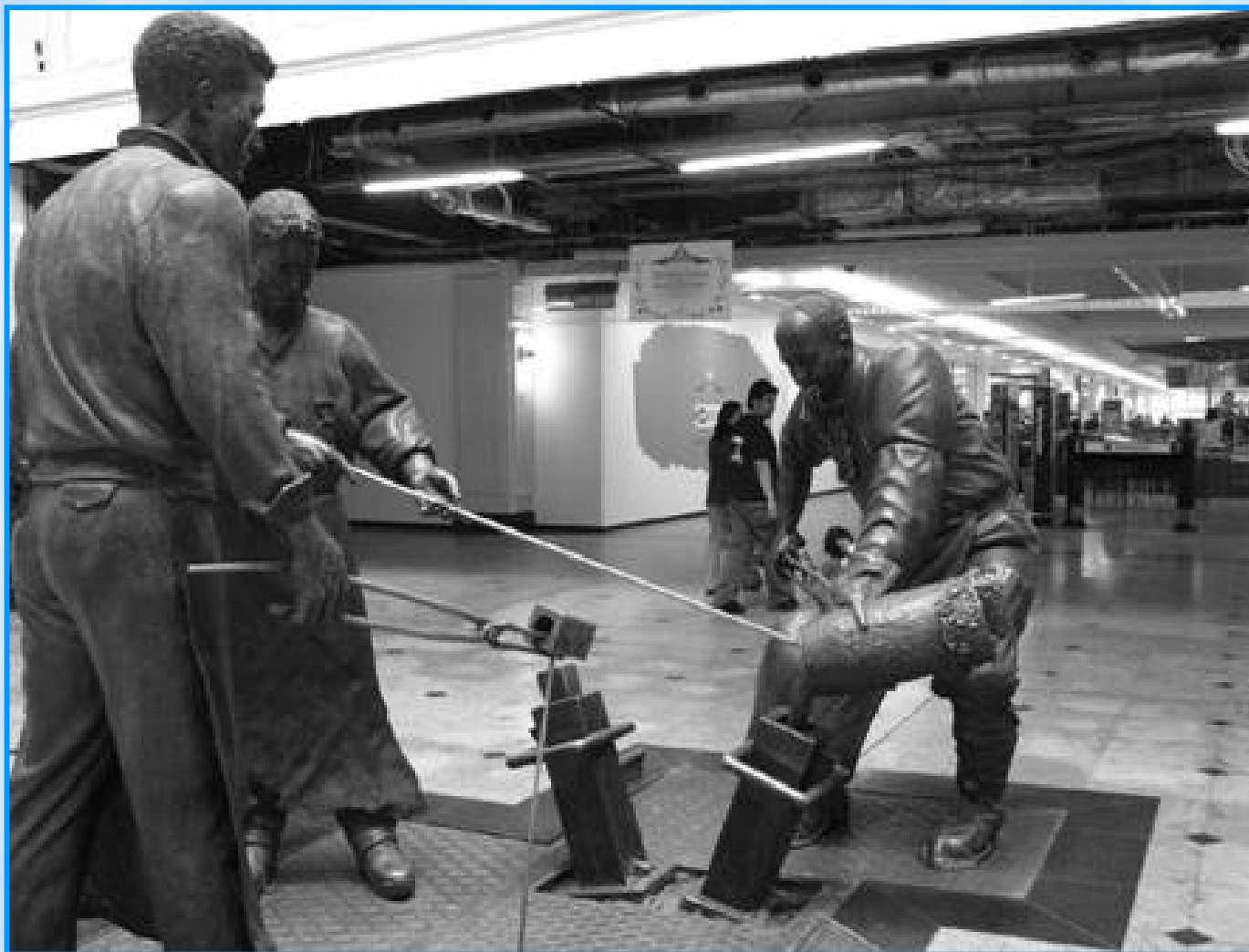


Optimal diagnosis and treatment of coeliac disease

March 2015

**Professor David S Sanders
Consultant Gastroenterologist
Royal Hallamshire Hospital & University of Sheffield**



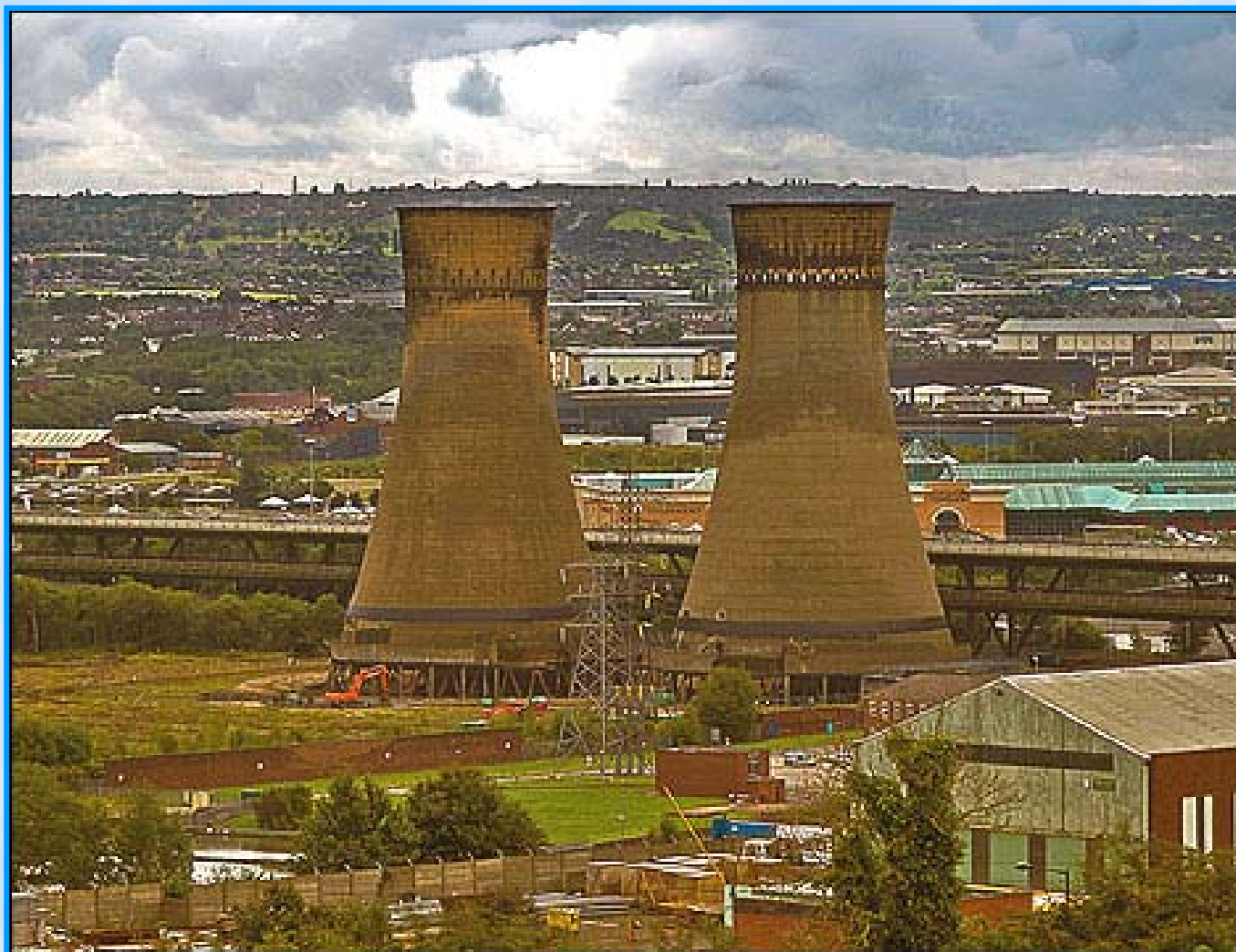


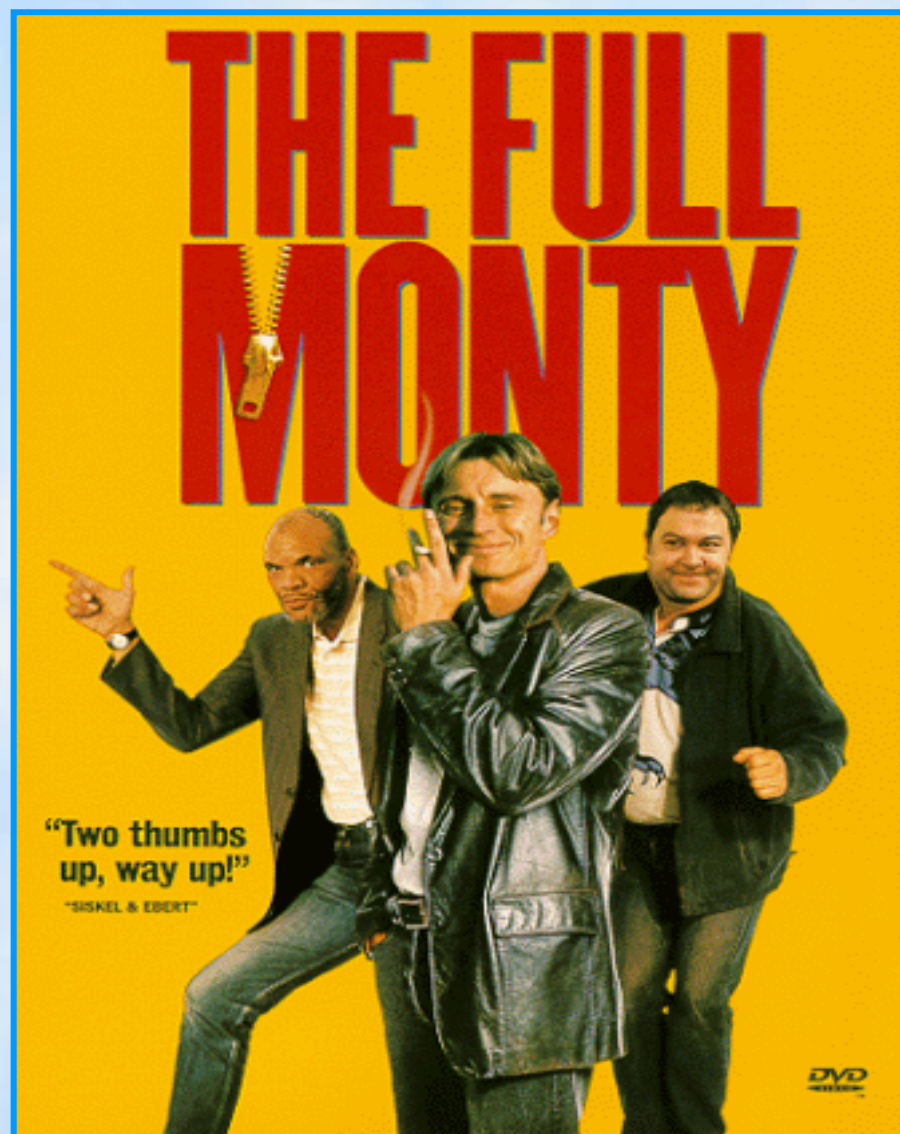


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Sheffield Teaching Hospitals **NHS**
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Sheffield.



