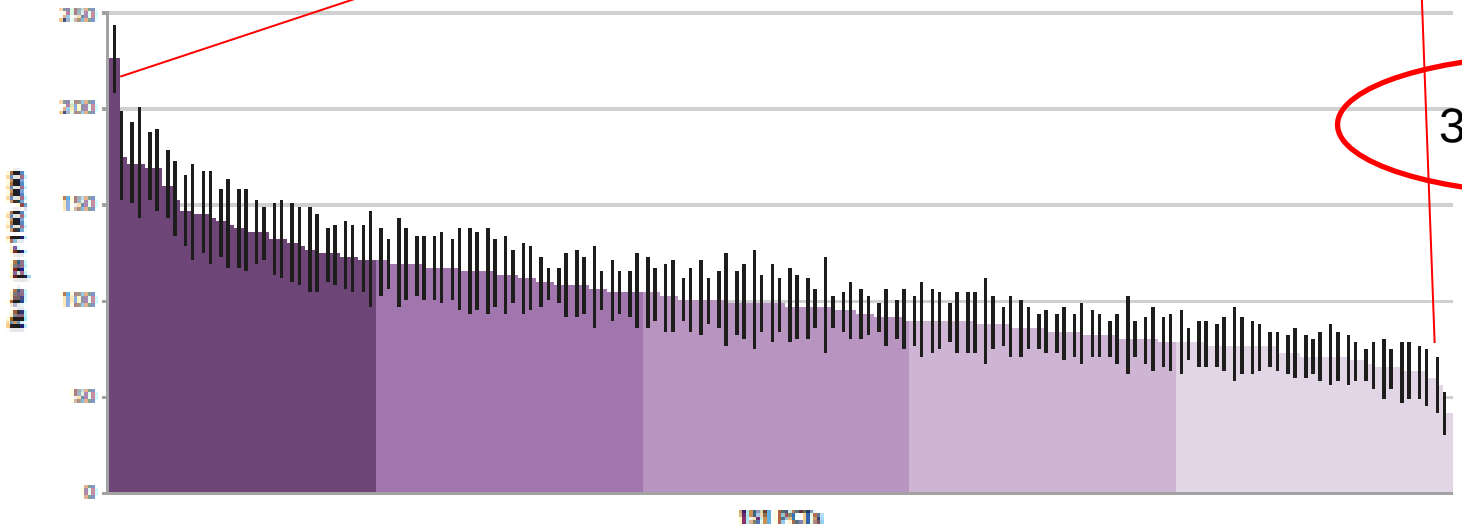
- Invasive
- Expensive
  - Needs GA / Sedation
- Unpleasant
  - Bowel preparation
- Crohn's
  - Disease is not limited to the mucosa
  - Or the limits of the endoscopes

NHS Atlas of Variation: Admissions for upper and lower endoscopies in children



220/100,000

30/100,000



Mucosal Healing

- Can we reliably demonstrate mucosal healing non-invasively ?
  - PCDAI
  - PUCAI
  - Videocapsule endoscopy
  - MRE
  - Faecal calprotectin (other biomarkers)

Polymeric Diet Alone Versus Corticosteroids in the Treatment of Active Pediatric Crohn's Disease: A Randomized Controlled Open-Label Trial

Clinical Gastroenterology and Hepatology
Volume 4, Issue 6, Pages 744-753 (June 2006)

	EEN	CS
Remission (ITT) (p=NS	79 %	67%
Mucosal Healing (p<0.05)	79%*	33%*

Mucosal Healing often does not relate to clinical response (Crohn's)

Healing of mucosa better in those who respond to enteral feeds than steroids (similar clinical response)

