



Refractory Coeliac Disease

**Rare Disease  
Collaborative Network**

Coeliac UK March 2019



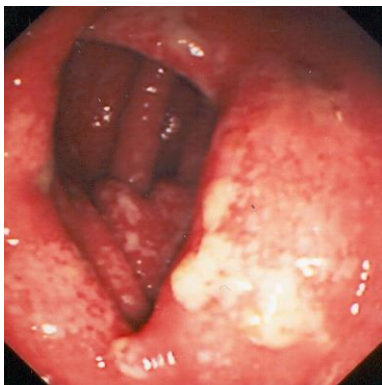
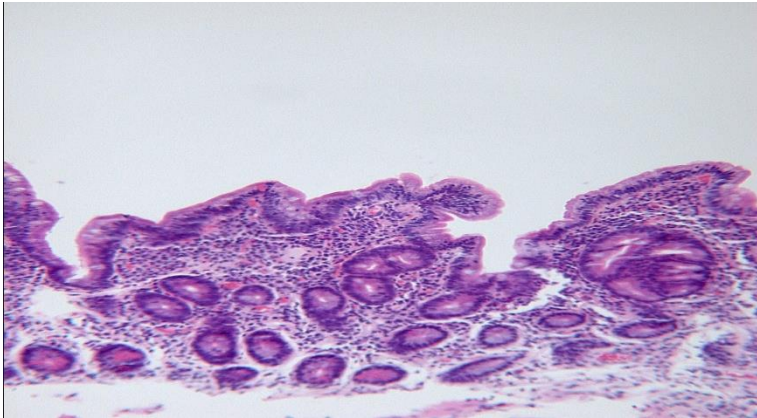
Professor David S Sanders

NHS England's Rare Diseases Collaborative Network (RDCN) for Non-Responsive and Refractory Coeliac Disease.

Royal Hallamshire Hospital & University of Sheffield

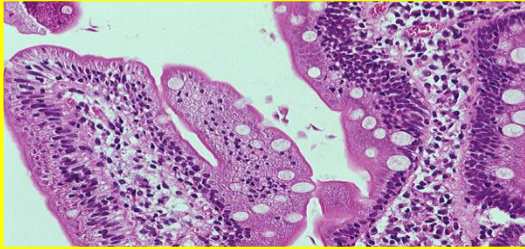


# What would you do with this case?



- 25 year old girl presents with abdominal pain and diarrhoea
- Weak positive EMA
- Symptoms don't respond on a GFD and losing weight after 3/12

# 30% of patients with serology negative VA have coeliac disease



Giardia on duodenal biopsy

- No cause found in 18% (n=36)
- Of these 72% (n=26/36) spontaneously normalised duodenal histology whilst consuming gluten
- Do not place patients with Antibody Negative Villous Atrophy on a Gluten Free Diet

Aziz I et al Gut 2016

Tropical sprue
Allergies to proteins other than gluten (cow's milk/soya)
Autoimmune enteropathy
Collagenous'sprue
Common variable immunodeficiency/AIDS
Drug-induced/radiation enteritis
Hypogammaglobulinaemic sprue
Ischaemia
Inflammatory bowel disease
Kwashiorkor
Helminth infestation/Giardia
Whipple's/Tuberculosis
Zollinger-Ellison syndrome
Olmesartan!

# Antibody negative coeliac disease prevalence ranges from 6.4-9.1% in cohorts of patients diagnosed with coeliac disease