Sheffield Teaching Hospitals **NHS**
NHS Foundation Trust



- Population >6-700,000
- 4th largest city in the UK
- Largest student population
- Cinemas and sport!
- Greenest city in England

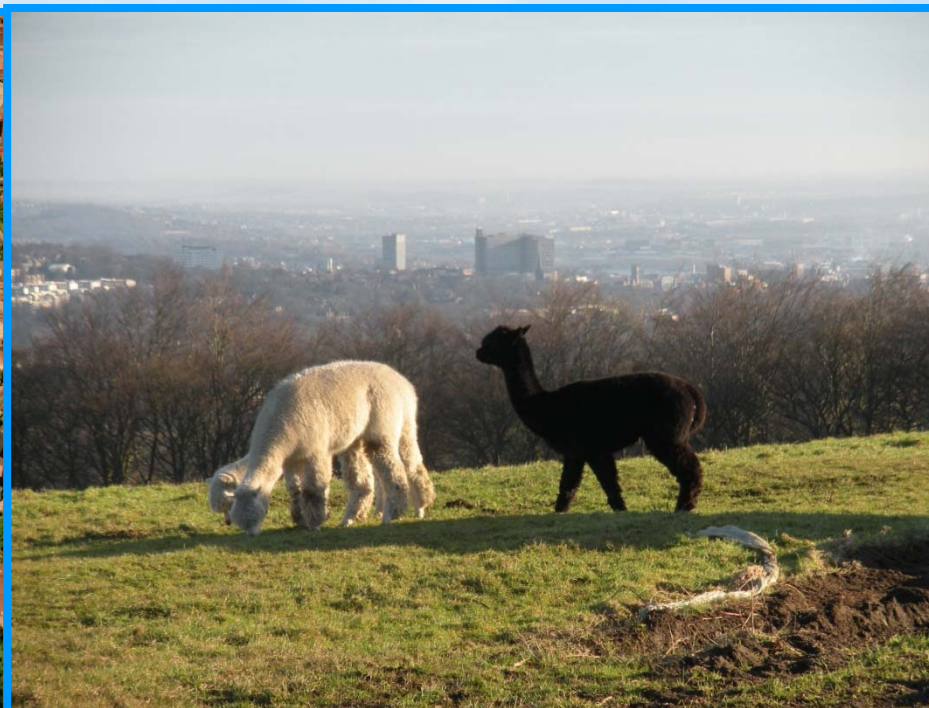


Jessica Ennis
Gold Medal in Heptathlon









Part 1:

- Coeliac Disease is uncommon?
- I don't really see coeliac disease
- When I see coeliac disease it is at Endoscopy
- What is the point of diagnosing Coeliac Disease?

Part 2:

- What is NCGS?

What is the estimated Prevalence of Adult Coeliac Disease in Europe?

-A:

1:100,000

-B:

1:10,000

-C:

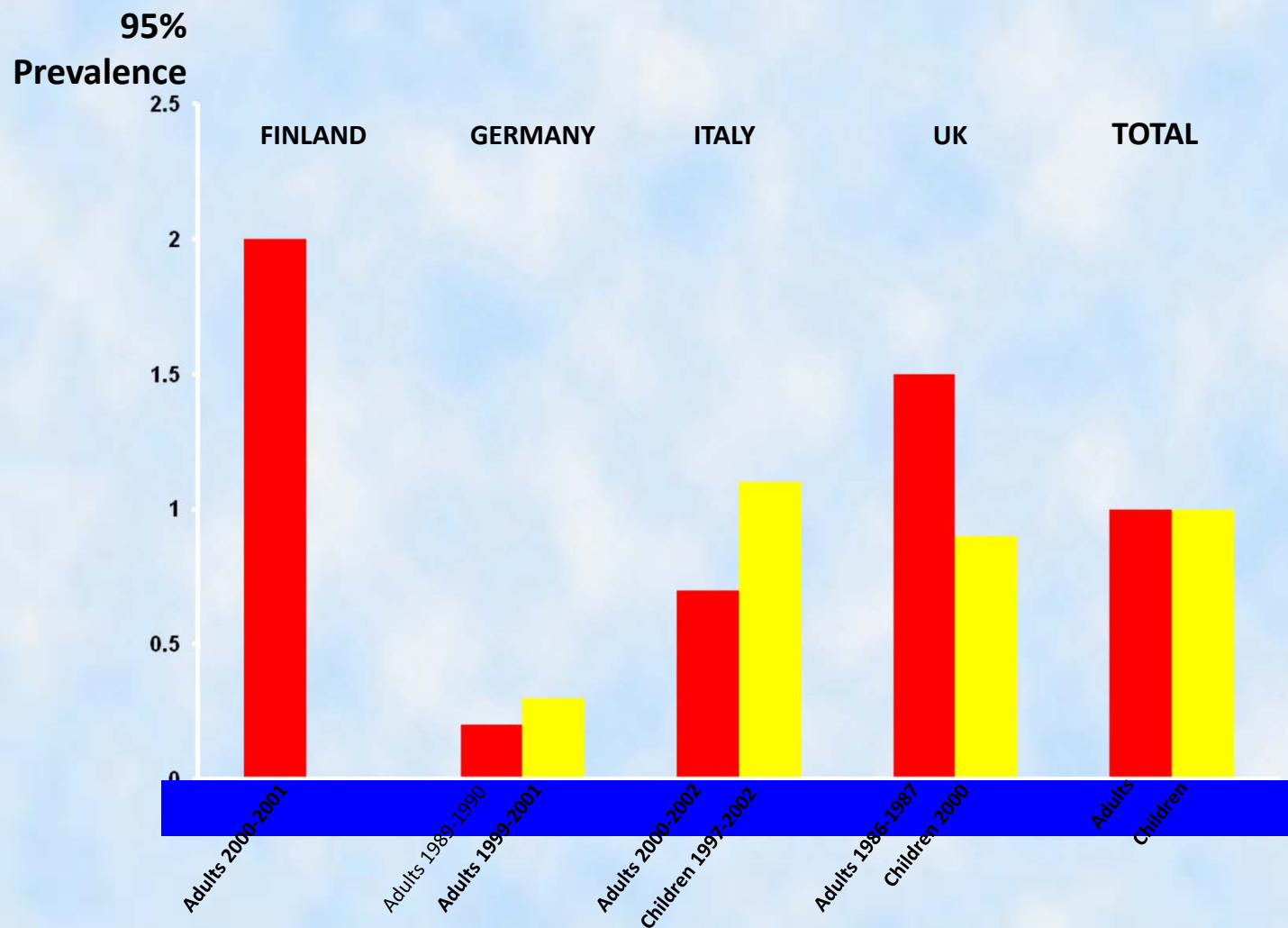
1:1,000

-D:

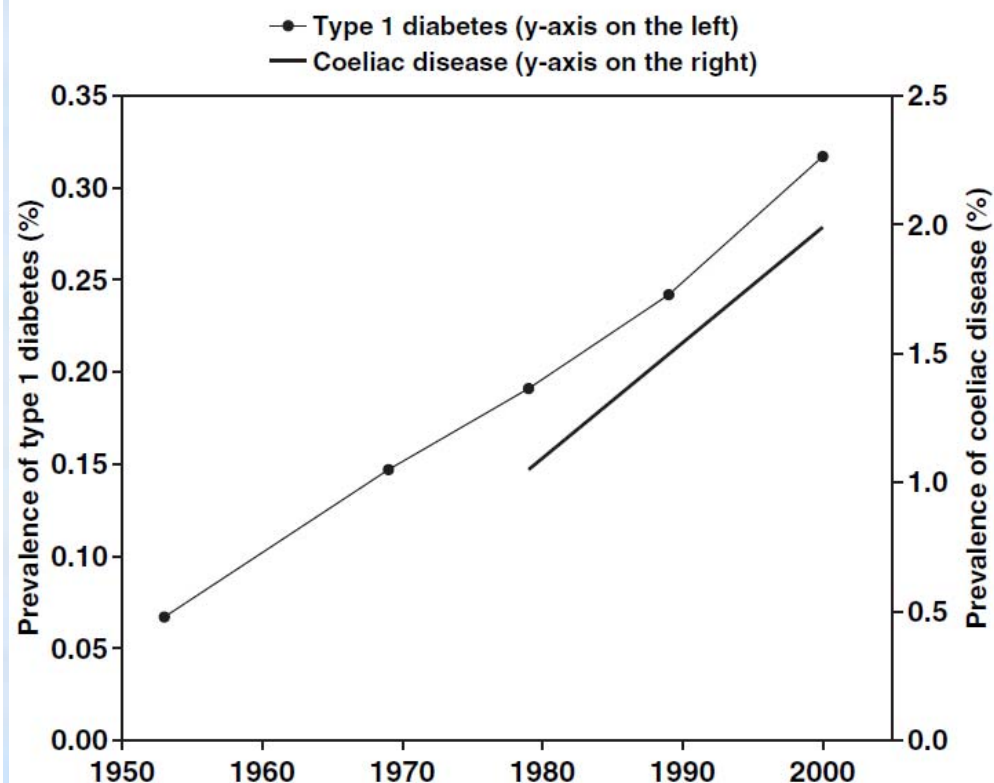
1:100

The prevalence of celiac disease in Europe: Results of a centralised, international mass screening project =1%!

Mustalahti K. *et al* *Annals of Medicine* 2010; 42: 587-595



Why is the prevalence increasing?



Lohi S et al *Aliment Pharmacol Ther* 2007;26(9):1217-25

Rubio-Tapia A et al *Gastroenterology* 2009;137(1):88-93

Catassi C et al *Ann Med* 2010;42(7):530-8

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 World Journal of Gastroenterology ISSN 1007-9327
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EDITORIAL

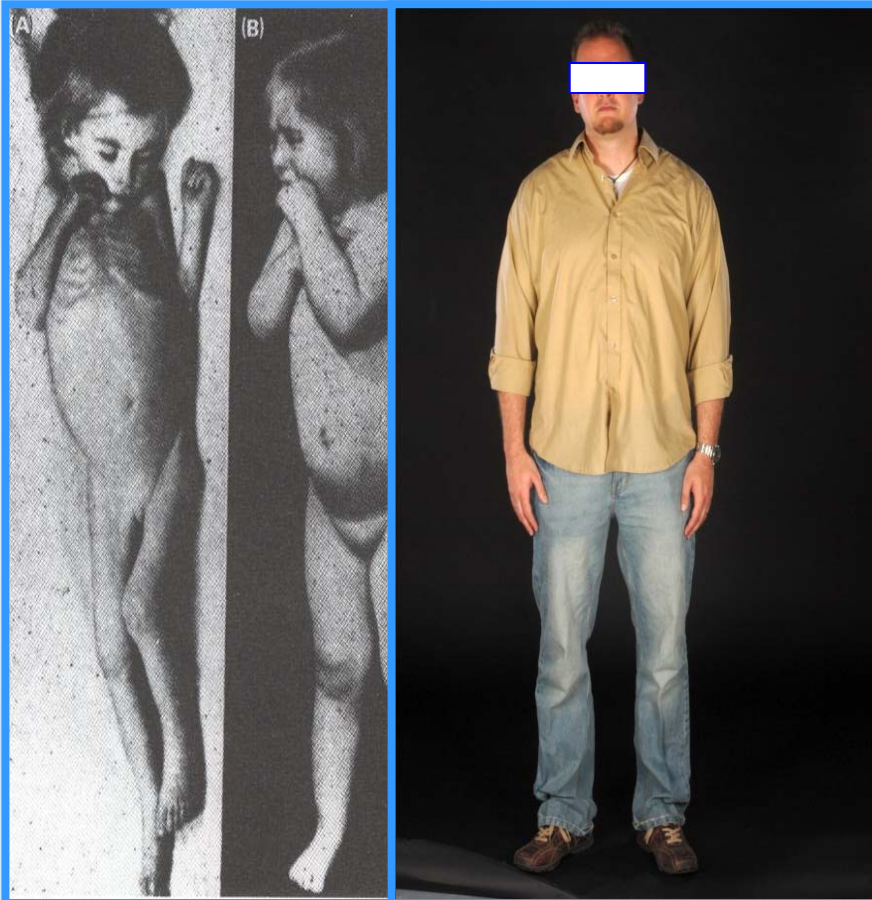
Indian task force for celiac disease: Current status

Rajesh Gupta, Duvvuru Nageshwar Reddy, Govind K Makharia, Ajit Sood, Balakrishnan S Ramakrishna, Surender Kumar Yachha, Babu Ram Thapa, Rupa Banerjee, Sekaran Anuradha, Usha Dutta, Amarendra Singh Puri, Ajay Kumar Jain, Chris JJ Mulder, Ajay Kumar, Sesikeran Boindala

Coeliac disease: emerging in China?

