Celiac Disease and Gluten Sensitive Enteropathy

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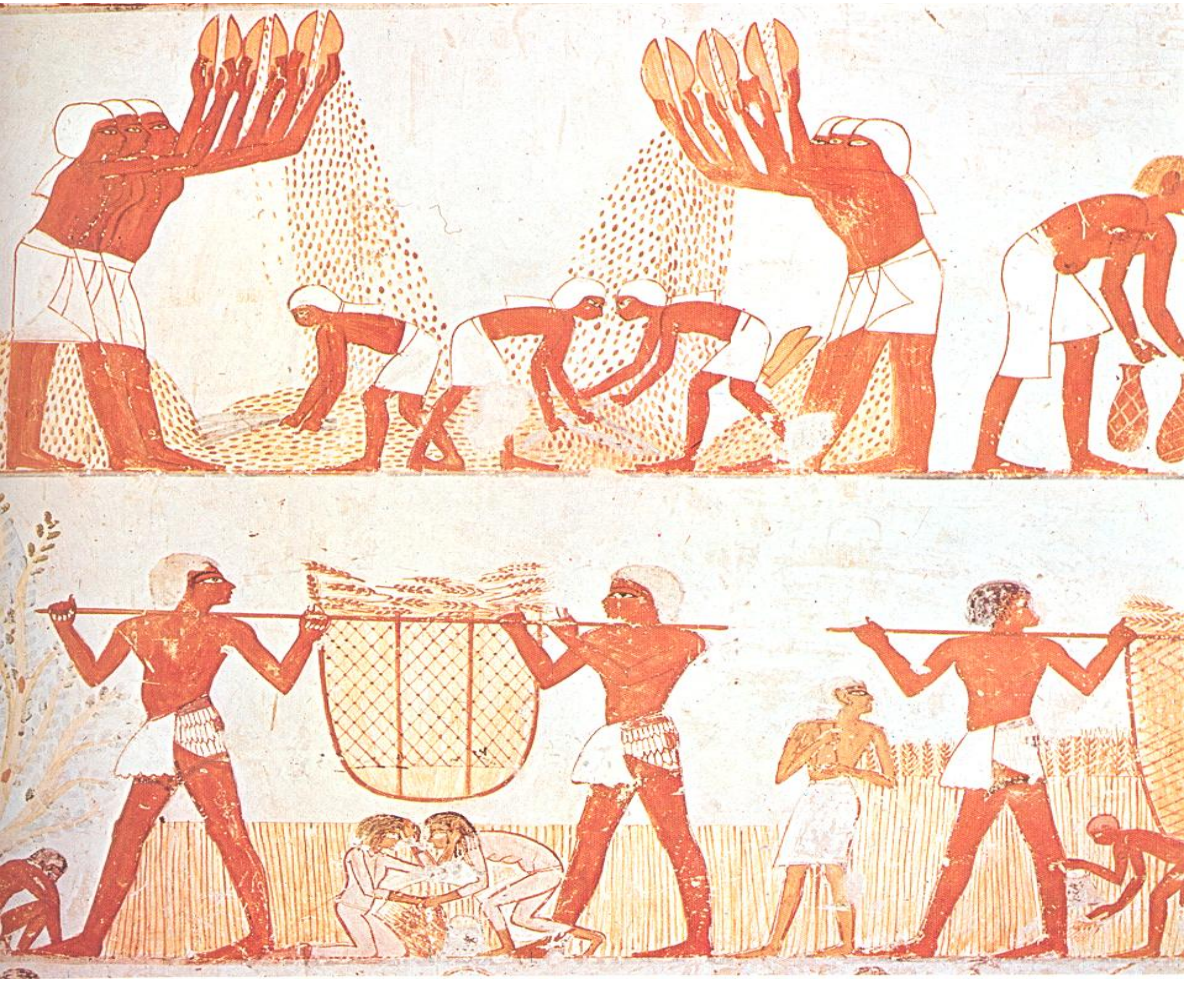
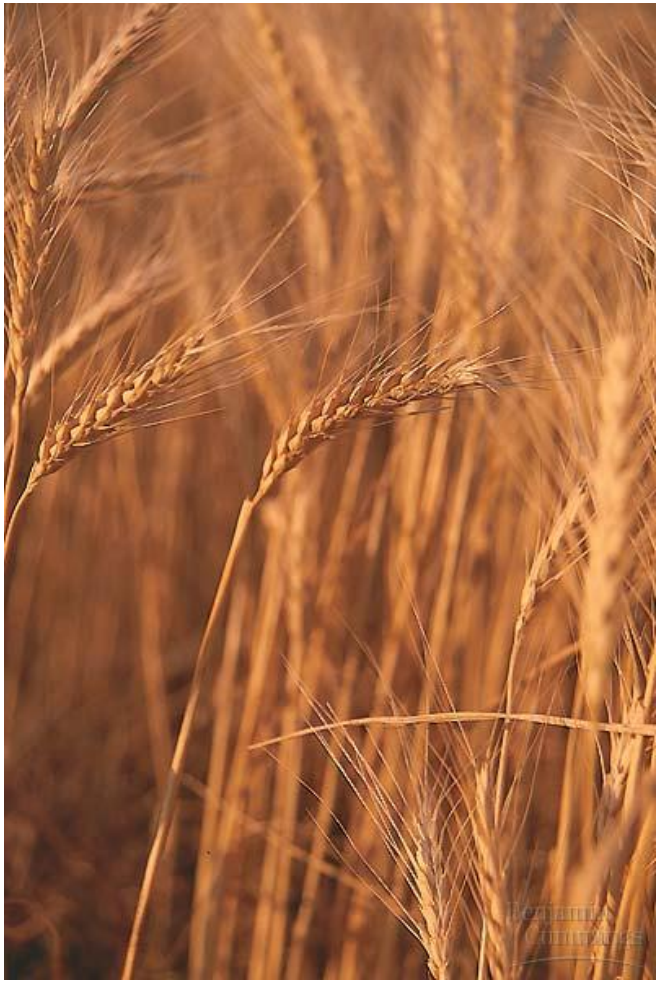
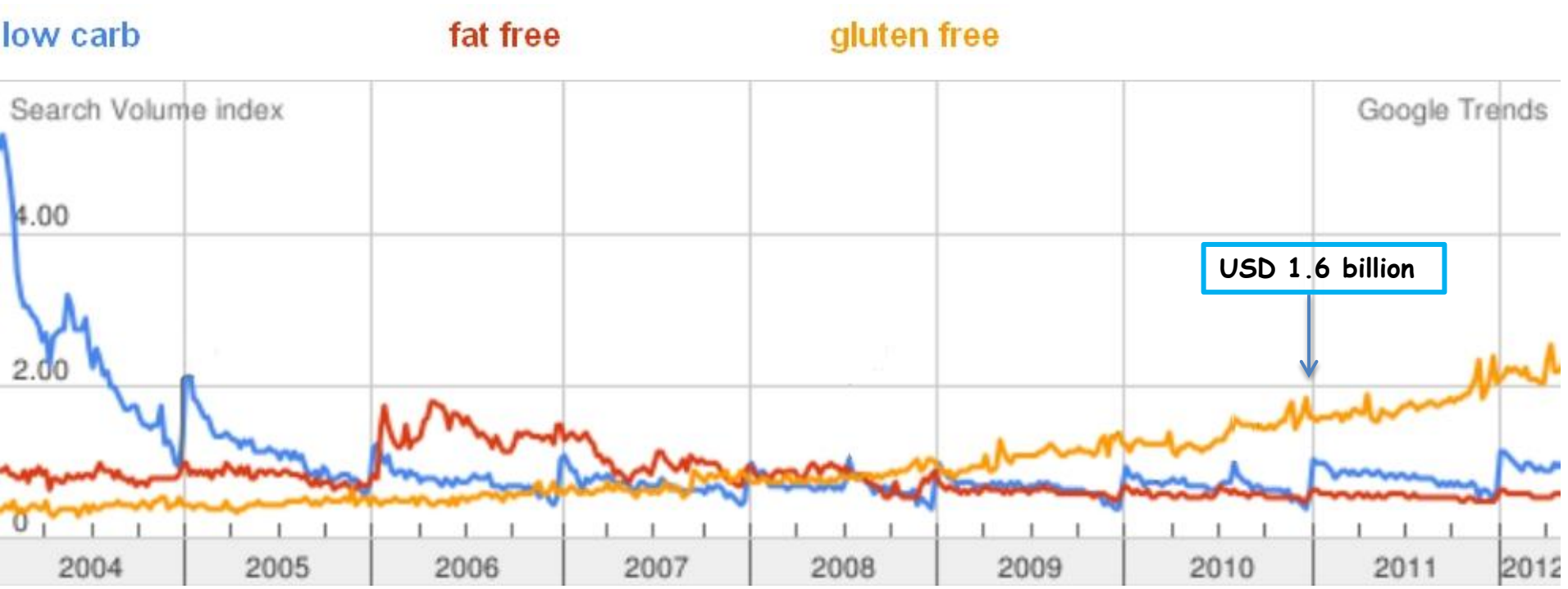
Le grandi civiltà mediterranee (fenici, egizi, etruschi, romani, arabi) dipendevano dal grano