## Why?

IgA deficiency

Early in disease

Late in disease

Immunosuppressants

Patient commenced a GFD prior to Testing

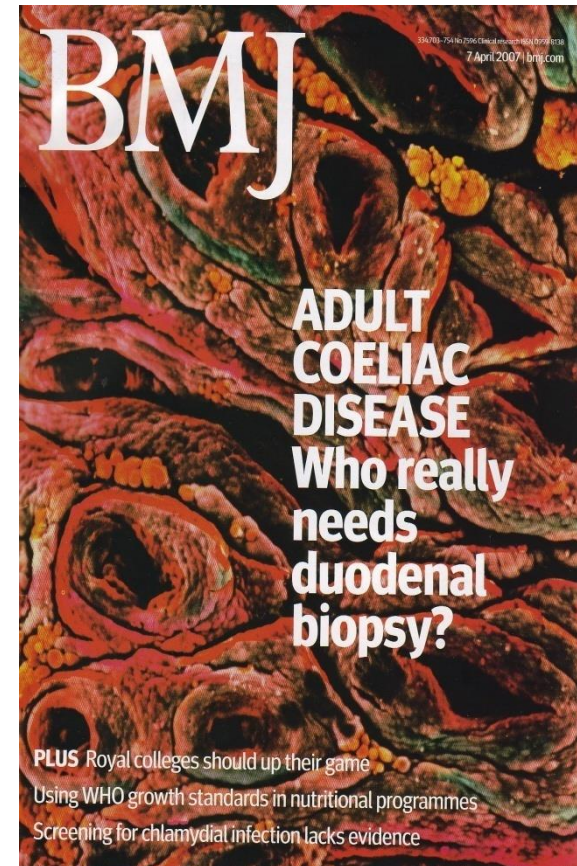
Family History: 1<sup>st</sup> degree relatives

Hopper AD et al *BMJ* 2007;334(7596):729

Hopper AD et al *Clin Gastro* 2008;6:314-20



**Imran Aziz**





# Adult patients with coeliac disease and persisting symptoms

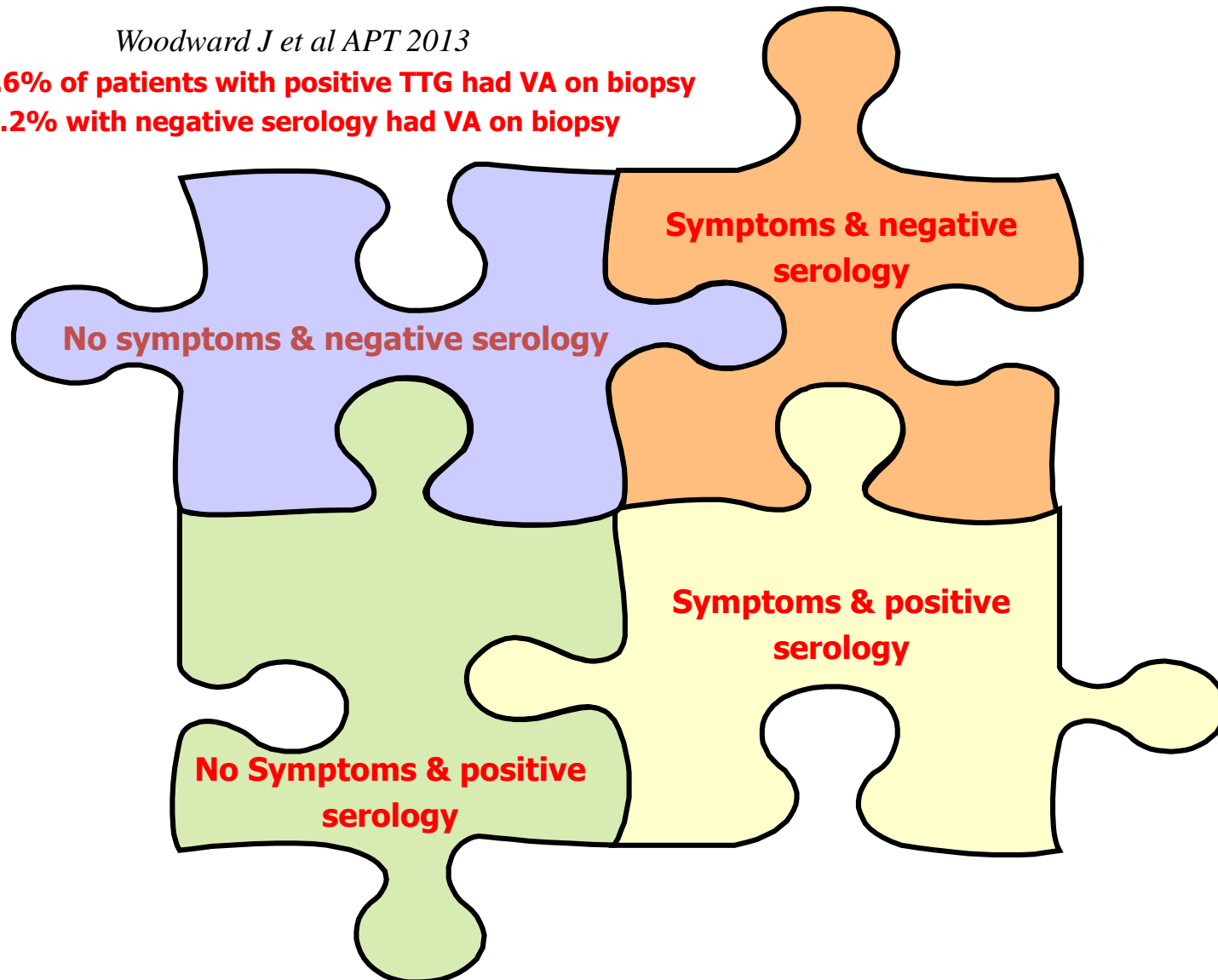
Review original CD diagnosis:  
histology, serology, HLA