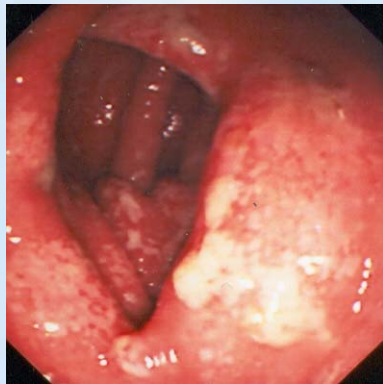
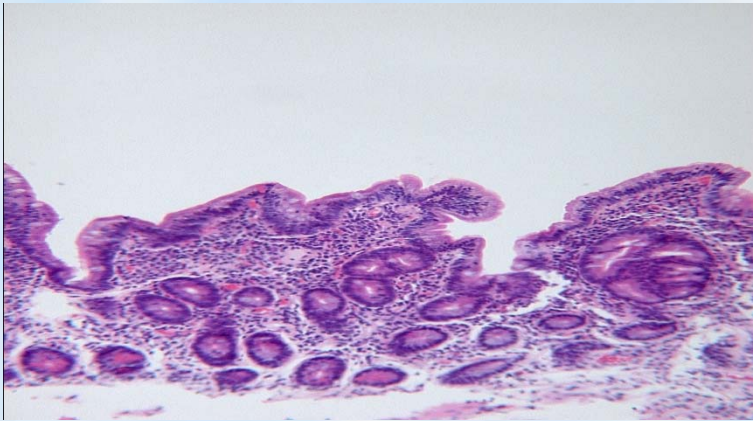
Wu J et al *Gut* 2010;59(3):418-9

Coeliac Disease affects ~ 1% of the adult population



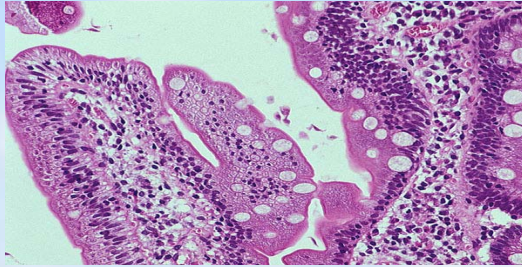
- The commonest age for presentation is between the 4th to 6th Decade
- For every paediatric case diagnosed there are 9 adult cases
- **Coeliac disease affects 1% of the adult population!**
- For every adult case diagnosed there are 7 cases still not recognised
- People with undiagnosed adult coeliac disease generally have a normal BMI and may even be overweight

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 6/52

Antibody negative coeliac disease accounts for 5-10% of all cases – but beware antibody negative villous atrophy



- Review the clinical case with a completely open mind
- Ask for histological review
- Inferred evidence: family history, HLA pattern, functional hyposplenism, previous antibody status

O'Mahony S et al *Aliment Pharmacol Ther* 1996;10:671-80

Evans KE et al *Proc Nutr Soc* 2009;68(3):242-8

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

Recognising coeliac disease in your gastroenterology clinics

- Dyspepsia/Reflux

Bardella MT et al *Arch Intern Med* 2000;160:1489-91

- Endoscopy

Dickey W et al *Am J Gastroenterol* 1999;94:2182

- IBS

Sanders DS et al *Lancet* 2001;357:1242

Sanders DS *Gastroenterology* 2001;120:1242

- NSAP (non-specific abdominal pain)

Sanjiv S et al *Gut* 2001;48:201-7

- Iron deficiency (Vitamin B12 and Folate)

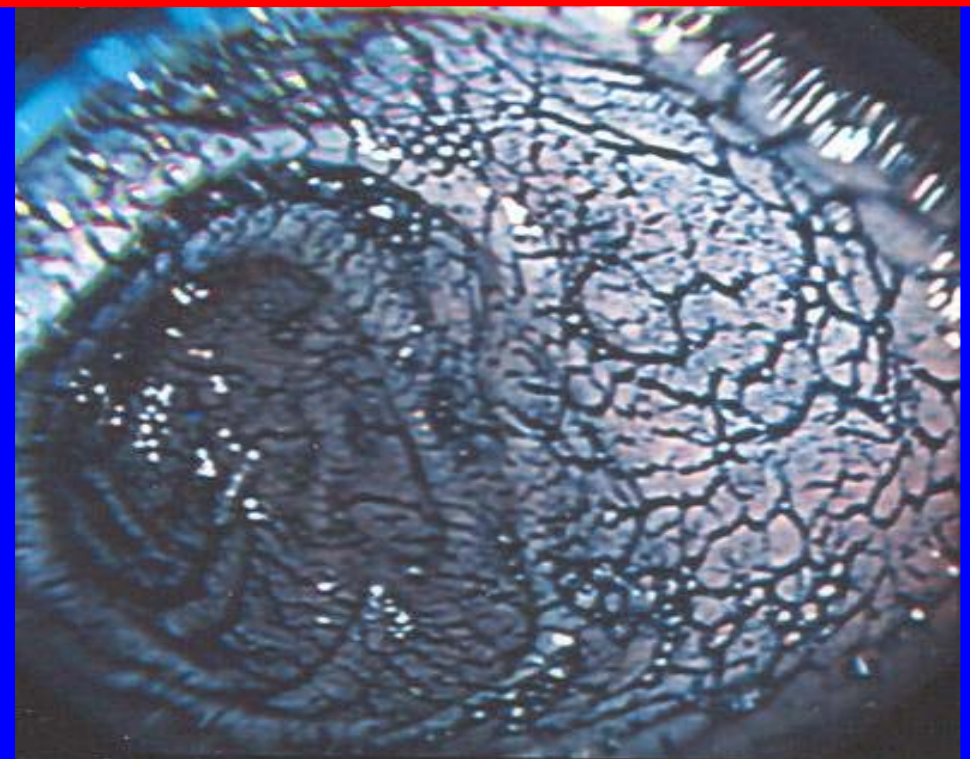
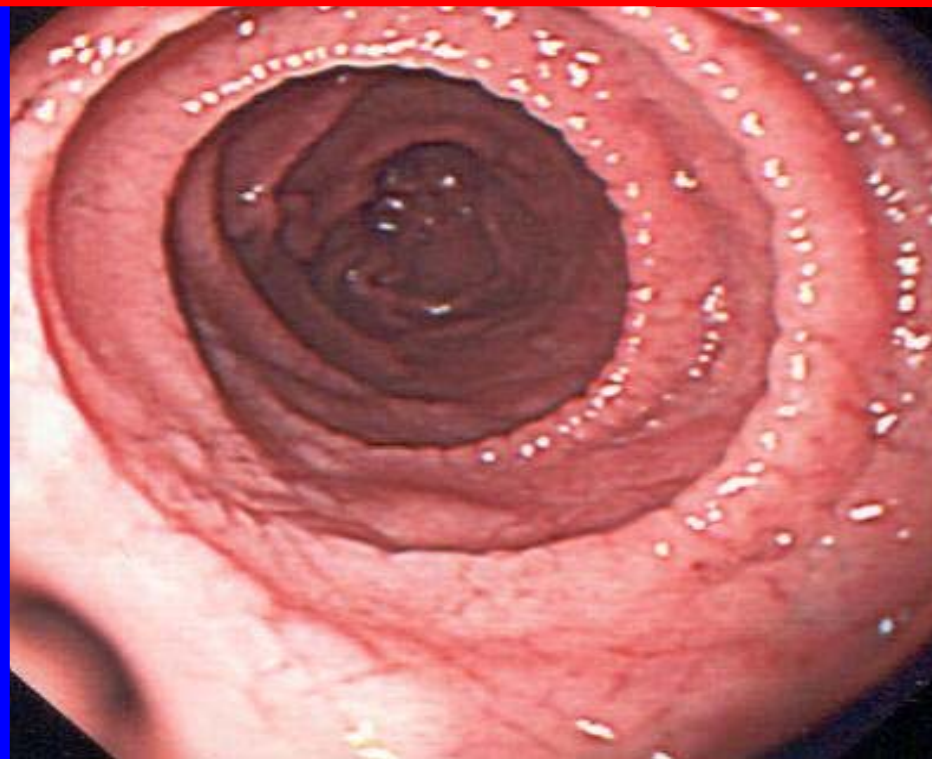
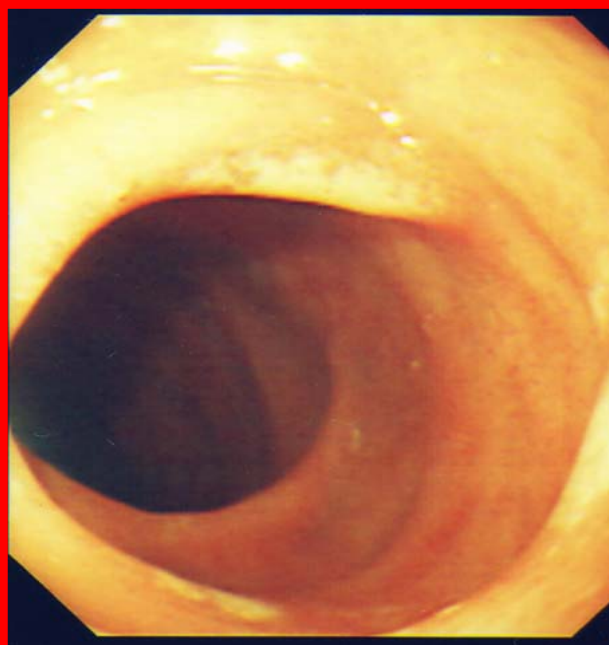
- Family history (1st degree relative) ~ 10% risk