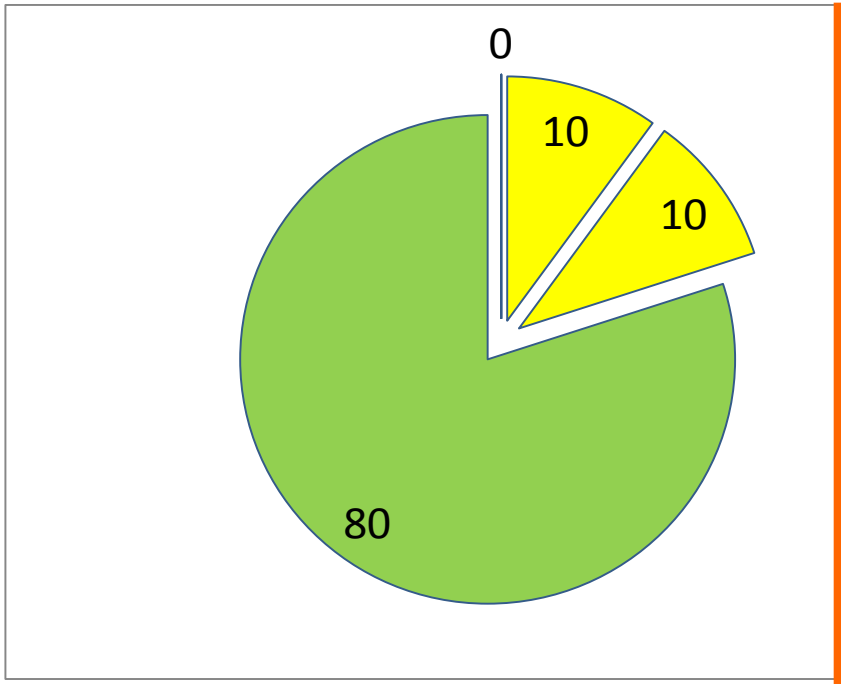
THE MARKET FOR *GLUTEN-FREE* FOOD



The demand for specialised gluten-free products has fuelled a global market approaching $2.5 billion (US) in global sales annually

Sapone et al., BMC Medicine 2012 10:13

GLUTEN AVOIDANCE IN FBD PATIENTS

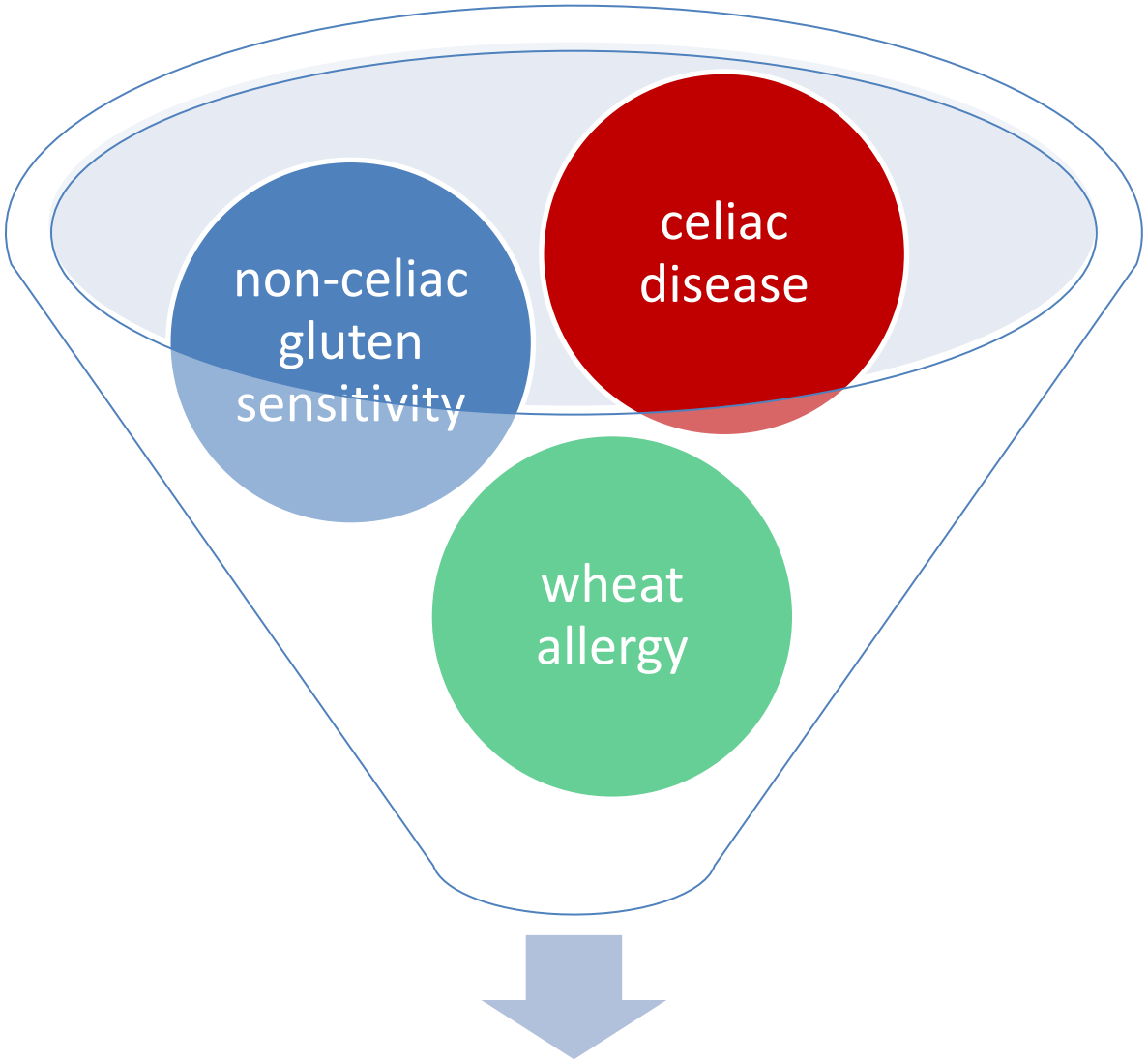


Percent of 1000 consecutive FBD Patients on gluten free diet based on:

- self diagnosis.
- unreliable tolerance tests.
- erroneous interpretation of anti **gliadin Ab or genetic tests.**

FBD=FUNCTIONAL BOWEL DISORDERS

Picarelli, Corazziari 2011



GLUTEN-RELATED DISORDERS

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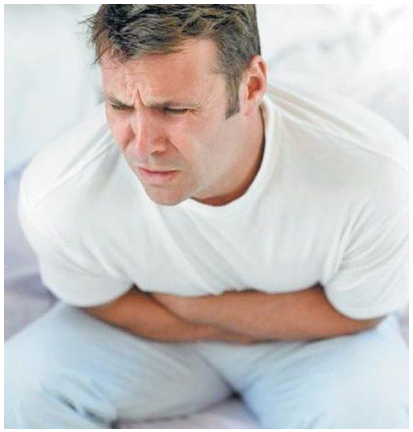
WHEAT ALLERGY