Not  
Coeliac  
Disease

# How do you assess adherence?

*Woodward J et al APT 2013*

**Only 43.6% of patients with positive TTG had VA on biopsy  
25.2% with negative serology had VA on biopsy**





# The only way to assess adherence is a biopsy!

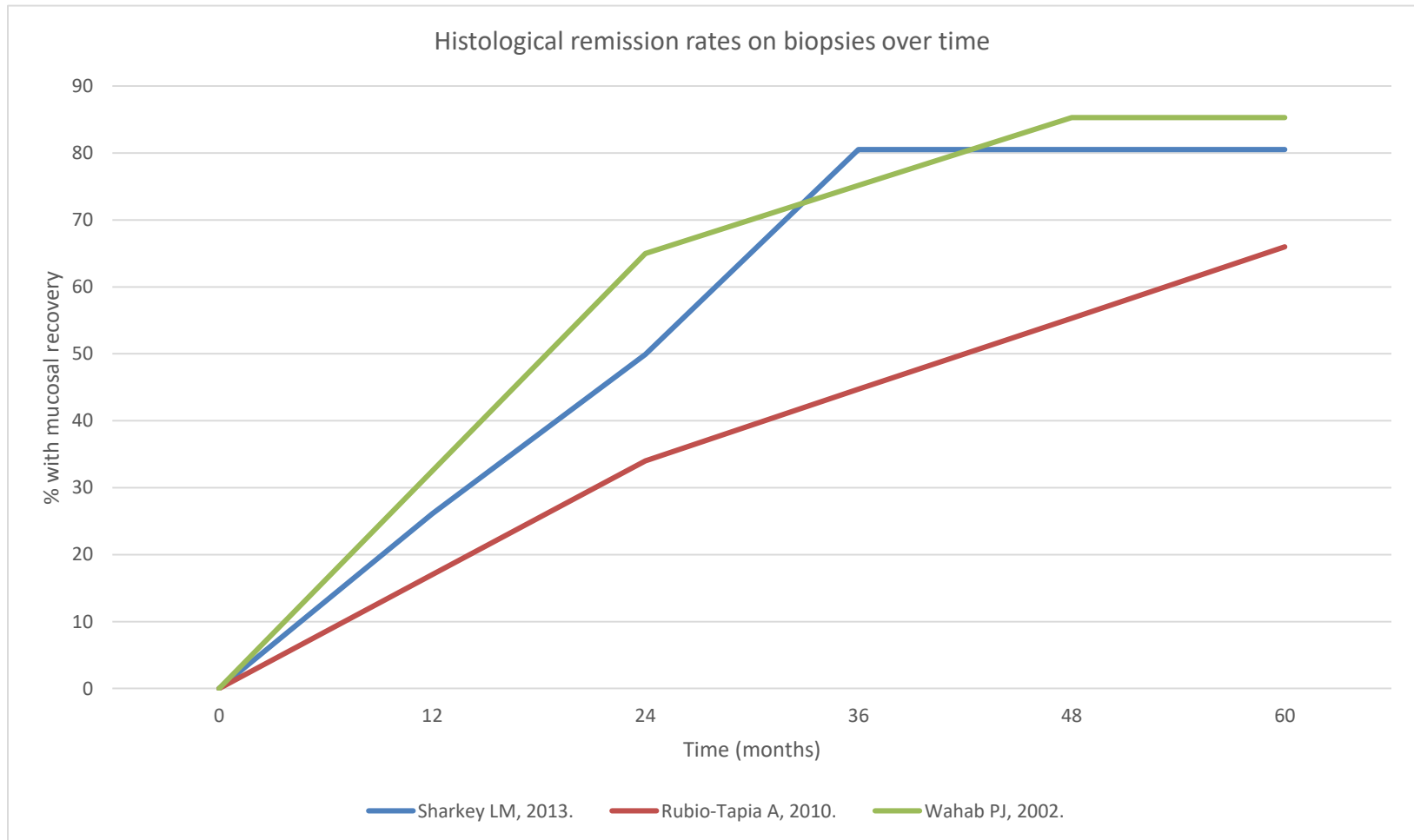
**Table 2.** The number of patients for each Marsh grade and the number and proportion of patients whose surrogate markers correctly identified the presence (Marsh 3a–c histology) or absence (Marsh 0–2 histology) of persistent VA