- 1 in 33 patients (n=129/4089) in clinic

Mooney PD et al *Dig Dis Liv* 2014;46:32-5

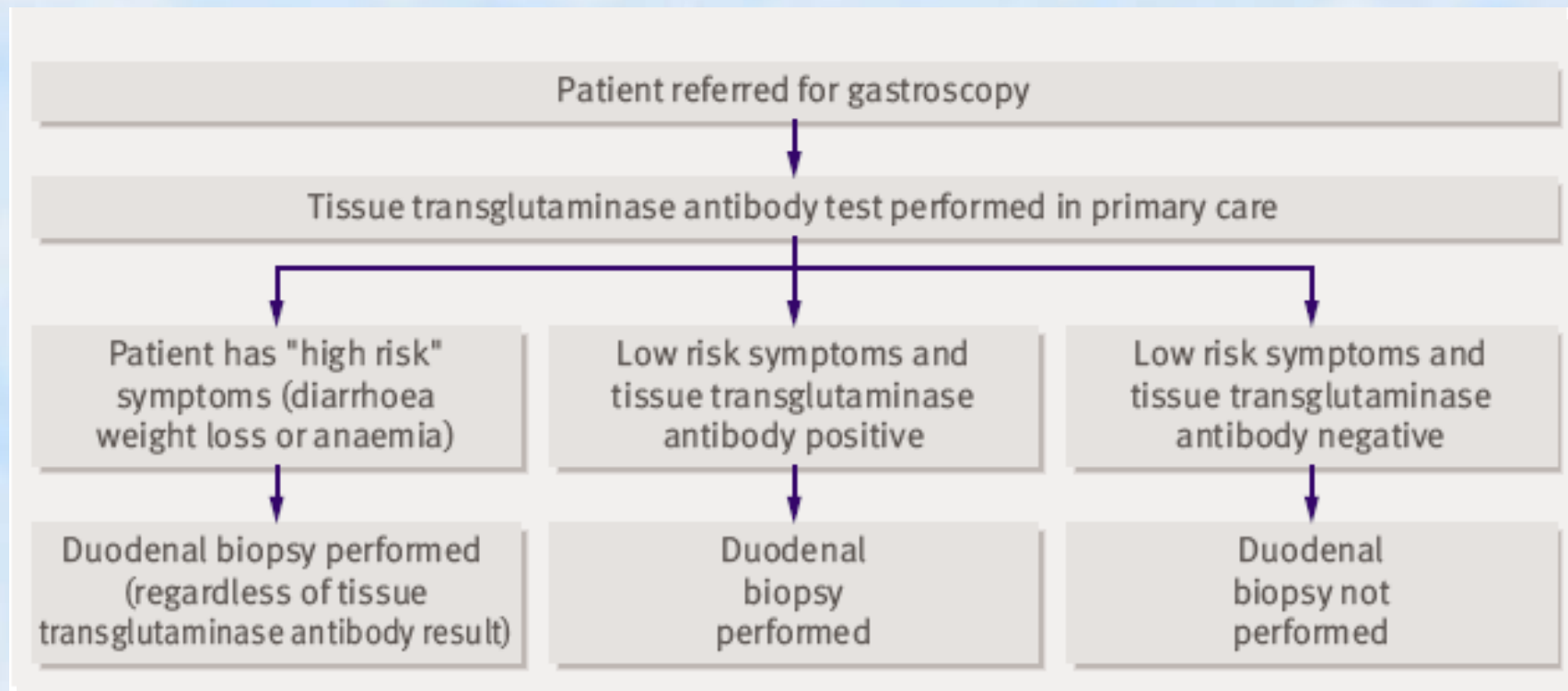
coeliac disease = VA in the presence of
EMA or TTG positive!





Who needs a duodenal biopsy?

- Retrospective analysis TTG negative coeliac patients all presented to endoscopy with symptoms of anaemia, diarrhoea or weight loss
- Prospective analysis



Who needs a duodenal biopsy?

- No symptoms of anaemia, diarrhoea or weight loss & negative TTG = 100% NPV. ie: no biopsy
- Pre-endoscopy serological testing and biopsy of "high risk" cases has a 100% sensitivity
- All patients referred for gastroscopy with high risk symptoms should be biopsied irrespective of their antibody profile
- Previous series 2002: 13.6% of CD patients at diagnosis have had a previous OGD without duodenal biopsy

What's New! Point of Care Testing



Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Serum tTG	97 (81-99)	41 (19-67)	74 (58-86)	88 (47-99)
Biocard	63 (44-79)	76 (50-92)	83 (60-94)	54 (33-74)
Coeliac Quick Test	80 (61-92)	59 (33-81)	77 (58-90)	63 (36-84)
Simtomax	93 (76 -99)	35 (15-61)	72 (55-84)	75 (36-96)

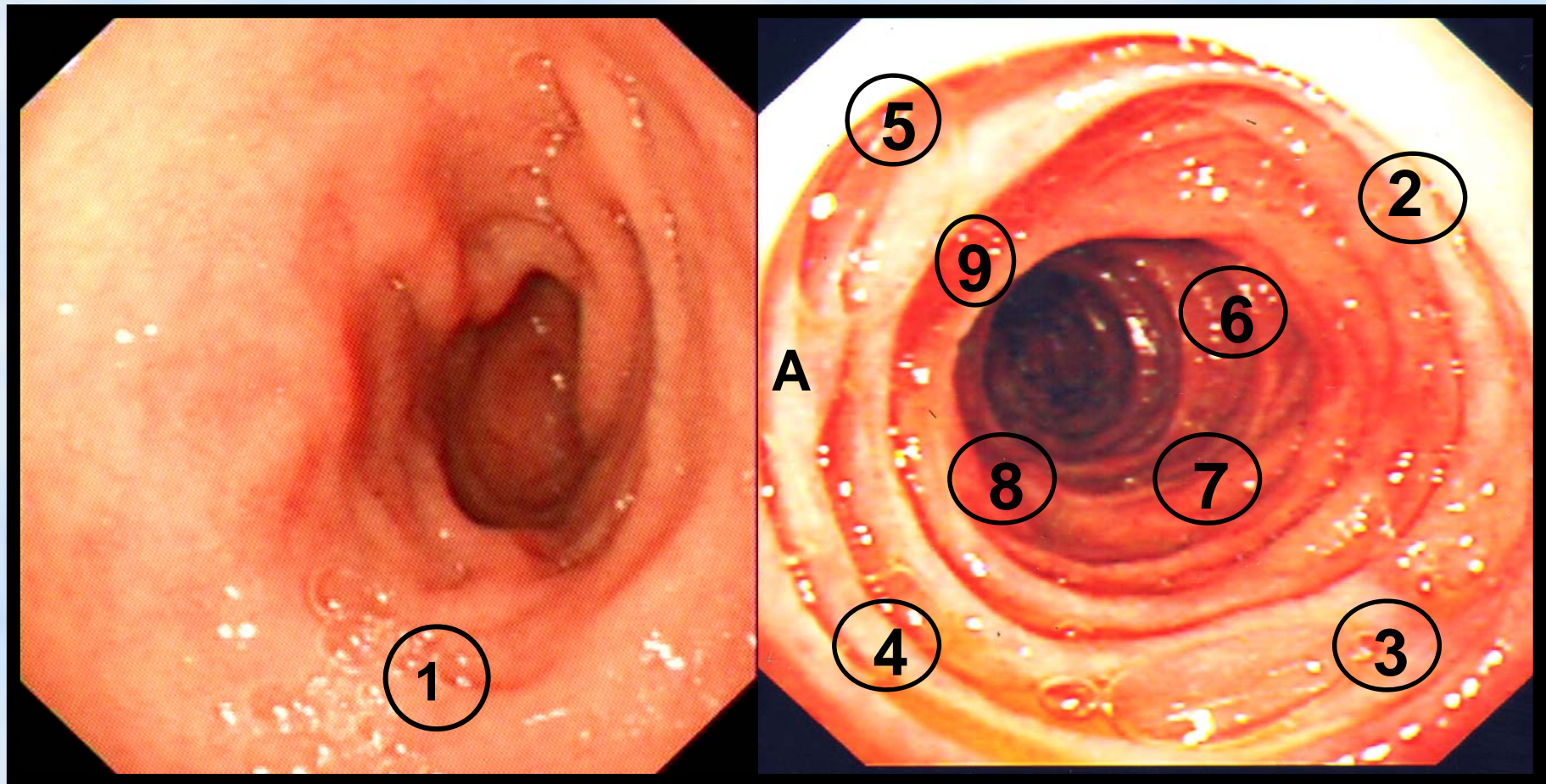
In-press Clin Gastro
Hep 2015



Pitfalls in Biopsy

4 biopsies from second part of duodenum and a further 5th biopsy from the duodenal bulb

Hopper AD et al *Endoscopy* 2008;40:219-24.



Cost effective?



- Cost of separate D1 specimen £30
- Cost of separate D1 biopsy for 100 patients
 - $100 \times 30 = £3000$
- Cost of gastroscopy £450
- Cost of gastroscopy for 9/100 new coeliac patients with villous atrophy in the bulb only
 - $9 \times 450 = £4050$



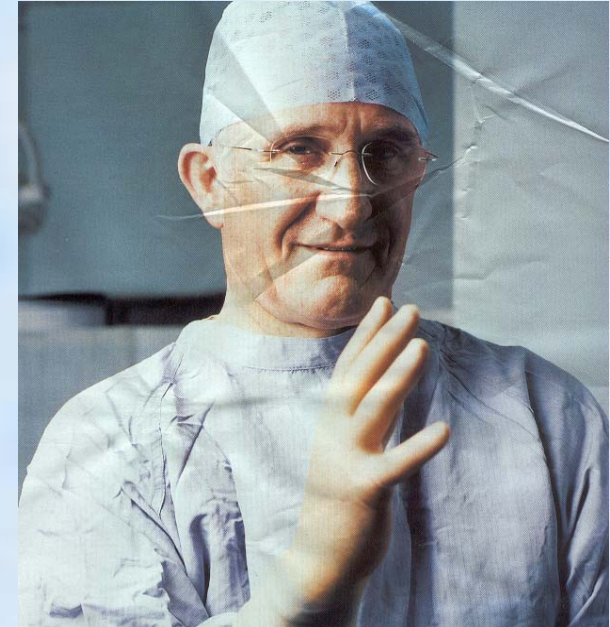
Think of the patient-diagnostic delay, inconvenience, repeated invasive testing

Evans KE et al *Am J Gastro* 2012

Are we adhering to biopsy guidelines?

- N=1423
- 12.4% new patients with coeliac disease had a previous gastroscopy within 5 years and no duodenal biopsy taken
- Adherence to guidelines 40.2%
- Adherence to guidelines increases diagnostic yield from 4.6 to 10.1% ($p<0.0001$)
- Taking single bites per pass of biopsy forceps increases median biopsy rate from 3 to 4 ($p=0.03$)

Mooney PD et al *Gut* suppl 2014

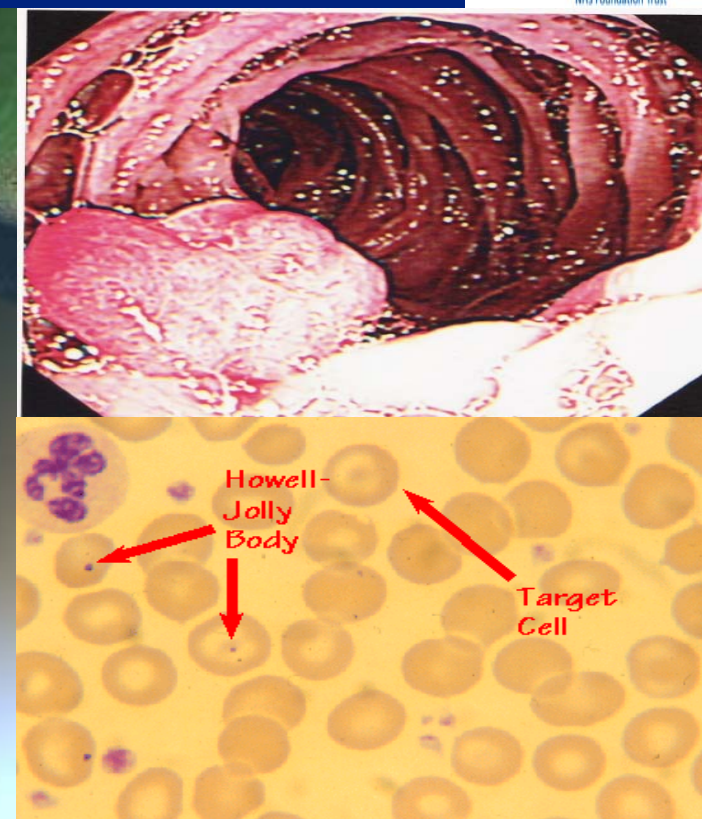
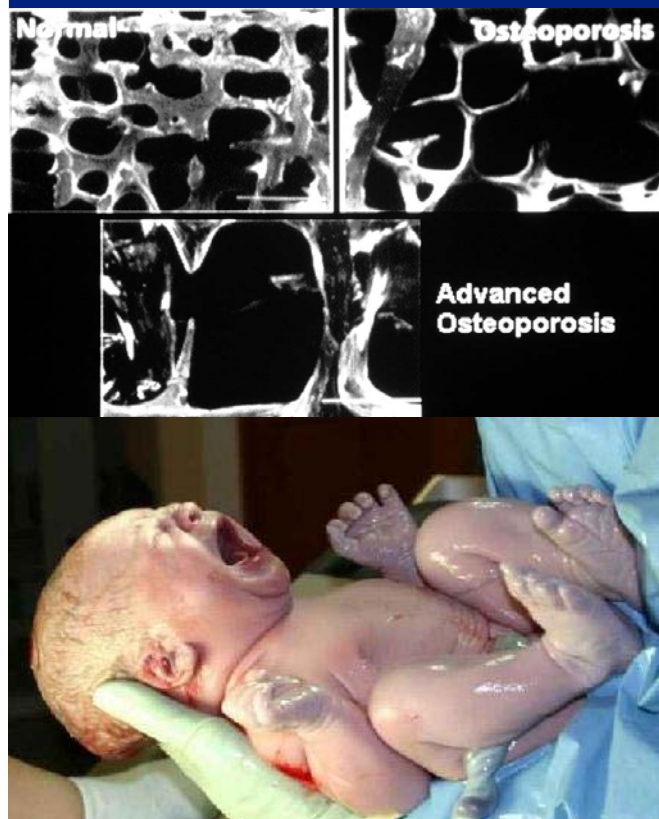