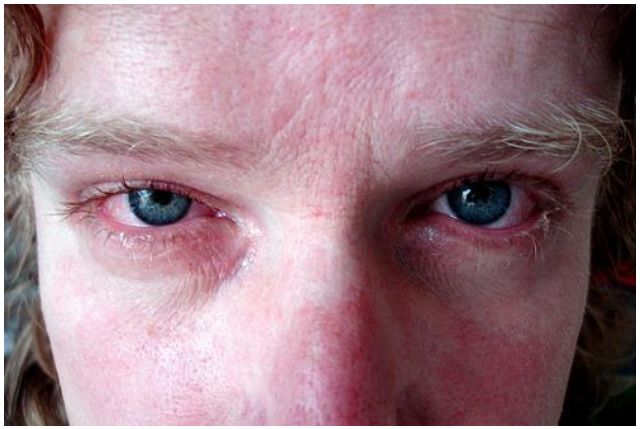
Prevalence: ≈ 0.1 %

Gastrointestinal symptoms: diarrhea, abdominal pain, bloating
Extraintestinal symptoms: +++ dermatological lesions

Diagnosis: PRIST, RAST (wheat, barley, gluten, rye)

Therapy: Recede after a gluten-free diet



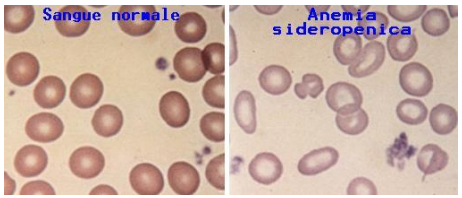


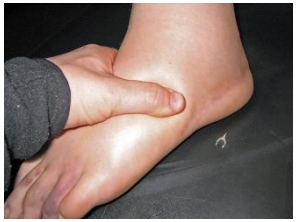
Inomata N. Curr Opin Allergy Clin Immunol. 2009

CELIAC DISEASE

Celiac Disease (CD) is an **immune-mediated disease** dependent on **gluten** (a protein present in wheat, rye or barley).

Most individuals have **improvements within few weeks** after starting a gluten-free diet (GFD).



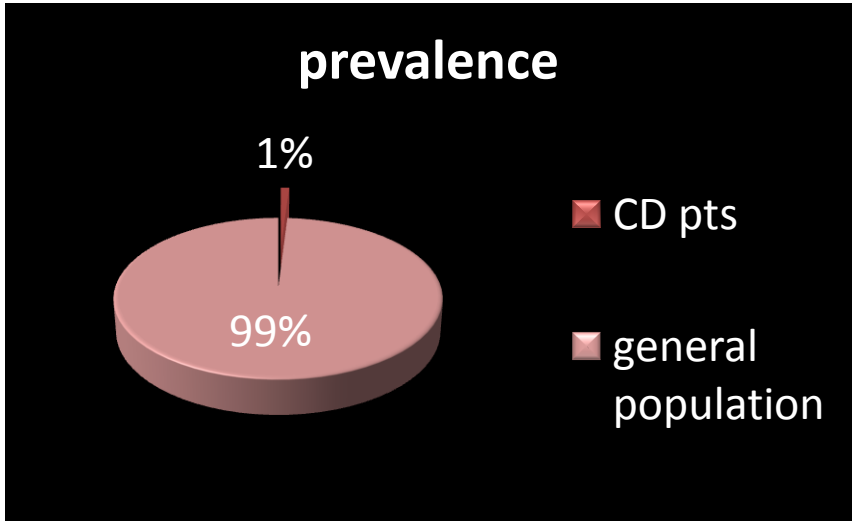


CELIAC DISEASE

- **PREVALENCE:** 1 %
- **GENETIC SUSCEPTIBILITY:** HLA DQ2 (>90%) and/or DQ8 (5%)

- **HISTOLOGICAL PICTURE (duodenal biopsy)**: villous atrophy + crypt hyperplasia + lymphocytosis
- **SEROLOGICAL AB:** EMA, anti t-TG, AGA DGP (IgA and IgG)

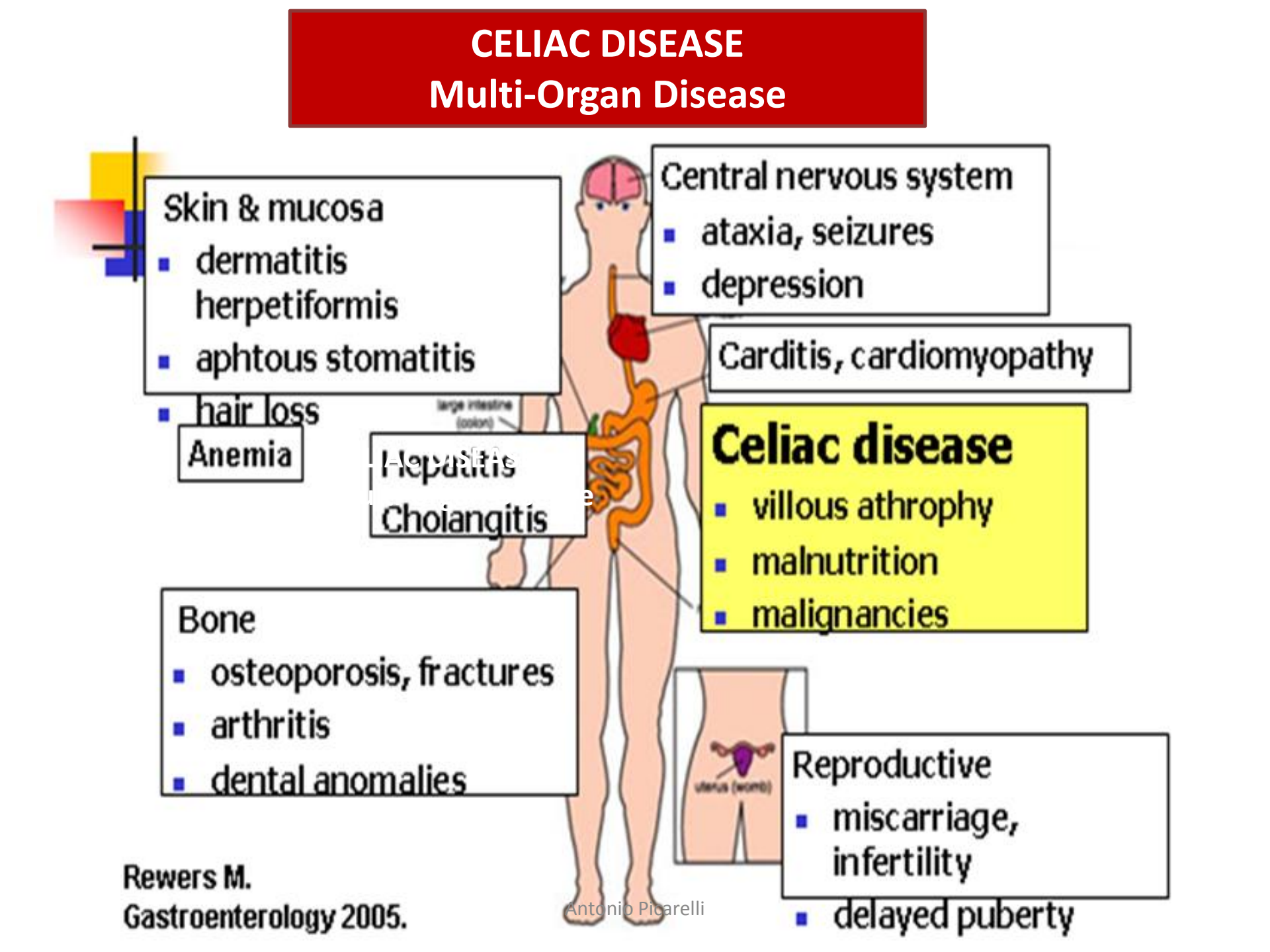
- **DIAGNOSIS SUPPORT:** Organ culture of duodenal biopsy



- **THERAPY:** gluten-free diet

Bao F et al. - Arch Pathol Lab Med. 2012
Cerf-Bensussan N - J Pediatr Gastroenterol Nutr. 2003
Picarelli A et al. - Transl Res. 2013
Fasano A et al. - N Engl J Med. 2003

CELIAC DISEASE
Multi-Organ Disease



Rewers M.
Gastroenterology 2005.