	Marsh 0	Marsh 1	Marsh 2	Marsh 0–2	Marsh 3a	Marsh 3b	Marsh 3c	Marsh 3a-c
No. of patients	78	37	17	132	38	24	23	85
Simtomax	48 (61.5%)	23 (62.2%)	7 (41.2%)	78 (59.1%)	21 (55.3%)	21 (87.5%)	15 (65.2%)	57 (67.1%)
TTG	73 (93.6%)	30 (81.1%)	15 (88.2%)	118 (89.4%)	9 (23.7%)	12 (50.0%)	11 (47.8%)	32 (37.6%)
EMA	70 (89.8%)	30 (81.1%)	14 (82.4%)	114 (86.5%)	9 (23.7%)	16 (66.7%)	13 (56.5%)	38 (44.7%)
Adherence score	69 (88.5%)	31 (83.8%)	14 (82.4%)	114 (86.4%)	4 (10.5%)	9 (37.5%)	8 (34.8%)	21 (24.7%)

Surrogate markers correctly testing negative for VA.

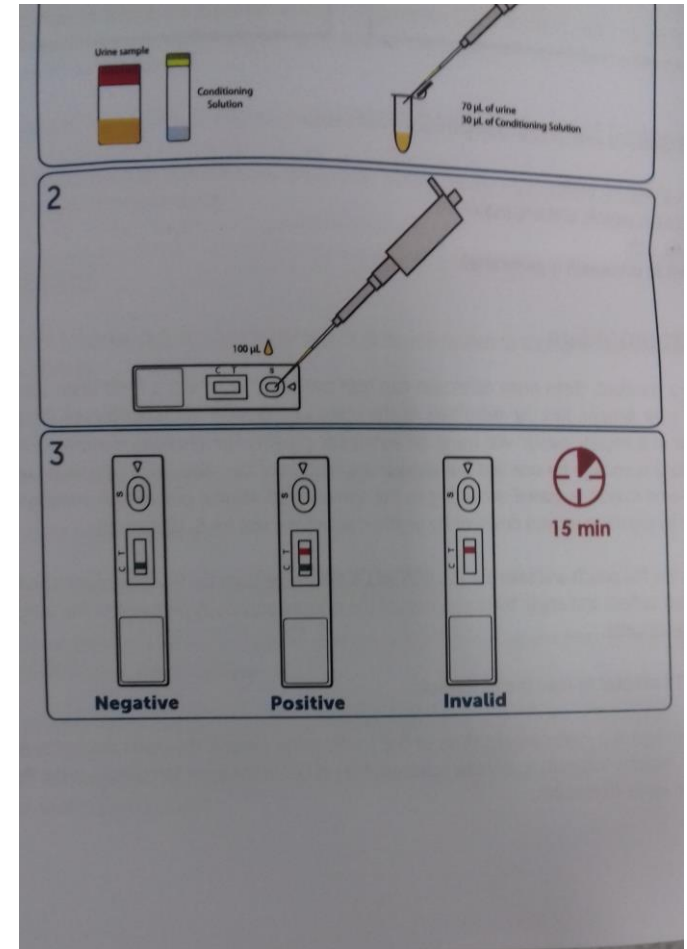
Surrogate markers correctly testing positive for VA.