- Nurse endoscopists
 - Median biopsies = 4
 - Guideline adherence 51.2%
 - Diagnostic yield 6.7%

- Physicians
 - Median biopsies = 3
 - Guideline adherence 41.8%
 - Diagnostic yield 7.1%

- Surgeons
 - **Median biopsies = 2 (fewest $p<0.0001$)**
 - **Guideline adherence 18.2% ($p<0.0001$)**
 - Diagnostic yield 3.0%

Why Bother Treating Coeliac Disease?!! 'the gluten-free diet is such a hassle'



Prevalence of Thyroid Disorders in Untreated Adult Celiac Disease Patients and Effect of Gluten Withdrawal: An Italian Multicenter Study

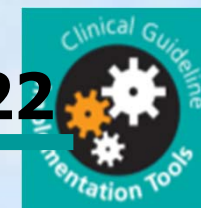
C. Sategna-Guidetti, M.D., Ph.D., U. Volta, M.D., C. Ciacci, M.D., P. Usai, A. Carlino, L. De Franceschi, M.D., A. Camera, M.D., A. Pelli, M.D., Ph.D., and C. Brossa, Ph.D.
University of Torino, Torino; University of Bologna, Bologna; University of Napoli, Napoli; University of Cagliari, Cagliari; and University of Perugia, Perugia, Italy

Causes of Death in People With Celiac Disease Spanning the Pre- and Post-Serology Era: A Population-Based Cohort Study From Derby, UK

Matthew J. Grainge, PhD¹, Joe West, PhD, MRCP^{1,2}, Timothy R. Card, PhD, MRCP¹⁻³ and Geoffrey K.T. Holmes, MD, PhD, FRCP⁴

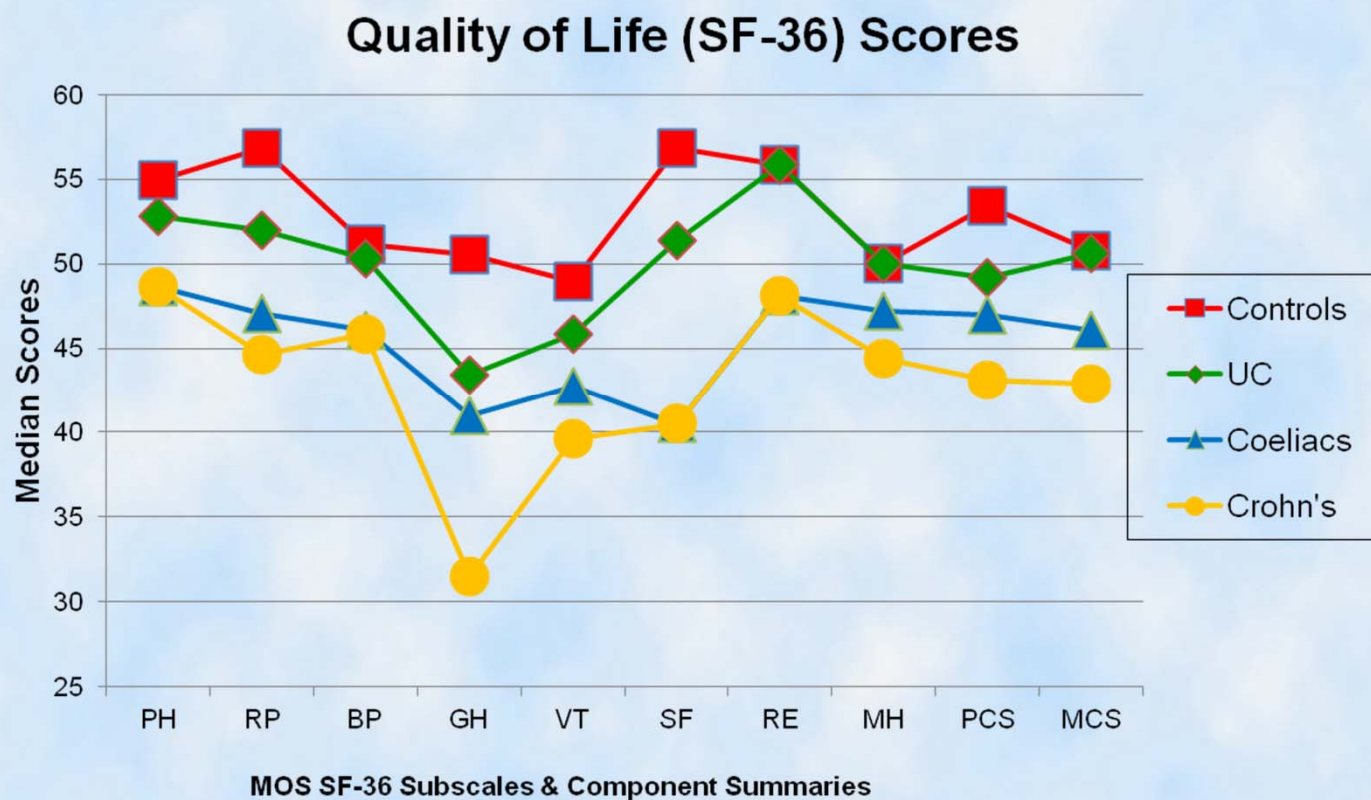
Costs per 100,000 population- 'testing is cost effective from a QUALY perspective'

Recommendations with significant incremental costs	Incremental costs (£ per year)
Gastrointestinal specialists	6,812
Obtaining samples for serological testing	17,573
Intestinal biopsies	16,833
Serological testing	4,504
Estimated incremental cost of implementation	45,722



Quality of life in coeliac disease is comparable to other gastrointestinal diseases

Barratt SM et al *Eur J Gastroenterol Hepatol* 2011



Conclusion – Part 1

- Coeliac Disease affects 1% of the adult population
- Coeliac Disease is everywhere in our clinical practice, in clinic or out-patients, and at endoscopy
- Duodenal biopsies and bulb biopsies should be taken in patients with positive serology, anaemia, weight loss and diarrhoea
- There is emerging data that supports point of care testing and in particular Simtomax
- What is the point of diagnosing Coeliac Disease? – the patient gets better sometimes after years of being misdiagnosed or unrecognised

Question: Non-coeliac Gluten Sensitivity or irritable bowel syndrome?

How do we as clinicians distinguishing the two?!

To do this we must first agree on our definition of coeliac disease!





What is potential coeliac disease?

Potential

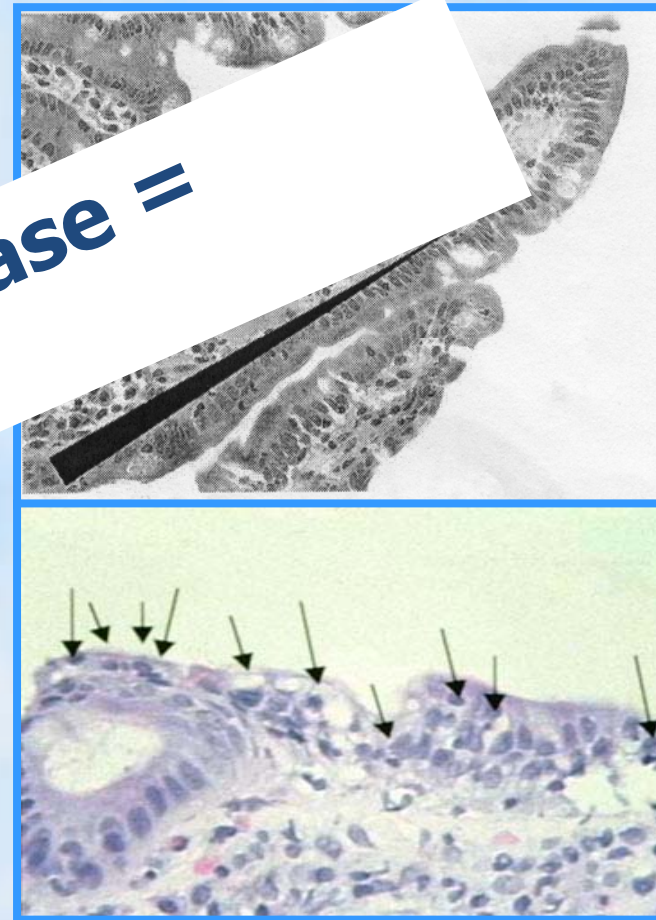
- The presence of EMA (and perhaps now high levels of TTG?)
- High Intraepithelial Lymphocyte (IEL) counts
- In uncomplicated coeliac disease, IEL's express CD8 and suppress the immune response to gluten challenge!