CELIAC DISEASE
Clinical Presentation

- ❑ **Typical**
- ❑ **Atypical**

- **Silent** form**:**

  (asymptomatic, only serological and histological positive results)
- **Latent** form

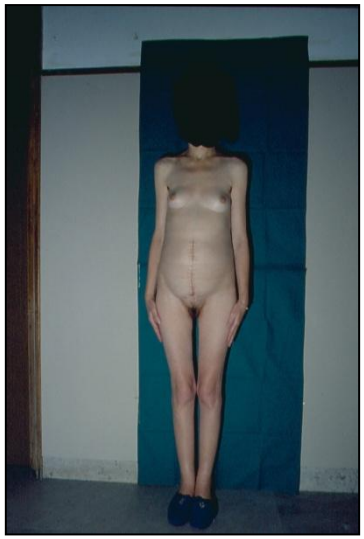
  (only serological positive results)
- **Potential** form

  (HLA-DQ2 and/or HLA-DQ8 positive results)

CELIAC DISEASE
Clinical Features

Can Develop at Any Age.

- *Diarrhea (> 200-300 g / 24h in adults)*
- *Constipation*
- *Steatorrhea*
- *Asthenia*
- *Weight Loss*
- *Dyspepsia And Vomiting*
- *Stop Growth*
- *Iron Deficiency Anemia*
- *Osteoporosis*
- *Amenorrhea*
- *Poliabortivity*
- *Sterility*
- *Vitiligo*
- *Cerebellar Ataxia*
- *Tetanus Crisis*
- *Epilepsy*
- *Psoriasis*
- *Dermatitis Herpetiformis*



- *Alopecia*
- *Aphthous Stomatitis*
- *Peripheral Neuropathy*
- *Hypoplasia Of Tooth Enamel*

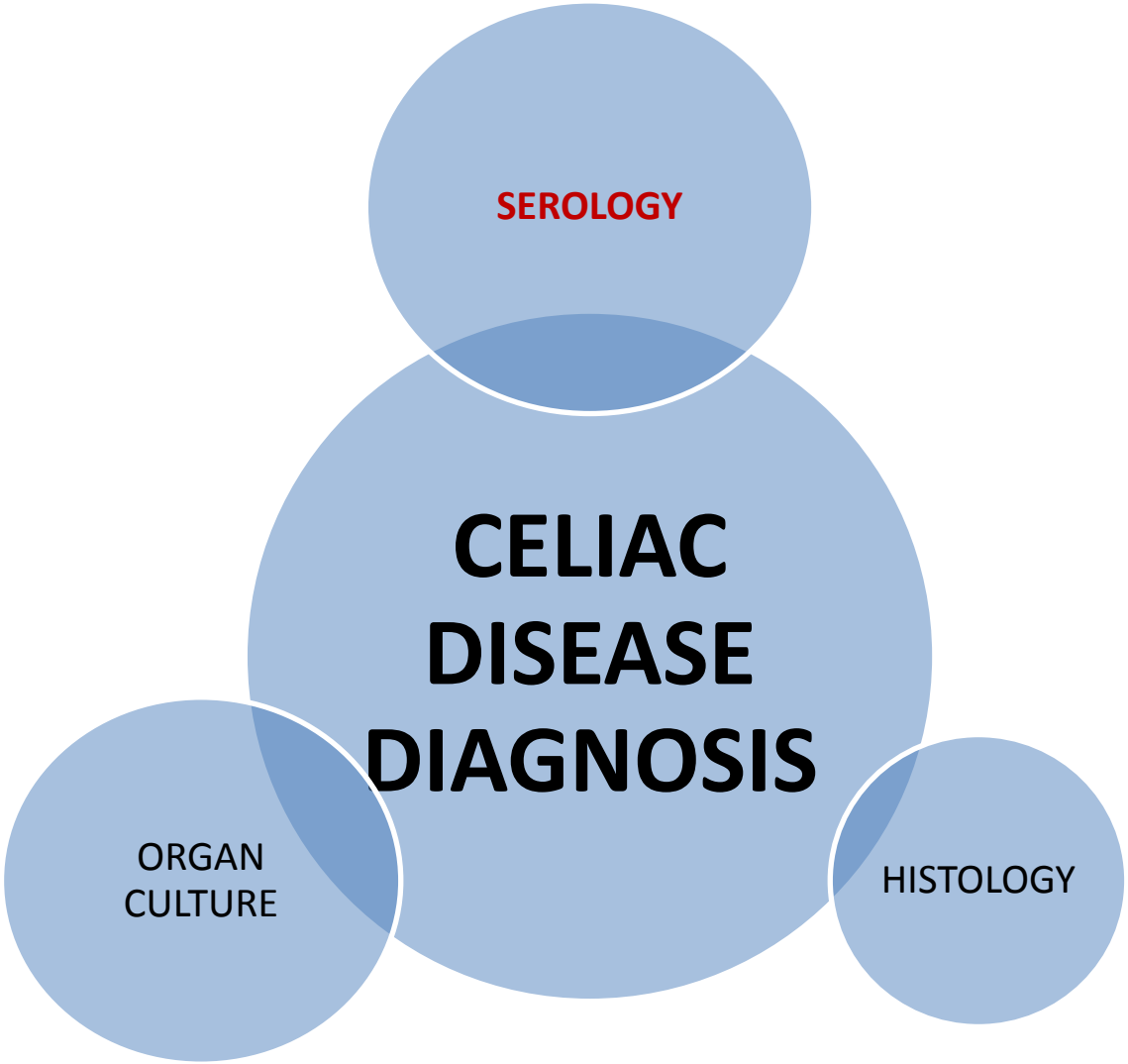
CELIAC DISEASE
Who Should Be Screen

Table 1. Proposal for Serologic Screening for Celiac Disease in Adults

Screening recommended	Screening recommended, when subtle symptoms consistent with celiac disease are present	Screening not necessary
Malabsorption, isolated iron deficiency[a]	Family history of celiac disease	General population
Infertility	Autoimmune thyroid disease	Acute or short-term gastrointestinal symptoms
Osteoporosis	Sjögren's syndrome	Atopic symptoms
Ataxia and polyneuropathy	Type I diabetes[b]	Type I diabetes[c]
Arthritis of unknown etiology	Addison's disease	
Chronic liver disease of unknown etiology	Autoimmune endocrinologic diseases in general	
Suspicion of dermatitis herpetiformis (consider skin biopsy)	Any chronic gastrointestinal symptoms[a]	
Irritable bowel syndrome[a]		
Lactose intolerance		

[a]Consider small intestinal biopsy when screening test is negative.
[b]With symptoms indicative of celiac disease.
[c]Without any symptoms indicative of celiac disease.

Pekka Collin - Gastroenterology 2005


SEROLOGY
CELIAC DISEASE DIAGNOSIS
ORGAN CULTURE
HISTOLOGY

Am J Gastroenterol. 2010

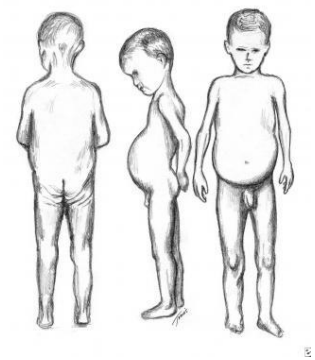
Update on serologic testing in celiac disease.

Leffler DA, Schuppan D.