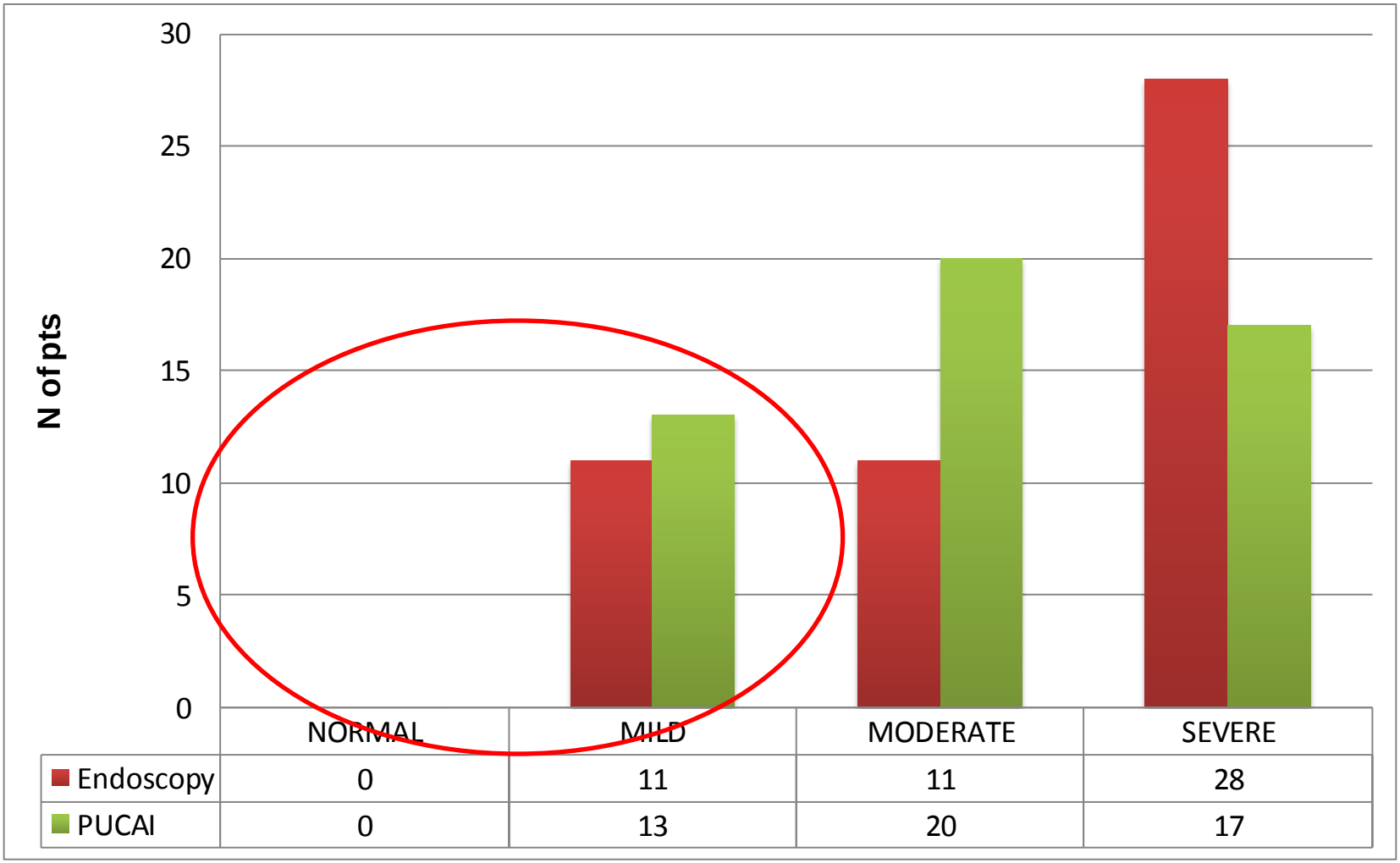
- Fell et al APT 2000
- Berni Canani et al Dig Liver Dis, 2006
- Borelli, 2006

Mucosal healing does not correlate with improved QOL (in those treated with EEN)