**Potential coeliac disease =
gluten sensitivity!**

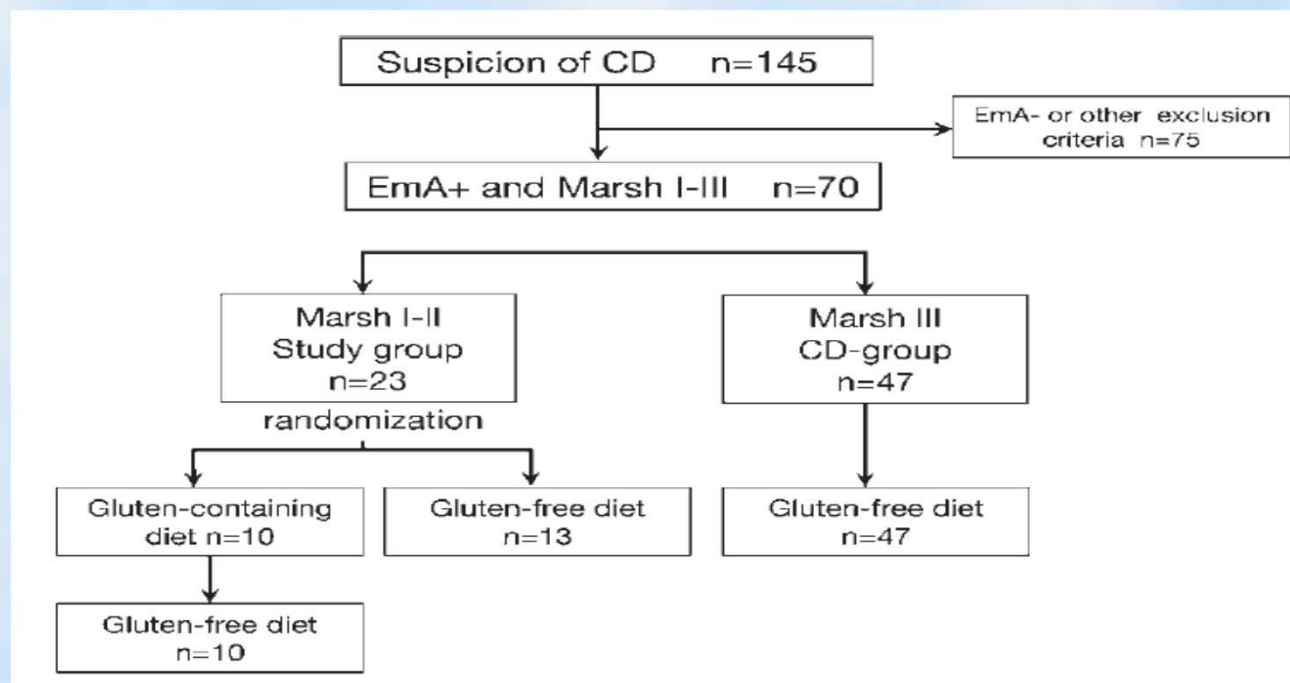
Fergusson *Gut* 1993;34:150-1

Tronchetti R et al *Acta Paediatr Suppl*

1996;412:10-14



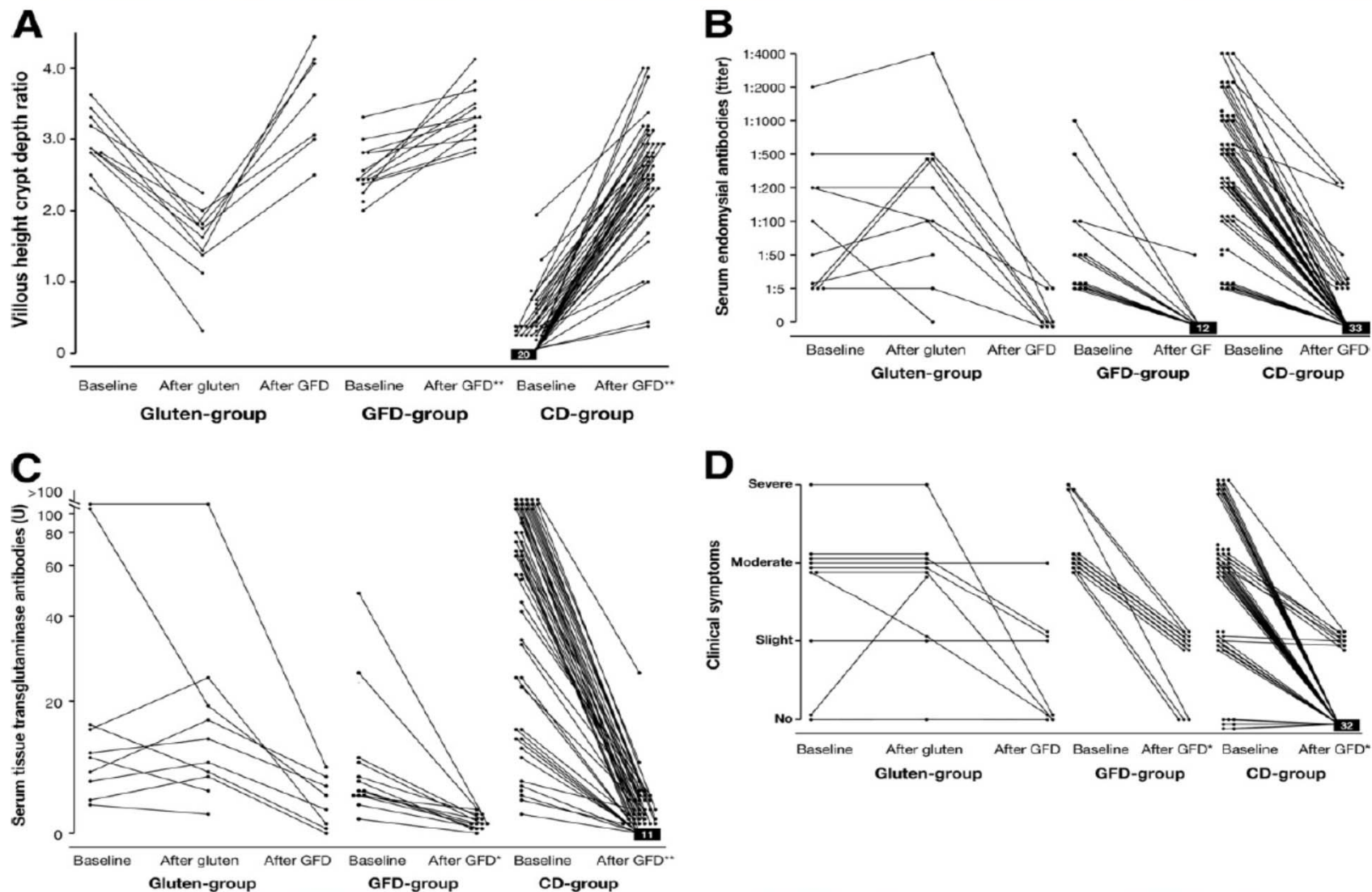
Marsh 1 with +ve EMA



- Raised IELs with +ve EMA were all HLA +ve in this study

Kaukinen et al. Diagnosing mild enteropathy Coeliac disease: A randomised, controlled clinical study. *Gastroenterology* 2009;136: 816-823

Marsh 1 with +ve EMA



Health?!





BMJ Hand eczema in healthcare workers
Monoclonal antibodies: why so costly?
What's with personal health budgets?
Managing supraventricular tachycardia
BMJ GROUP AWARDS: VOTE NOW

340-505 May 2007 Clinical research ISSN 0950-0804
15 December 2012 bmj.com



**THE CHALLENGE
OF NON-COELIAC
GLUTEN
SENSITIVITY**

NCGS Prevalence

Country	Year	Prevalence
	2012	5.9% - secondary care referrals
	2012	~4% of NZ children report gluten avoidance
	2013	0.5% - National Health and Nutrition Examination Survey
	2013	13% report symptoms related to gluten population survey but only 3.7% on GFD

Population survey – 1002 adults, mean age 39 years, female 55%

Aziz I et al *Eur J Gastroenterol & Hepatol* Oct 2013

Variable	Gluten sensitive n 129 (13%)	Not gluten sensitive n 873 (87%)	P-value
Mean age \pm SD	39.5 \pm 17.7	39 \pm 19.7	NS
Sex	79% female : 21% male	51% female : 49% male	<0.0001*
White British	94.6%	94.8%	NS
Anxiety	21%	6.8%	<0.0001*
Depression	13%	6.3%	0.0093*
Chronic fatigue syndrome	3.1%	0.9%	0.0108*
Fibromyalgia	0.8%	0.3%	NS
Rome III criteria for irritable bowel syndrome	20%	3.89%	<0.0001*
Gastrointestinal cancers	0.8%	0.46%	NS
Heartburn/reflux	8.5%	4.5%	NS
Nut allergy	3.1%	1.0%	NS
Egg allergy	3.1%	0.1%	0.0012*
Dairy intolerance	3.9%	0.9%	0.0179*

3.7% consuming GFD, with doctor-diagnosed CD being 0.8%

- 200 adults with “gluten-related GI symptoms”
- 84% female
- Mean age 39.6 years
- Gluten challenge: CD 7% vs. NCGS 93%
- HLA DQ2/DQ8: CD 100% vs. 53% NCGS $P 0.0003$

Comparison between CD and NCGS at baseline diagnosis

Patient characteristics	Coeliac disease (CD) n 329	Non-coeliac gluten sensitivity (NCGS) n 186	P - value
Mean age \pm SD	49.8 \pm 15.7	39.6 \pm 15.2	< 0.0001*
Sex	71% female : 29% male	84% female : 16% male	0.0013*
Autoimmune history	23.1%	9.7%	0.0001*
Family history of CD	7.3%	12.4%	NS 0.058
Anaemia	25.4%	3.3%	< 0.0001*
Low Ferritin	48.3%	16.2%	< 0.0001*
Folate deficiency	29.1%	7.2%	< 0.0001*
Vitamin B12 deficiency	13.3%	3.9%	0.0017*
Hypoalbuminaemia	10.2%	2.8%	0.003*
Mean BMI \pm SD	23.7 \pm 5.45	25.8 \pm 5.59	0.001*

Emerging Data Pathophysiology: Non-Coeliac Gluten Sensitivity?

Sapone et al. *BMC Medicine* 2011, **9**:23
<http://www.biomedcentral.com/1741-7015/9/23>



RESEARCH ARTICLE

Open Access

Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity

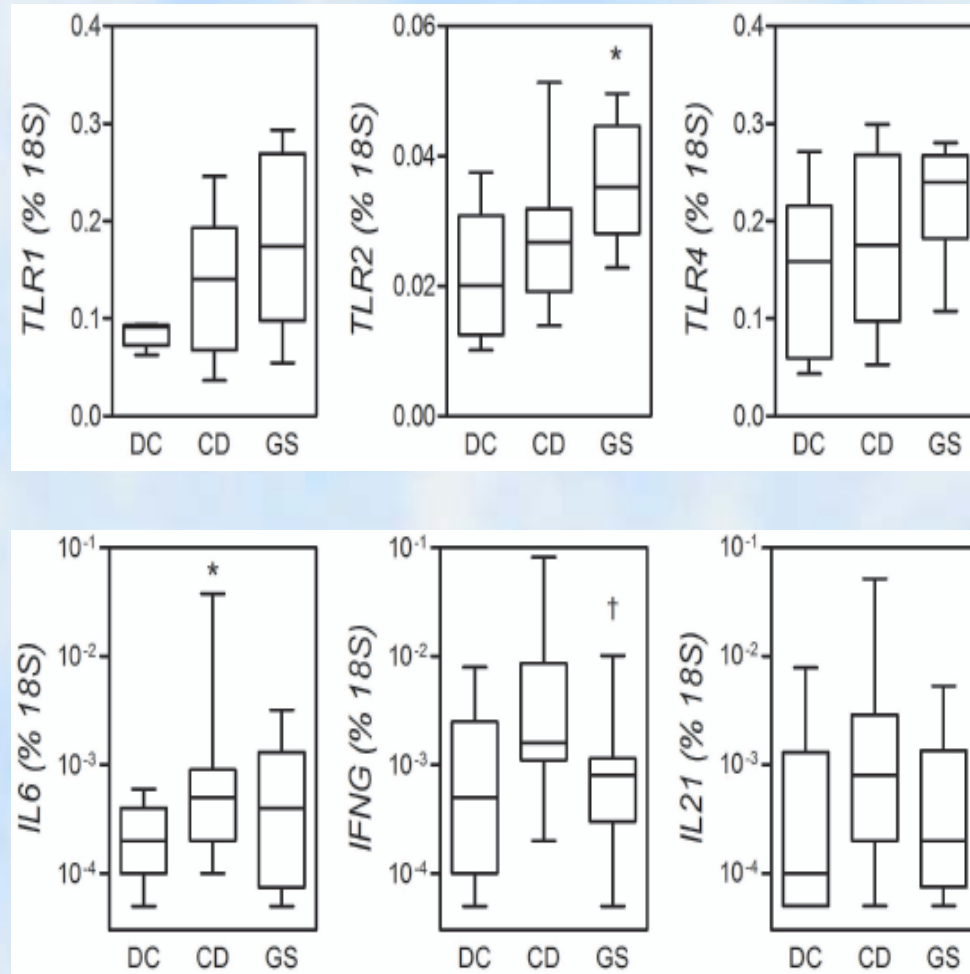
Anna Sapone^{1,2}, Karen M Lammers², Vincenzo Casolaro^{2,3}, Marcella Cammarota⁴, Maria Teresa Giuliano⁴, Mario De Rosa⁴, Rosita Stefanile⁵, Giuseppe Mazzearella⁵, Carlo Tolone⁶, Maria Itria Russo⁷, Pasquale Esposito⁷, Franca Ferraraccio⁸, Maria Carteni⁴, Gabriele Riegler¹, Laura de Magistris¹, Alessio Fasano^{2*}

Differential Mucosal IL-17 Expression in Two Gliadin-Induced Disorders: Gluten Sensitivity and the Autoimmune Enteropathy Celiac Disease

Anna Sapone^{a, b} Karen M. Lammers^b Giuseppe Mazzearella^d Irina Mikhailenko^c
Maria Carteni^a Vincenzo Casolaro^{b, e} Alessio Fasano^b

^aSezione Biotecnologia e Biologia Molecolare, Dipartimento di Medicina Sperimentale, Seconda Università degli Studi di Napoli, Naples, Italy; ^bMucosal Biology Research Center and ^cCenter for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, Md., USA; ^dIstituto Scienze Alimentari, CNR, Avellino, Italy; ^eDivision of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, Md., USA

NCGS: innate immune response?