Table 1. Summary of test characteristics of celiac serologies

Test	Sensitivity (reported range) (%)	Specificity (reported range) (%)	Positive predictive value(%),pretest probability of 5%	Negative predictive value (%), pretest probability of 5%
IgA AGA	85 (57–100)	90 (47–94)	18	99
IgG AGA	85 (42–100)	80 (50–94)	31	99
EMA	95 (86–100)	99 (97–100)	83	99
IgA anti-tTG[a]	98 (78–100)	98 (90–100)	72	99
IgG anti-tTG[b]	70 (45–95)	95 (94–100)	42	99
IgA anti-DGP	88 (74–100)	95 (90–99)	44	99
IgG anti-DGP	80 (63–95)	98 (90–99)	68	99
IgA/IgG anti-DGP	97 (75–99)	95 (87–100)	51	99

Is it possible to diagnose CD without duodenal biopsy ? (1)



The new ESPGHAN 2012 guidelines for diagnosis of **pediatric CD**
avoid biopsy if:

- HLA DQ2/DQ8+
- symptomatic (gluten-related)
- EMA+ / anti-tTG+ (ULN >x10)

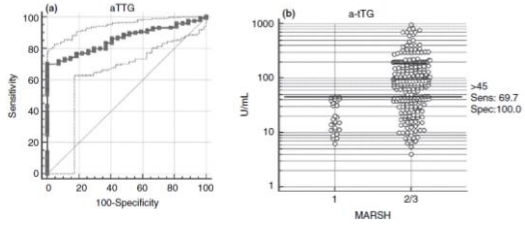


Figure 1
a-tTG 45 U/mL (**ULN x6.4**) → **Marsh ≥2**

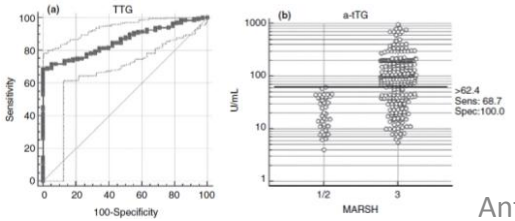


Figure 2
a-tTG 62.4 U/mL (**ULN x8.9**) → **Marsh 3**

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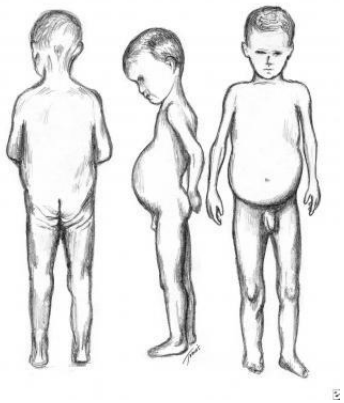
Tortora R. et al. Aliment Pharmacol Ther. 2014

Is it possible to diagnose CD without duodenal biopsy ? (1)



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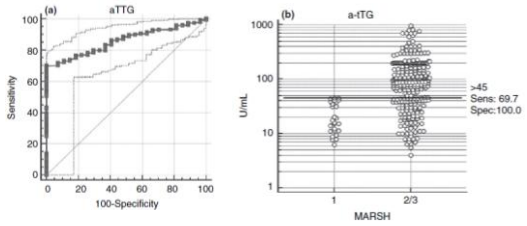

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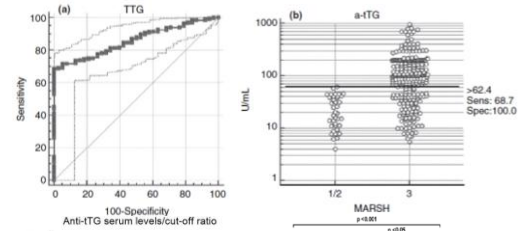

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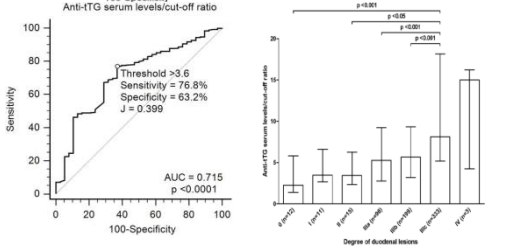

Figure 3
(**ULN x3.6**) → **Marsh 3**

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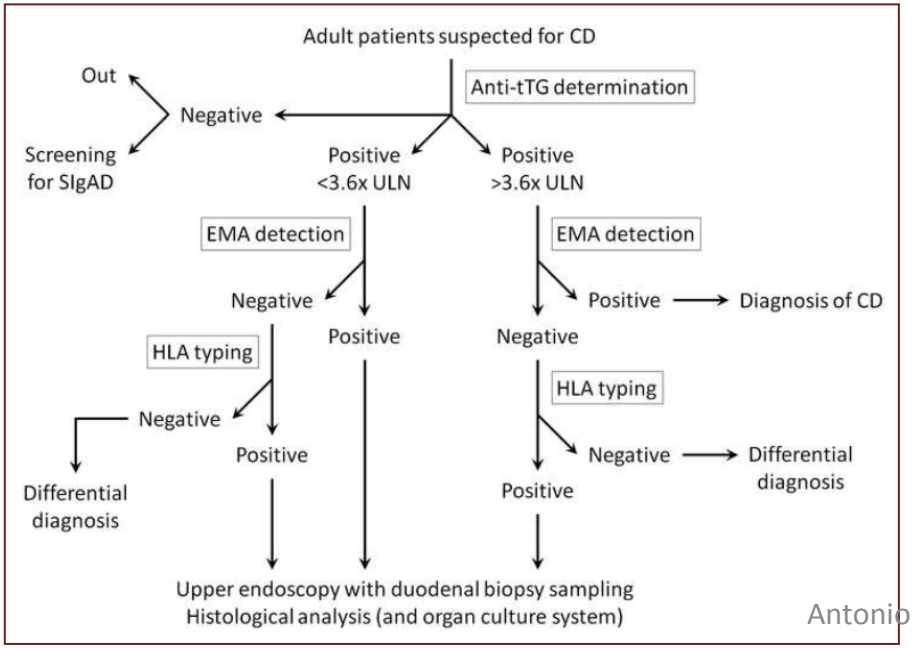
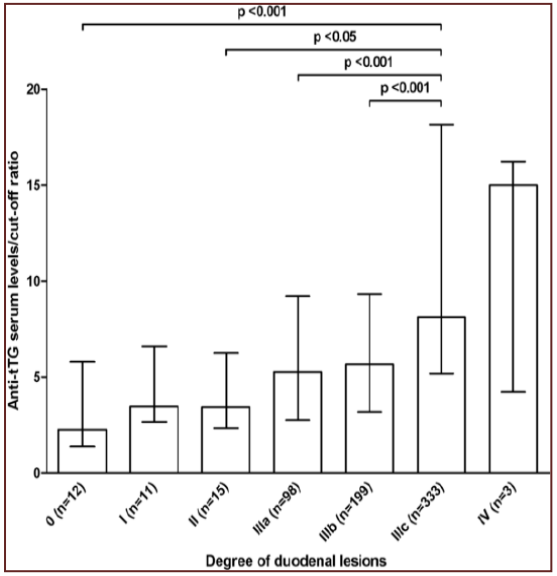
Tortora R. et al. Aliment Pharmacol Ther. 2014
Di Tola M, Picarelli A, Borghini R, et al. J Gastroenterol. 2016

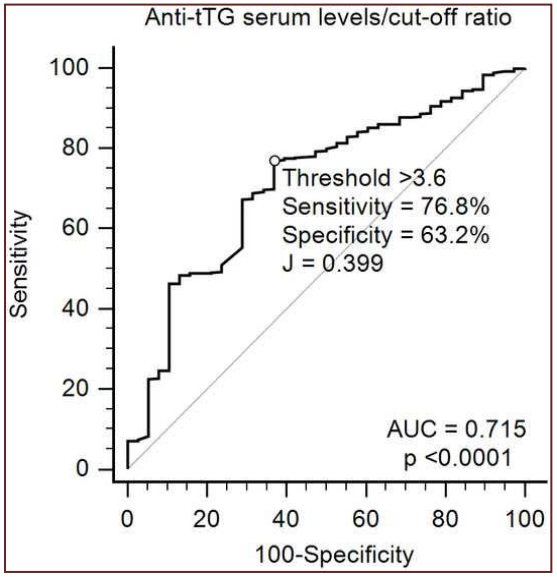
Is it possible to diagnose CD without duodenal biopsy ? (2)

Table 1– Diagnostic performance of anti-tTG serum levels/cut-off ratio obtained using different threshold values

Diagnostic performance	Anti-tTG serum levels/cut-off ratio	
	Threshold value >3.6	Threshold value >10
Sensitivity % (95% CI)	76.8 (73.3 – 80.0)	33.5 (29.8 – 37.3)
Specificity % (95% CI)	63.2 (46.0 – 78.2)	89.5 (75.2 – 97.1)
Youden index	0.399	0.230
PPV % (95% CI)	97.2 (95.4 – 98.5)	98.1 (95.3 – 99.5)
NPV % (95% CI)	14.0 (9.2 – 20.2)	7.5 (5.2 – 10.3)
Diagnostic accuracy % (95% CI)	76.0 (72.6 – 79.1)	36.7 (33.1 – 40.4)







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Di Tola M, Picarelli A, Borghini R, et al. J Gastroenterol 2016

Ab detection **MUST BE PERFORMED**:

- on a gluten containing diet

Ab detection **SHOULD NOT BE PERFORMED**:

- on a gluten free diet
- during immonosoppressive therapy

IMPORTANT !