- Afzal, APT 2004

Ulcerative colitis

Disease activity according to PUCAI, endoscopy

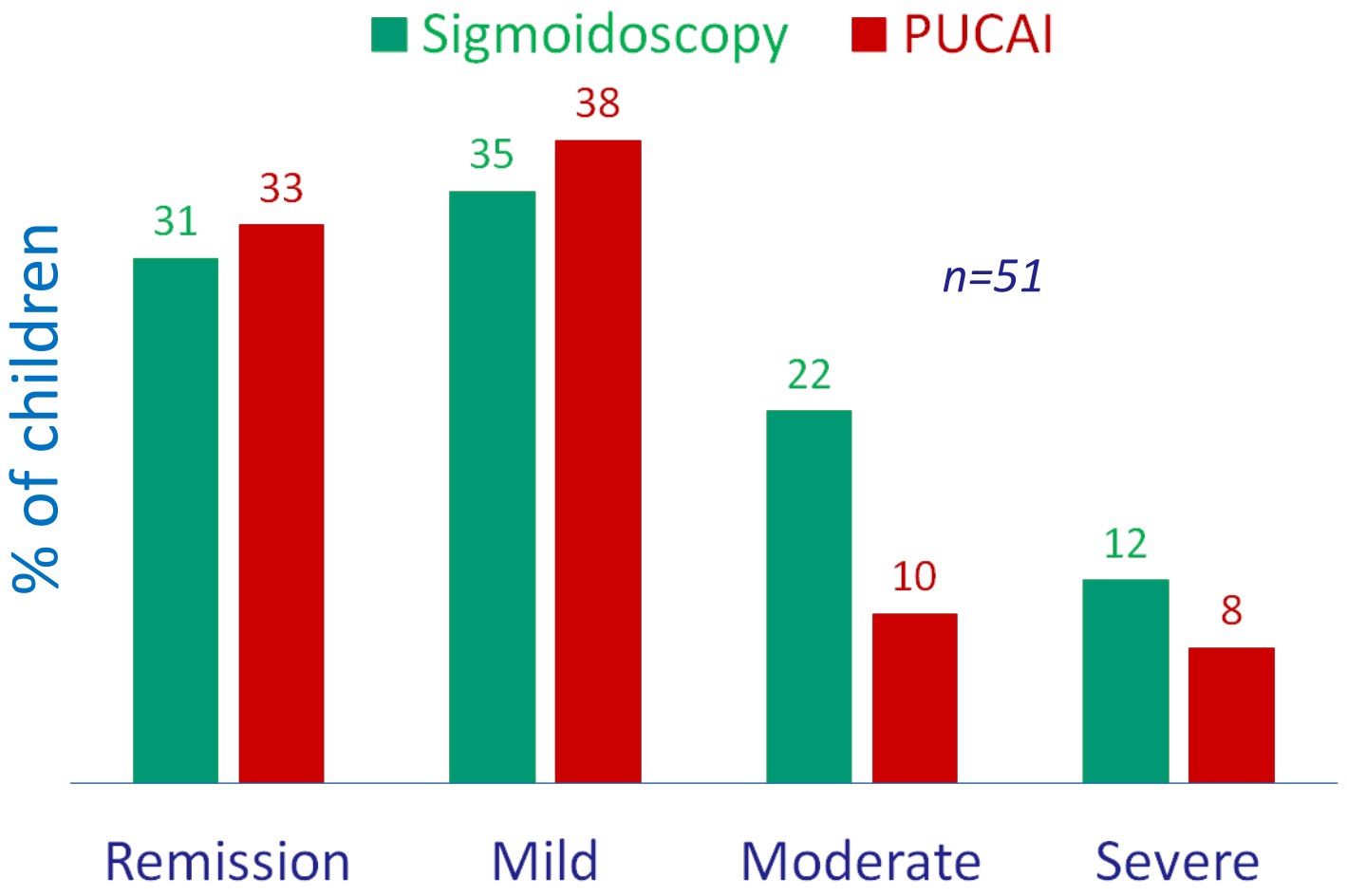


	NORMAL	MILD	MODERATE	SEVERE
Endoscopy	0	11	11	28
PUCAI	0	13	20	17

Civitelli F. et al. J Pediatr 2014

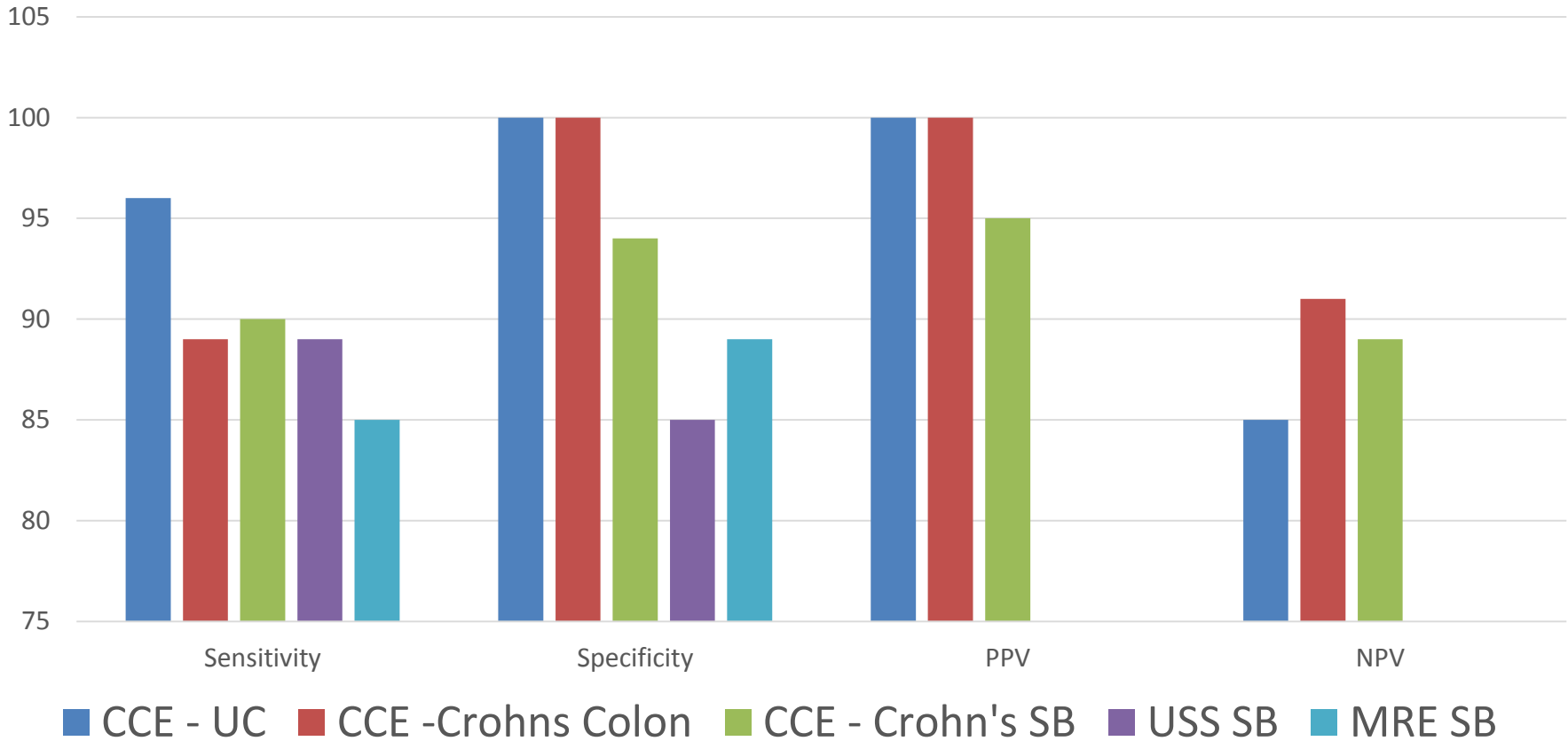
PUCAI – sigmoidoscopy correlation

results from the T72 trial of infliximab in pediatric UC



Turner et al. CGH 2013;11:1460–1465

Colon capsule endoscopy in Children



UC: Endoscopy 2014 Jun;46(6):485-92

Crohn's: ESPGHAN Annual Meeting 2015

Radiology

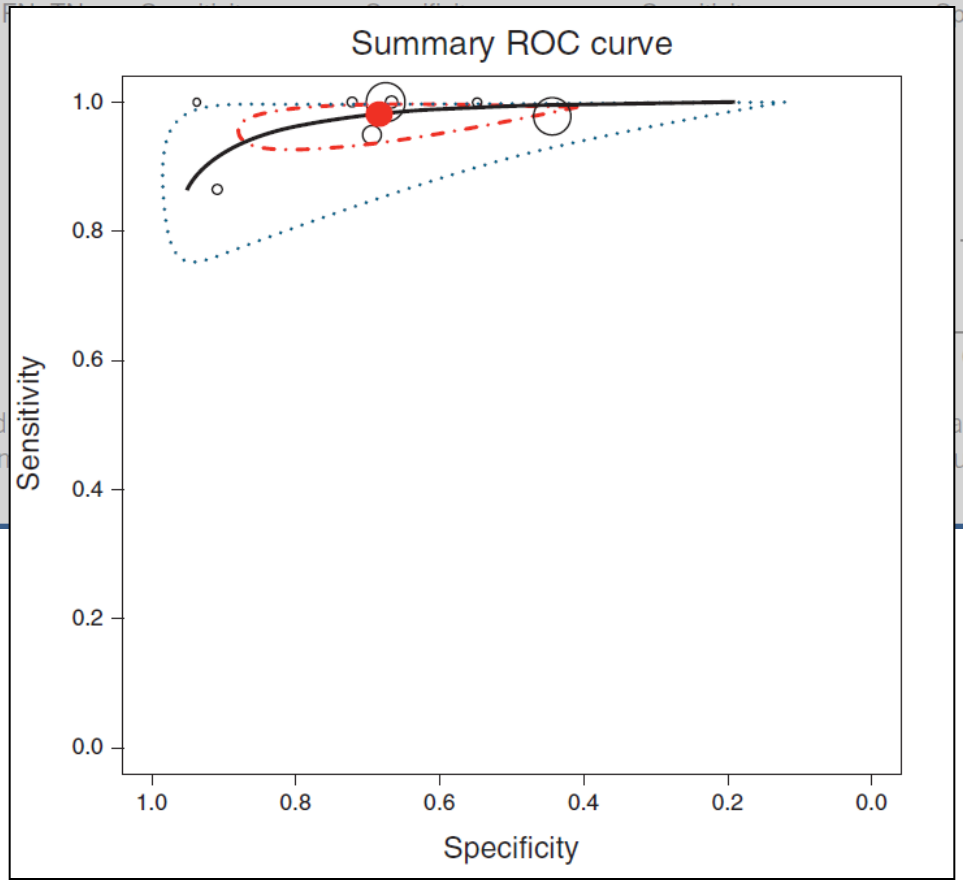
- MRE
  - Assesses both mucosal and extra mucosal disease
  - No radiation
  - Less bowel prep

- But:
  - Not good for young children
  - Takes long
  - Availability at short notice
  - Quantification and disease responsiveness

The Diagnostic Accuracy of Fecal Calprotectin During the Investigation of Suspected Pediatric Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