# How do you assess adherence? You must biopsy and not rely on serology





# Urine and Faecal markers have arrived!



The Role of an IgA/IgG-Deamidated Gliadin Peptide Point-of-Care Test in Predicting Persistent Villous Atrophy in Patients With Celiac Disease on a Gluten-Free Diet

Michelle S. Lau, MBChB, MRCP<sup>1</sup>, Peter D. Mooney, MBChB, MRCP, MD<sup>1</sup>, William L. White, BMedSci<sup>1</sup>, Michael A. Rees, BMedSci<sup>1</sup>, Simon H. Wong, MBChB<sup>1</sup>, Matthew Kurien, MBChB, MRCP, MD<sup>1</sup>, Nick Trott, BSc (Hon)<sup>1</sup>, Daniel A. Leffler, MD, MS<sup>2</sup>, Marios Hadjivassiliou, MBChB, MD, FRCP<sup>1</sup> and David S. Sanders, MBChB, MD, FACG, FRCP<sup>1</sup>

## Gluten Immunogenic Peptides

Marino M et al *Gut* 2016 & Comino I et al *Am J Gastro* 2016

# Confirmed diagnosis of CD

## Repeat gastroscopy with duodenal biopsies

Colonoscopy with biopsies  
Faecal elastase  
Faecal calprotectin  
Stool culture  
Bloods (inc. inflammatory markers,  
thyroid function)

Persisting villous atrophy

## Dietitian review

*Non-adherence to GFD (inadvertent or  
advertent)*  
Supersensitive or Slow Responder

Consider RCD I and II

Microscopic colitis  
Exocrine pancreatic insufficiency  
Giardiasis  
Hyperthyroidism