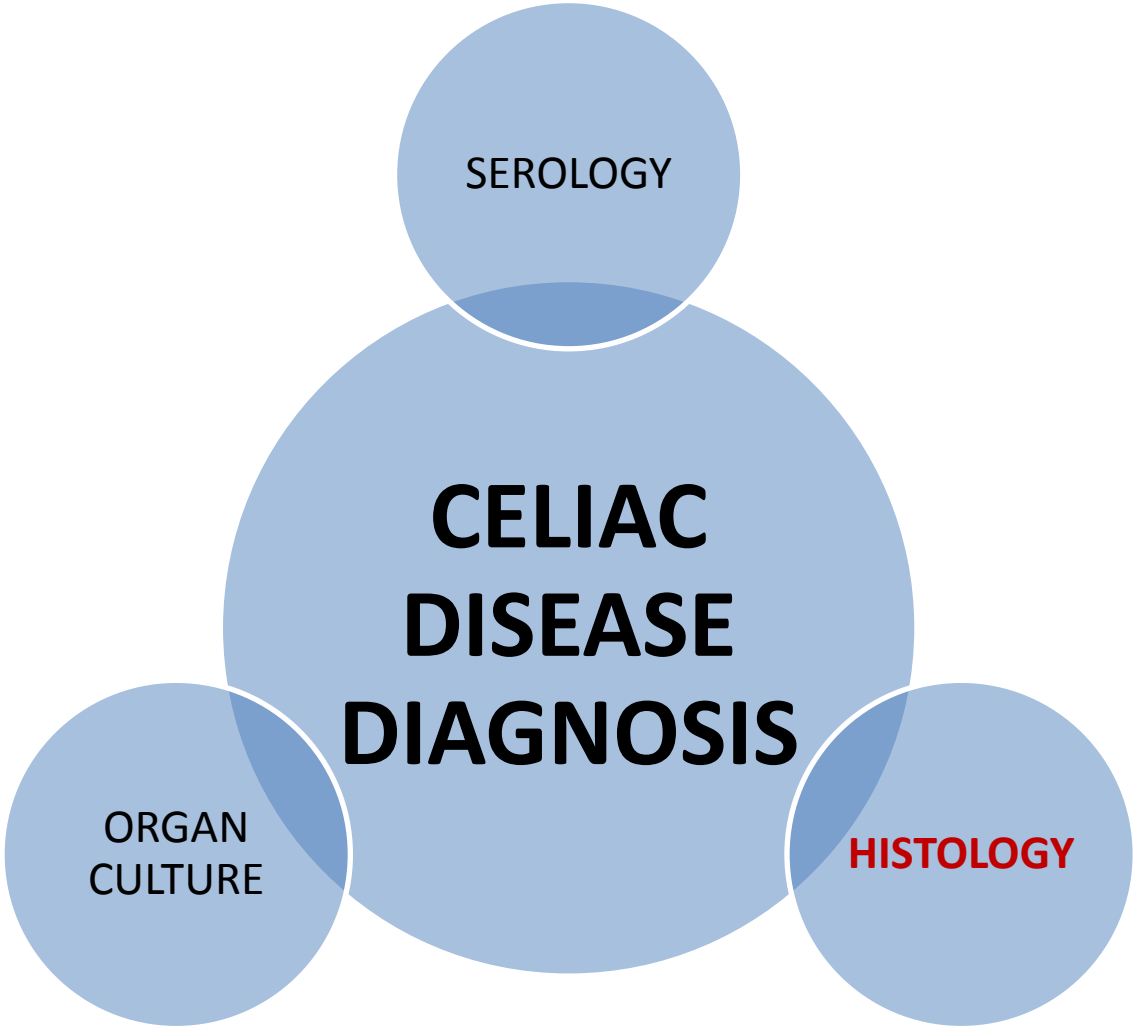
Gluten challenge (reintroduction)
necessary if gluten free diet have been already started.

Tortora R. et al. - Am J Gastroenterol 2011

It is mandatory to be very confident while making diagnosis of CD because its treatment consists of an **absolute and lifetime gluten-free diet (GFD).**

The use of **non-standardized food intolerance tests** and/or the **absence of a correct diagnostic work-up** can be **misleading**.

Mazzarella G. et al. – Gastroenterology 2008.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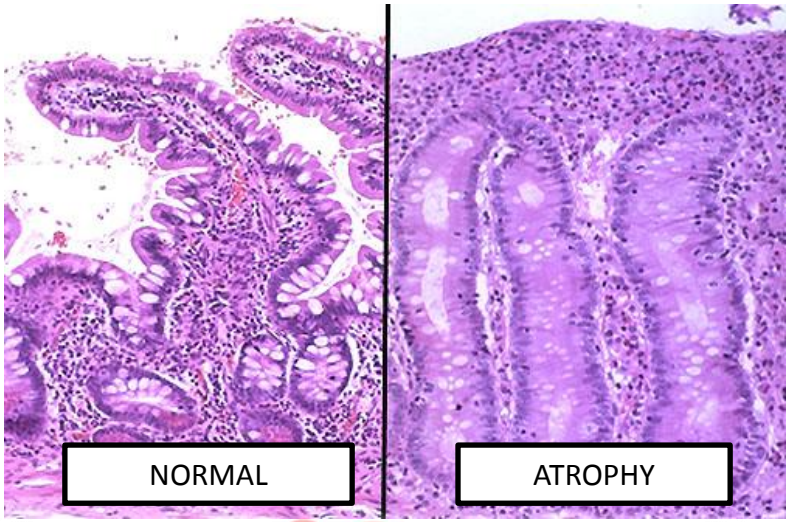
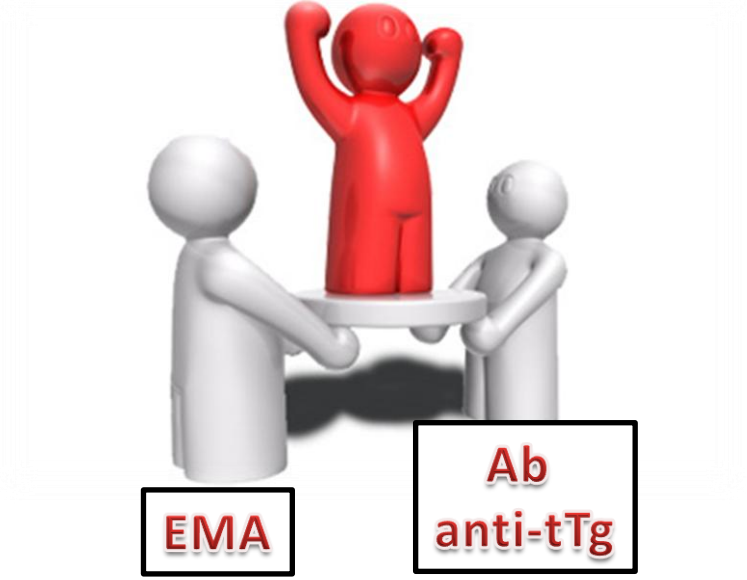
HISTOLOGY

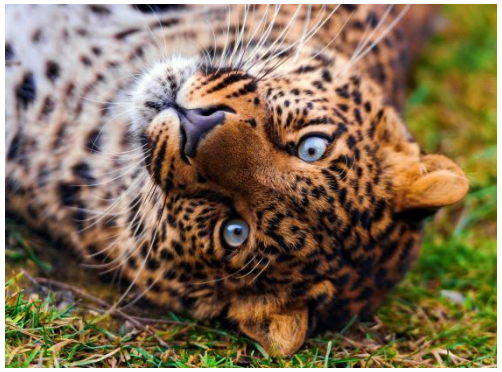
HISTOLOGY:
Gold stard for CD diagnosis → duodenal mucosa atrophy