Paul Henderson, MBChB, MRCPCH, PhD[1,2], Niall H. Anderson, BSc (Hons), PhD[3] and David C. Wilson, MD, FRCP, FRCPCH[1,2]

Study	TP	FP
Ashorn *et al.*, 2009	32	1
Bonnin *et al.*, 2007	12	14
Canani *et al.*, 2006	27	5
Diamanti *et al.*, 2010	117	26
Fagerberg *et al.*, 2005	20	1
Henderson *et al.*, 2012	89	55
Perminow *et al.*, 2009	56	11
Sidler *et al.*, 2008	31	10



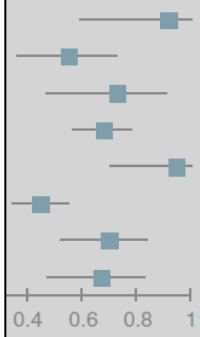


Figure 3. A 2×2 diagnostic accuracy table and … al calprotectin during the investigation of suspected pediatric inflamm… ue negative. Numbers in brackets represent 95% confidence intervals.

Henderson P, et al. Am J Gastroenterol. 2013

Faecal calprotectin: Edinburgh 10 years of use clinical practice

- Good screening test
  - has reduced endoscopy usage in suspected GI inflammation
- Quiescent IBD <100 ug/g
  - Accept <300 ug/g in some of the more refractory cases
- Serial testing in IBD
  - less endoscopic reassessment in general
  - earlier targeted reassessment as needed
  - More appropriate use of IBD therapies with *optimisation*
  - Less overuse of IBD therapies (other cause of symptoms)
- Biggest problem is patient providing sample !
- Rapid and home tests undergoing evaluation

Summary: Assessment of mucosal healing

- Ileo-colonoscopy
  - Good for UC, not so good for Crohn's
  - FUTURE Colon capsule endoscopy: Good for UC, quite good for Crohn's (includes small bowel)

- PUCAI
  - predicts mucosal healing quite well, replace colonoscopy
- PCDAI
  - Not so good

- Calprotectin
  - Good for screening
  - evidence for monitoring in trials not there yet

Conclusion: Outcome measures

Primary outcomes:

- UC
  - PUCAI (or TUMMY) (+/- calprotectin ?)
- Crohn's
  - Needs a PRO measure
  - wPCDAI
    - +/- ileo colonoscopy in a sub-set (CCE or MRE in the future ?)

Quality of life (disease specific)

- IMPACTIII