- Innate markers

- Adaptive markers

PROINFLAMMATORY WHEAT ATTACKS ON THE INTESTINE: ALPHA-AMYLASE TRYPSIN INHIBITORS AS NEW PLAYERS

Junker Y, Zeissig S, Kim SJ, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of Toll-like receptor 4. J Exp Med 2012;209:2395-2408.

Dietary factors play a major role in many gastrointestinal diseases such as celiac disease, inflammatory bowel diseases (IBD), or gastrointestinal cancers. Mechanisms of action have remained mostly unclear. It is believed that various dietary factors might exert either detrimental (ie, proinflammatory) or beneficial (ie, anti-inflammatory) effects on the gastrointestinal immune system. Consumption of wheat, barley, or rye causes small intestinal inflammation in celiac disease patients. It has long been assumed that certain wheat components might also affect innate immunity.

Junker et al of Schuppan's group now demonstrate that members of the non-gluten alpha-amylase/trypsin inhibitor (ATI) family, which are enriched in wheat and related cereals, are potent activators of various innate immune cells such as dendritic cells (DCs) and macrophages. In their studies, pepsin/trypsin (PT)-digested gliadin caused a dose-dependent secretion of interleukin (IL)-8, tumor necrosis factor, and monocyte-chemotactic protein-1 in the human monocytic cell lines THP-1 and U937. Cytokine production was

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Isolated gliadin antibodies are prevalent in the general population but more prevalent in IBS

Table 2 Coeliac antibody results

	Antibody negative	IgG antigliadin antibody only	IgA antigliadin antibody only	IgG and IgA antigliadin antibodies	EMA only	EMA and IgG antigliadin antibody	All three antibodies
Volunteers (n = 1200)	1038	139	10	4 (1 declined*)	3	4	2
Biopsy-proven coeliac disease		1**	1	1	3	4	2
Normal histology			6	1			
Intraepithelial lymphocytes			3	1			

* A 79-year-old female declined biopsy due to recent stroke.

** Also one case of coeliac disease diagnosed coincidentally having been referred to secondary care for investigation of irritable bowel syndrome.

	Antibody negative	IgG antigliadin only	IgA antigliadin only	IgG and IgA antigliadin	EMA only	EMA and IgG antigliadin	EMA and IgA antigliadin	All three antibodies
Study group (n=300)	234	49	4	1	6	4	1	1
Coeliac disease (n=14)*	..	1	1	1	5	4	1	1
Controls (n=300)	256	41	1	2
Coeliac disease (n=2)	2

EMA=endomysial antibodies. *One patient refused to undergo biopsy.

Table 2: Coeliac antibody results

Summary of IBS and Gluten, Wheat or FODMAP studies

Lead Author	Country	Year	Patients	Outcome
Wahnschaffe	Germany	2001	102 IBS-D without CD	Stool frequency significantly improved in patients with HLA DQ2/DQ8
Wahnschaffe	Germany	2007	145 IBS-D without CD	HLA-DQ2 predicted response to GFD
Biesierski	Australia	2010	34 self reported gluten sensitive IBS	Significant reduction in overall symptoms in GFD group
Carroccio	Italy	2011	920 gluten sensitive patients with IBS	70 patients wheat sensitive and 206 multiple food sensitivities including wheat
Vazquez-Roque	USA	2012	45 IBS-D	Increased intestinal permeability in patients receiving gluten
Biesierski	Australia	2013	37 self reported gluten sensitive patients with IBS on GFD	All patients responded to reduction in FODMAPs during run-in but no difference between GFD and gluten containing arms
Vazquez-Roque	USA	2013	45 IBS-D	Reduction in stool frequency in patients on GFD

No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates

JESSICA R. BIESIEKIERSKI,^{1,2} SIMONE L. PETERS,² EVAN D. NEWNHAM,¹ OURANIA ROSELLA,² JANE G. MUIR,² and PETER R. GIBSON²

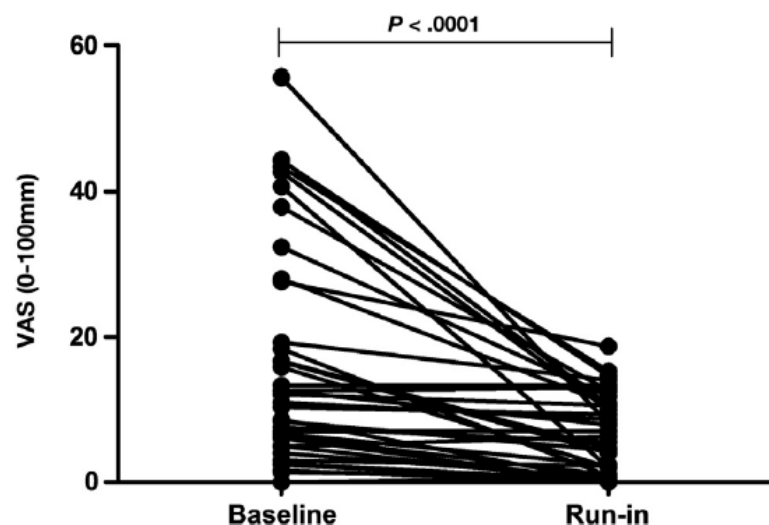
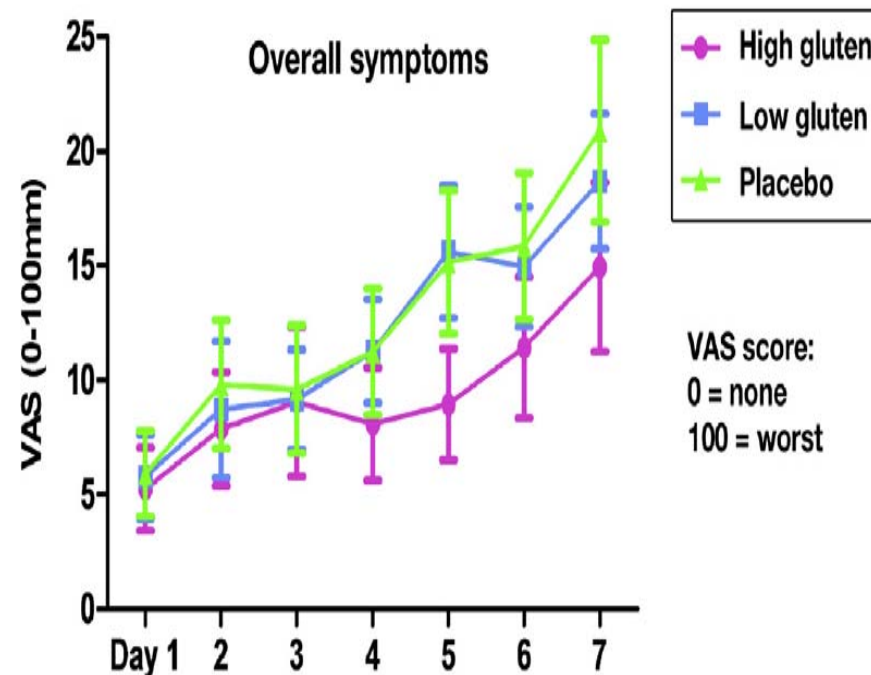
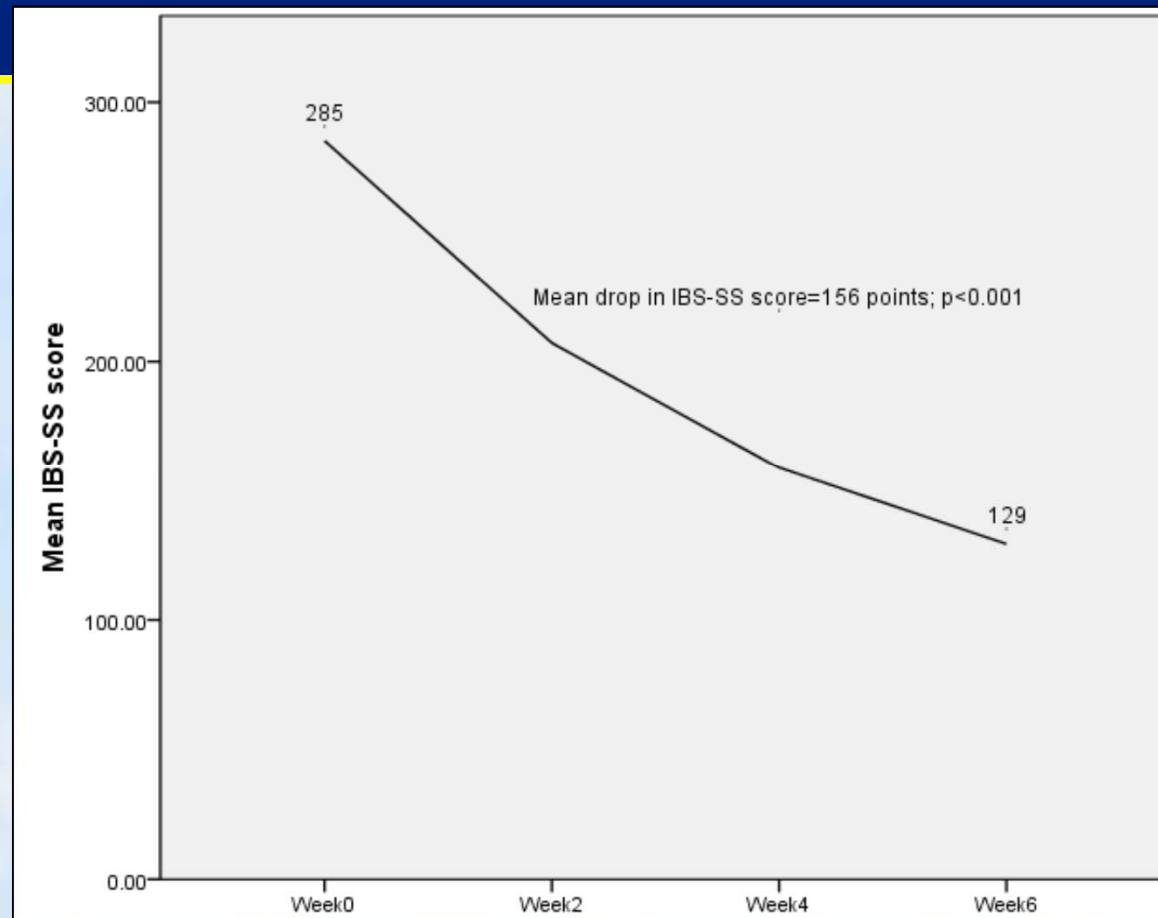


Figure 1. Individual responses in mean overall symptom severity score during the run-in period, where low FODMAP diet was commenced, compared with the baseline period, where participant's usual gluten-free diet was consumed during 7-day trial. Scores were significantly greater during the baseline period ($P < .0001$, Wilcoxon signed rank test).