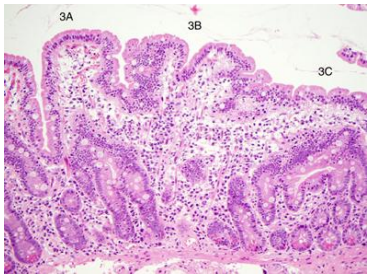


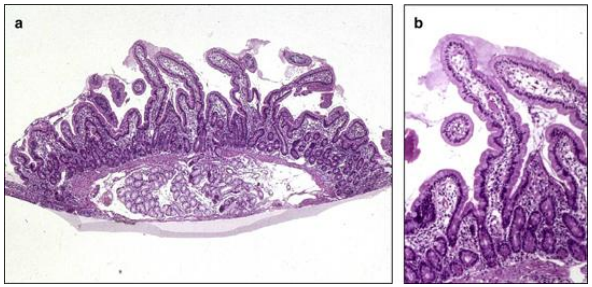
Di Sabatino A. at al. Lancet 2009
Ciacci C. et al. Gastroenterology 2002

LIMITS OF HISTOLOGY



- Sampling site (**patchy lesions**)
  - Variability **within the same** biopsy
  - **Cutting** technique/**orientations**





- Specific **experience** level of the histologist
- **lack of uniformity** in the use of Marsh–Oberhuber classification

Picarelli et al. Scand J Gastroenterol. 2014
Bao F et al. Arch Pathol Lab Med. 2012
Ravelli A et al. Pathol Res Pract. 2012

The Spectrum of Intestinal Non-celiac Villous Atrophy

- **Giardiasis**
- **Viral enteritis**
- **Whipple disease**
- **Tropical sprue**

- **Adult autoimmune enteropathy**

(serum Ab against enterocytes or goblet cells; Anti-transglutaminase antibodies in 1/3 pts;

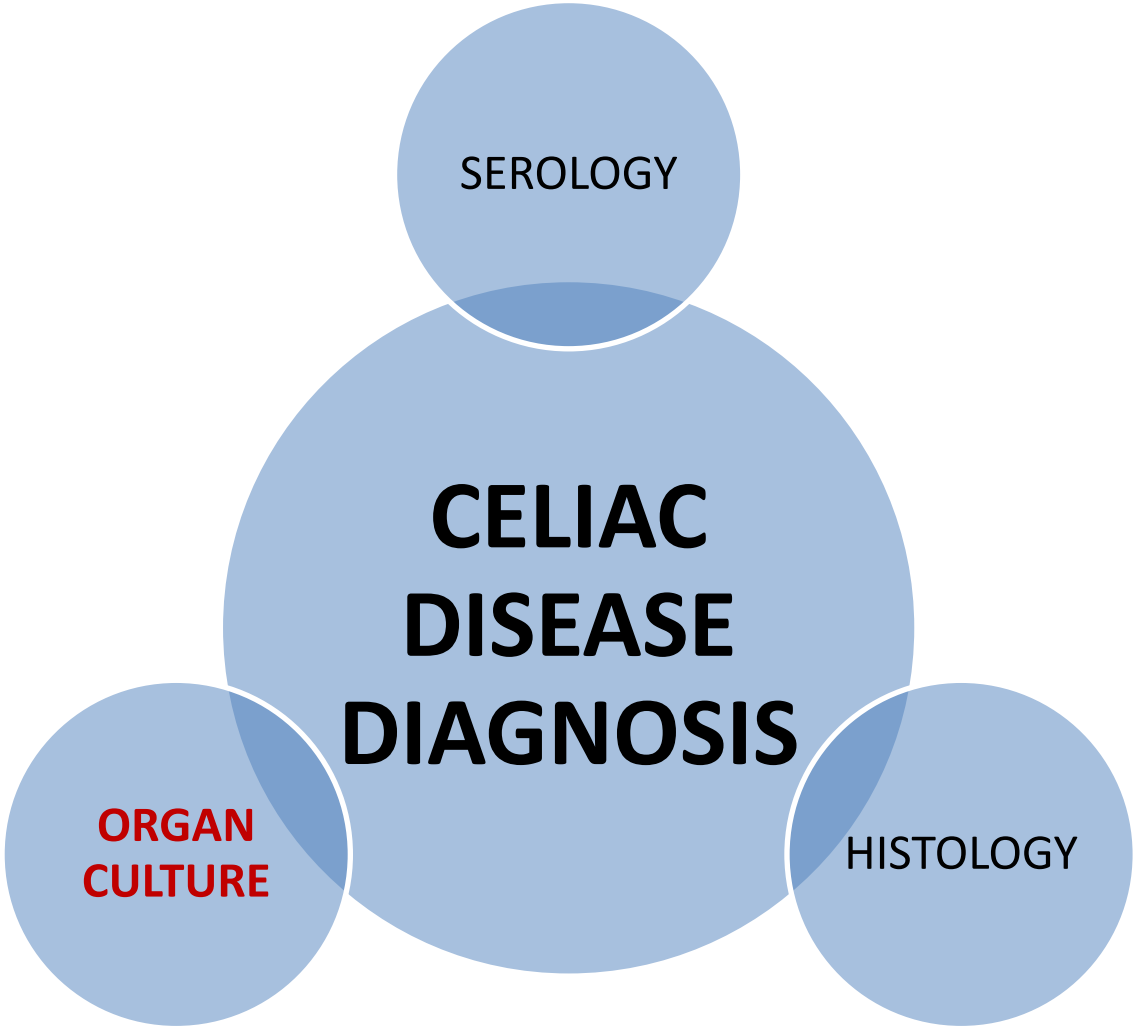
- **Hypogammaglobulinemia**
- **Common variable immunodeficiency (CVID)**

(chorionic plasmocytic rarefaction, nodular lymphoid hyperplasia, serum protein electrophoresis, frequent upper respiratory tract infections)

- **Crohn's disease**
- **Peptic duodenitis**
- **Collagenous sprue**

- **Mycophenolate mofetil**
- **Olmesartan**

Malamut G. et al. Expert Rev Gastroenterol Hepatol. 2015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HISTOLOGY

NEW DIAGNOSTIC OPPORTUNITY:

Cultural gluten challenge of duodenal biopsies

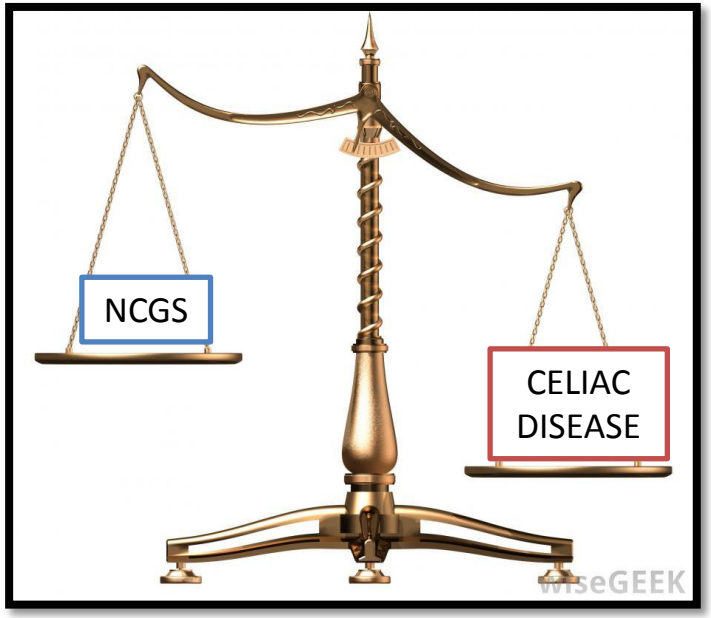
in patients:

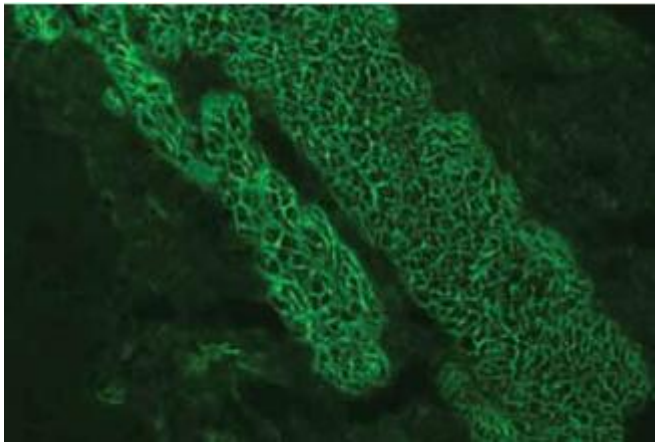
- with **atypical** CD
- already on a **GFD**
- in need of diagnostic **confirmation**