Normal villous architecture

Functional  
symptoms

SBBO  
Fructose intolerance  
Lactose intolerance

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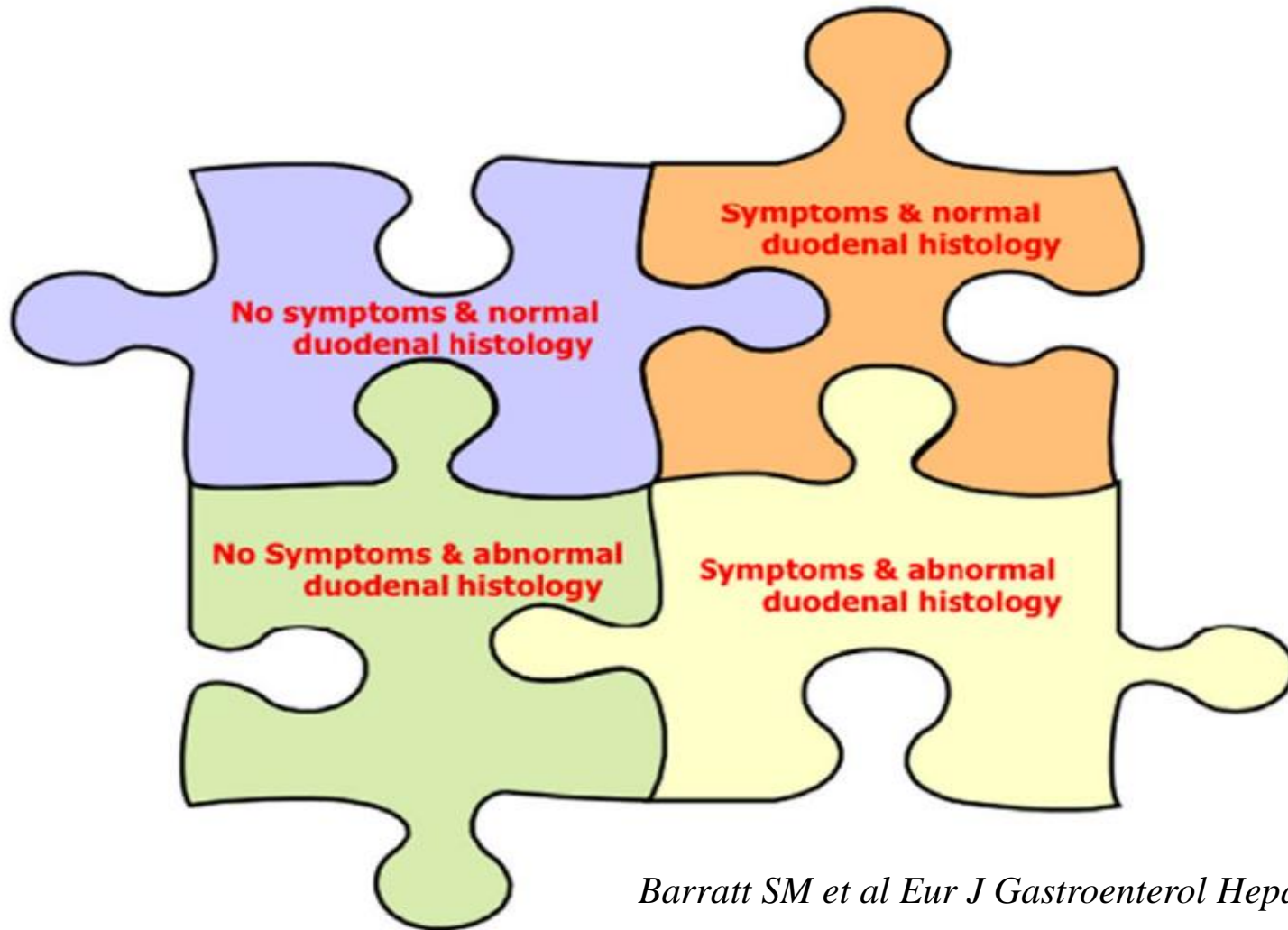
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# NRCD & RCD I & II



*Barratt SM et al Eur J Gastroenterol Hepatol 2011*

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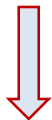
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Group of rare pre-malignant and malignant conditions arising in the abdomen and responsible for the increased mortality found in CD than in the general population.<sup>1</sup>

- **Refractory CD (RCD)**
- Ulcerative jejuno-ileitis (UJI)
- Enteropathy associated T-cell Lymphoma (EATL)
- Abdominal B-cell Lymphomas (BCL)
- Small bowel adenocarcinoma (SBC)
- Collagenous sprue?
- Oesophageal adenocarcinoma?



**Complicated CD (CCD)**

**Prevalence of RCD in CD: 0.3-4%<sup>2</sup>**

## RCD1:






- <20% aberrant IELs on flow cytometric analysis
- Polyclonal TCR $\gamma$

## RCD 2:

- >20% aberrant IELs on flow cytometric analysis (sCD3-)
- Clonal TCR $\gamma$  rearrangement (3)



# Natural history and outcomes in RCD

Author	Country	RCD patients N°	Evolution into EATL	Mortality	5-year survival rate
<b>Malamut G,</b> <i>Gastroenterology</i> 2009		Total= 57 RCD1= 14 RCD2= 43	Total=18 (32%) RCD1= 2 (14%) RCD2= 16 (37%)	Total=29 (51%) <b>RCD1=3 (21%)</b> <b>RCD2=26 (60%)</b>	<b>RCD1= 93%</b> <b>RCD2= 44%</b>
<b>Al-Toma A,</b> <i>Gut</i> 2009		Total= 93 RCD1= 43 RCD2= 50	Total=26 (28%) RCD1= 0 RCD2= 26 (52%)	Total=54 (58%) <b>RCD1= 3 (7%)</b> <b>RCD2=28 (56%)</b> RCD2+EATL=23 (88%)	<b>RCD1= 96%</b> <b>RCD2= 58%</b> RCD2+EATL=8%
<b>Rubio-Tapia A,</b> <i>Gastroenterology</i> 2009		Total= 57 RCD1= 42 RCD2= 15	Total= 10 RCD1= 0 RCD2= 10 (67%)	Total=15 (26%) <b>RCD1=8 (19%)</b> <b>RCD2=7 (46%)</b>	<b>RCD1= 80%</b> <b>RCD2= 45%</b>
<b>Daum S,</b> <i>Eur J Gastr Hepatol</i> 2009		Total= 32 RCD1= 23 RCD2= 9	Total= 4 (12%) RCD1= 0 RCD2= 4 (44%)	Total=8 (25%) <b>RCD1=4 (17%)</b> <b>RCD2=4 (44%)</b>	<b>RCD1= 90%</b> <b>RCD2= 53%</b>
<b>Nasr I,</b> <i>Nutrients</i> 2015		Total= 30 RCD1= 0 RCD2= 30	None	None	All alive