Open-label response to a GFD in D-IBS (n=40)



Mean-age (SD)	40.4 (14.9)
Female (%)	30 (75)
Mean GFD adherence score (SD)	3.1 (0.7)
Clinical response: IBS-SS drop by ≥ 50 points	28 (70)
Will continue GFD for the foreseeable future (%)	24 (60)
Happy to be discharged to GP (%)	36 (90)

Confusion, Confusion, Confusion!



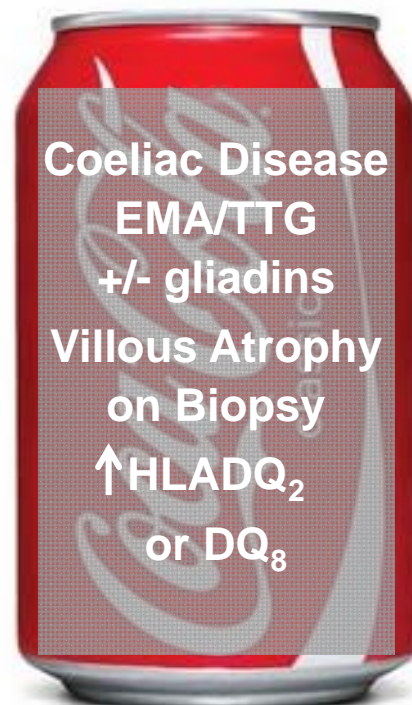
Gluten Related Disorders



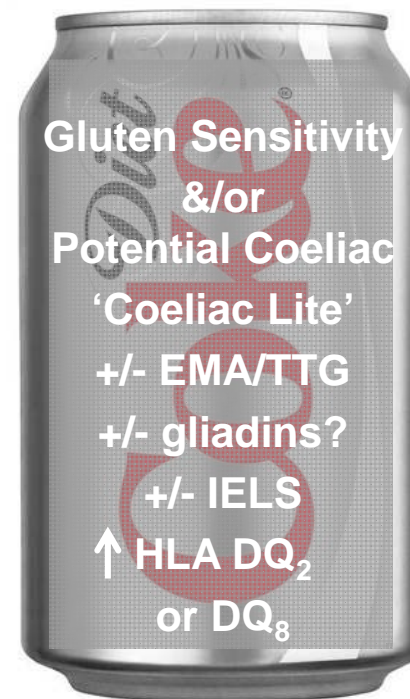
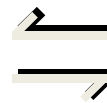
Coeliac Disease
EMA/TTG
+/- gliadins
Villous Atrophy
on Biopsy
HLADQ₂
or DQ₈

Adaptive Immune Response

Gluten Related Disorders

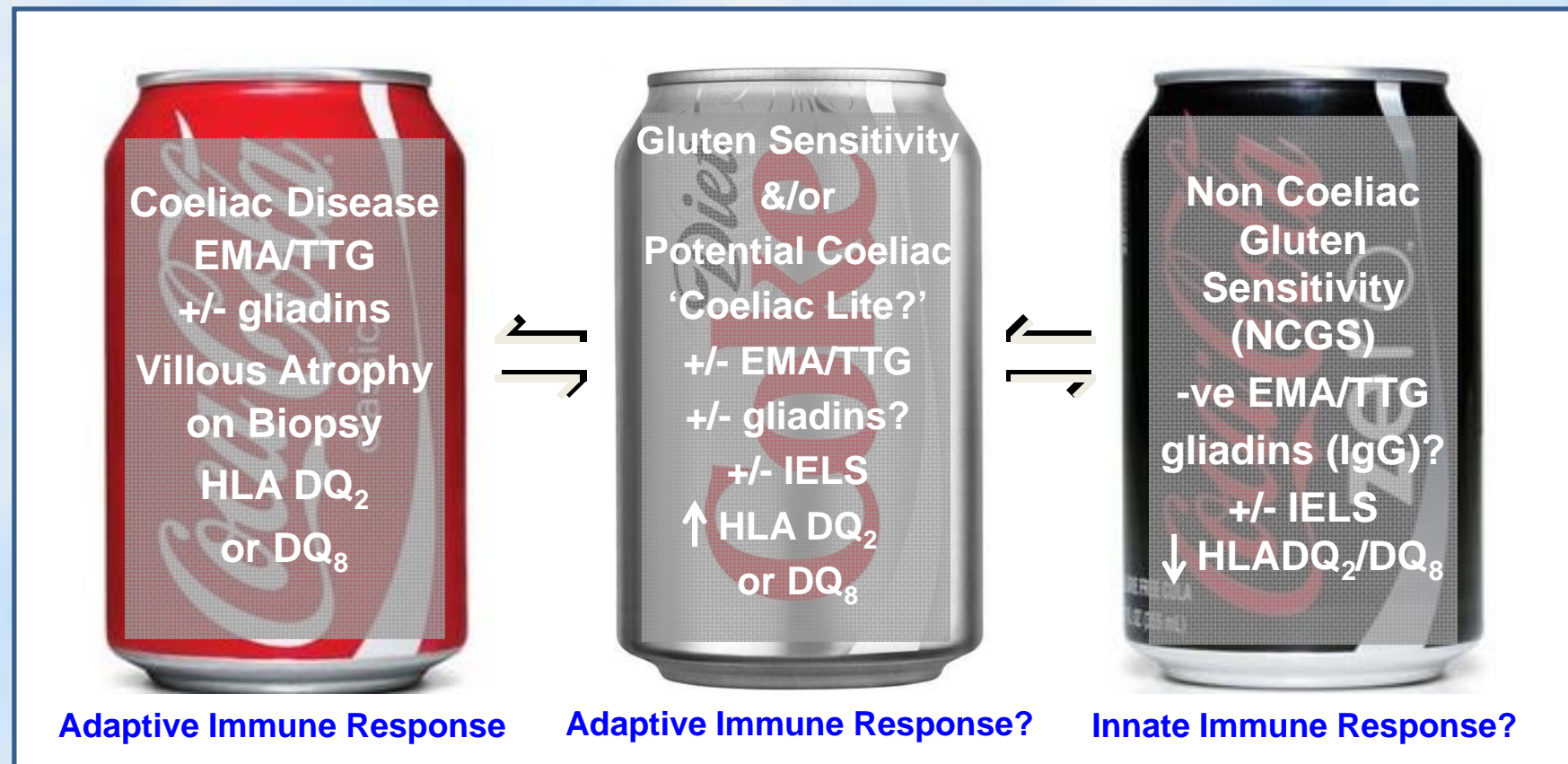


Adaptive Immune Response



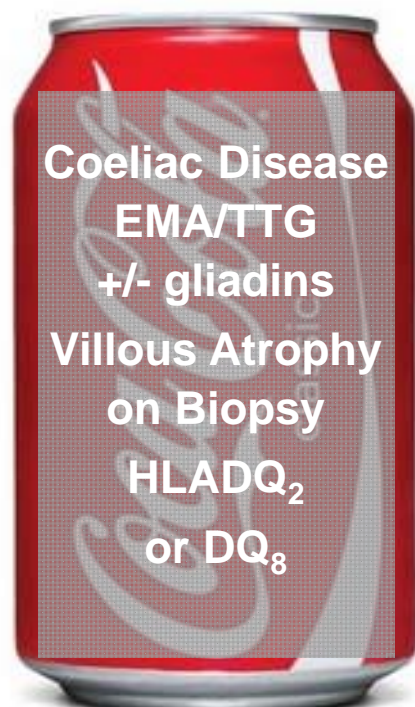
Adaptive Immune Response

Gluten Related Disorders: but what about other wheat components and FODMAP's?

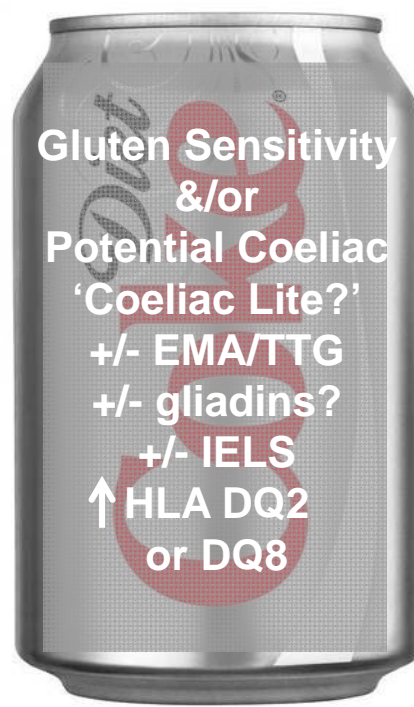


SPECTRUM

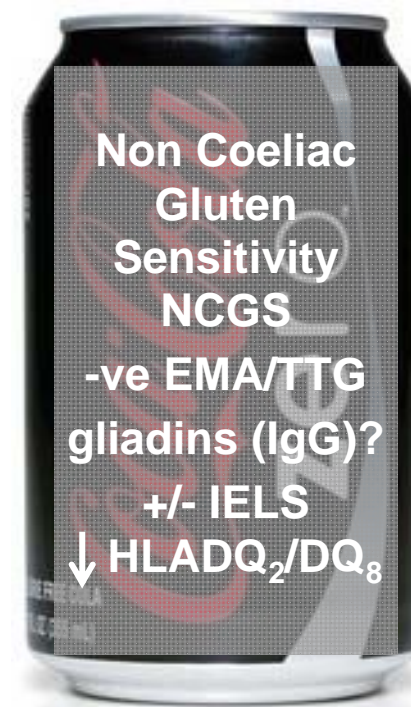
GI & Extra Intestinal Symptoms



Adaptive Immune Response



Adaptive Immune Response?



Innate Immune Response?

NCGS patients' interview

Vanessa

(right hand side
of picture)

55 years old,
Publican

Persisting
diarrhoea,
bloating,
incontinence

Back pain

'Quality of life
affected'

GP said 'IBS'



Non-coeliac gluten sensitivity (Part 2)

- **Essential to diagnose or exclude coeliac disease prior to commencing a gluten free diet**
- **IgE Wheat Allergy should be excluded**
- **Consider treating the Coeliac 'like' or 'lite' group with a gluten free diet**
- **Consider a wheat free diet or low FODMAP's**
- **The public is choosing a gluten free diet irrespective of medical advice (self reporting of symptoms may be a clue)**
- **The scientific jury is still out (there is no clear biomarker – yet??!)**
- **The medical community is on a learning curve!**





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Nina Lewis



**Mohammed
Karajeh**



John Leeds



Kate Evans



Dr Steve Barratt



**Andrew Hopper &
Reena Sidhu**



**Marios
Hadjivassiliou**

Royal Hallamshire GI and Liver Unit

Research



BSG Hopkins Endoscopy Prize 2012
Small Bowel Endoscopy



Cuthbertson Medal 2011
Nutrition Society & BAPEN
(British Association of Parenteral & Enteral Nutrition)



ASNEMGE

European Rising Star Award 2010
Association of National European & Mediterranean
Societies of Gastroenterology

Clinical



BSG Clinical Care Award
2011 Small Bowel Endoscopy
2014 Primary Care Services & GI Bleed Unit



Health Service Journal Awards 2012
Gastrostomy/PEG Feeding Service



Coeliac UK 2010 Patient Healthcare Award



Complete Nutrition 2013 Coeliac Healthcare Award



Medipex Award 2013 Small Bowel Endoscopy