The University Of Sheffield.

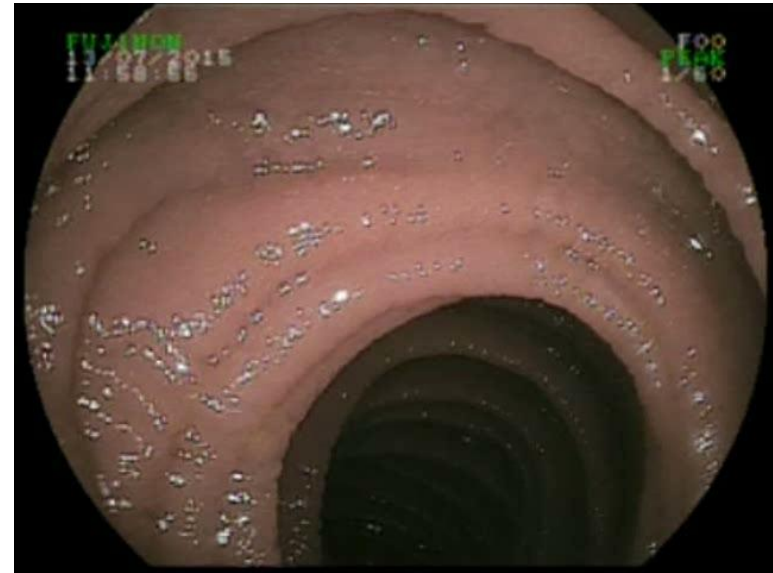
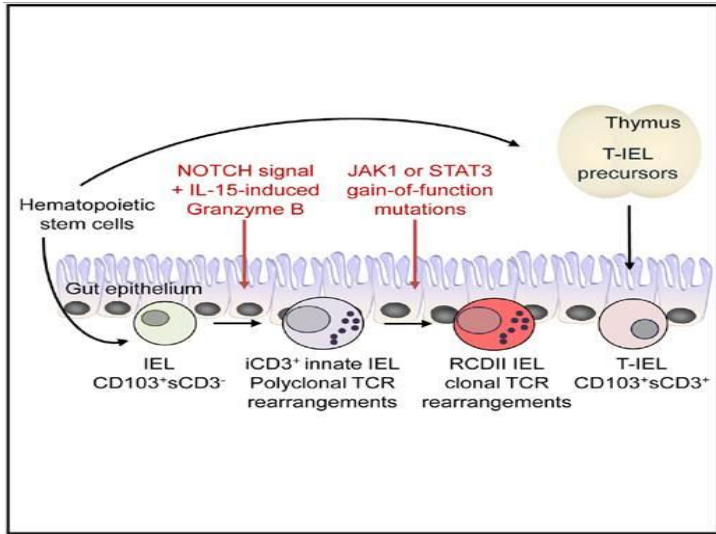
# PHENOTYPE?



Sheffield Teaching Hospitals NHS Foundation Trust



# IL-15 Antibody



Ulcerative Jejunitis at DBE



Refractory Coeliac Disease

Rare Disease Collaborative Network

We offer a second opinion  
 Distinguish between Type I & II  
 New Therapies  
 Shared Care  
[David.sanders@sth.nhs.uk](mailto:David.sanders@sth.nhs.uk)

# Sheffield Lions!