Khalesi M. et al. J Pediatr Gastroenterol Nutr. 2015

ARE WE DIAGNOSING TOO MANY PEOPLE WITH NON-CELIAC GLUTEN SENSITIVITY (NCGS)? USEFULNESS OF THE ORGAN CULTURE SYSTEM:

- **gluten-related signs and symptoms**
- **doubtful** serological EMA and anti-tTG IgA
- histology **not diagnostic** for CD
- HLA DQ2+
- **clear positive** EMA and anti-tTG IgA of II PD biopsy cultures





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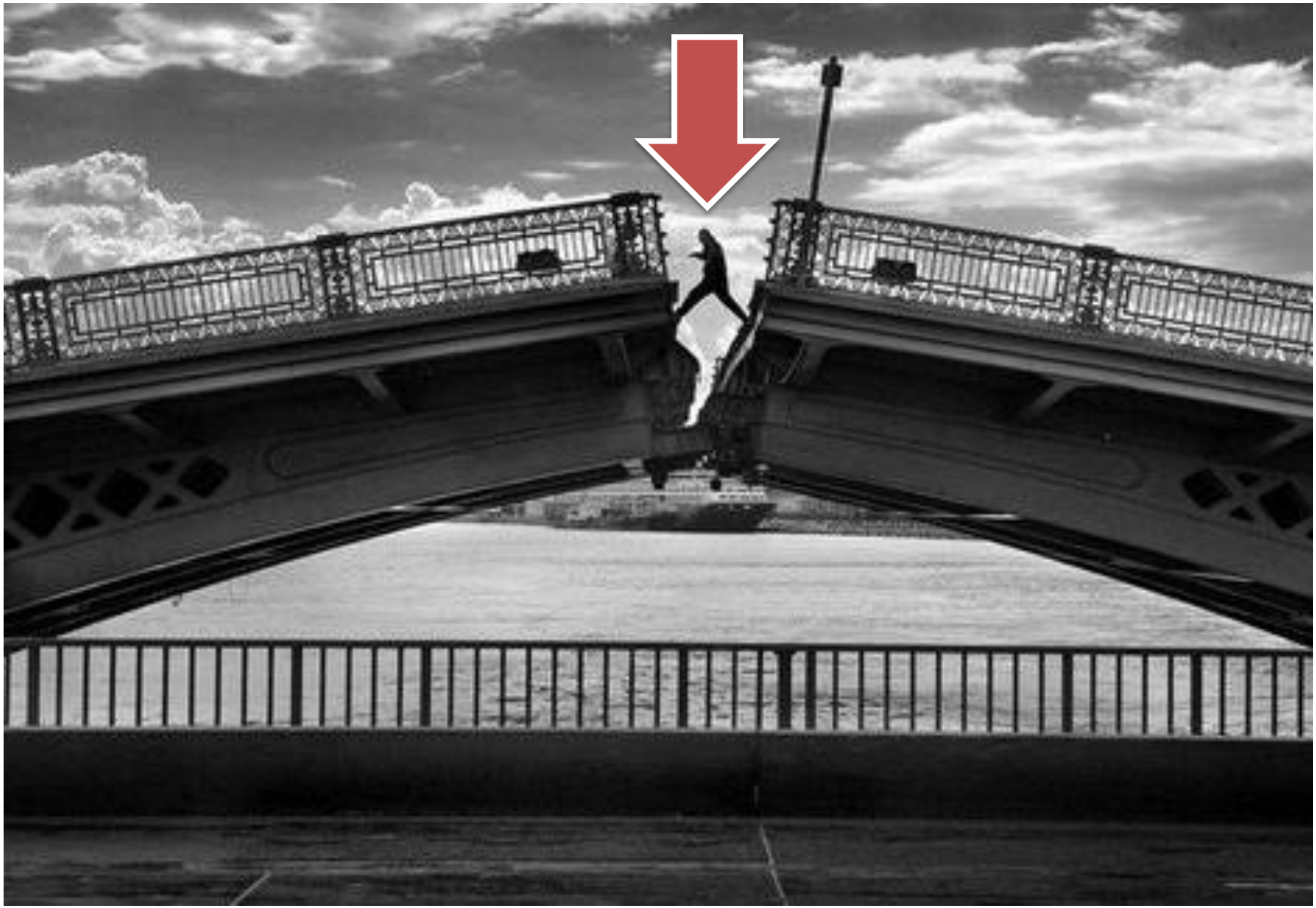
Borghini R., Picarelli A., et al. Turk J Gastroenterol. 2014

CD - causes of persistent symptoms

- Most common **causes of persistent symptoms (despite serological/histological negative results for CD)**:
  - constipation (low fiber in GFD)
  - lactose/fructose intolerance
  - Ni-containing foods adverse effect
  - microscopic colitis
  - FODMAPs
  - IBS

- And don't forget….
  - NSAIDs
  - infection
  - Crohn's Disease
  - Intestinal non-celiac villous atrophy
  - Microbiota/bacterial overgrowth



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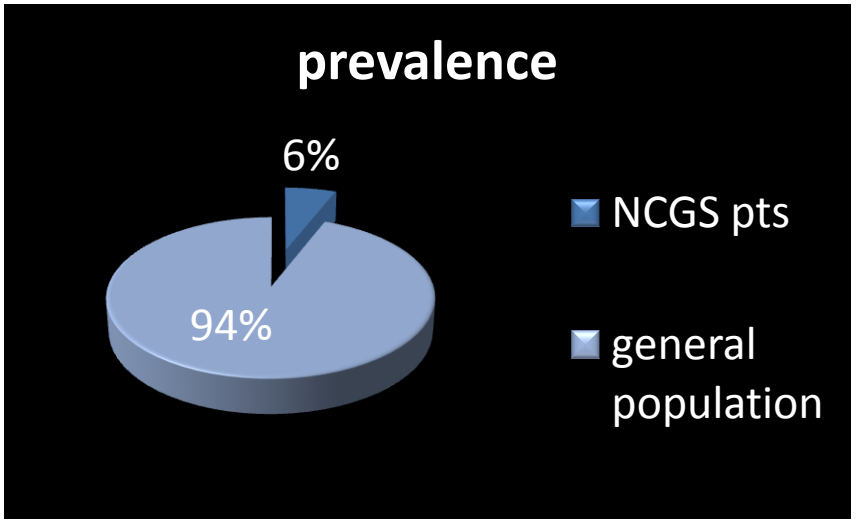
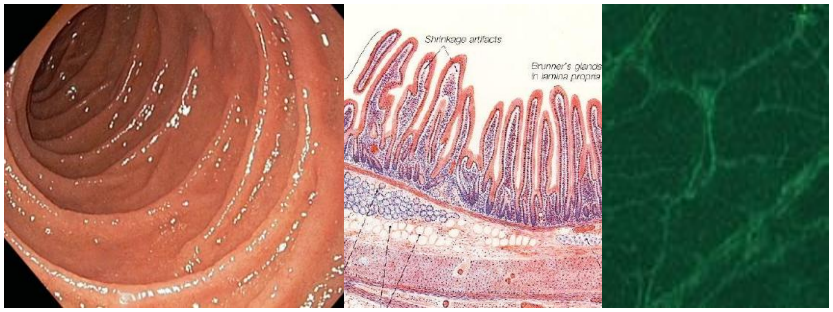
NON-CELIAC GLUTEN SENSITIVITY

- **PREVALENCE:** 6 %

- **IgG AGA (+)**: only 56,4%
- **HLA DQ2 and/or DQ8:** less than 50%
- **HISTOLOGICAL PICTURE** (duodenal biopsy)**:**
  often no specific alterations



MANIFESTATIONS	
Intestinal	Extraintestinal
diarrhea	headache
abdominal pain	Foggy mind
bloating	attention-deficit/ hyperactivity disorder
	ataxia
	recurrent oral ulceration
	psoriasis



- **THERAPY:** gluten-free diet

Sapone A et al. - BMC Med 2012
Bizzaro N et al. - Clin Rev Allergy Immunol. 2012

NON-CELIAC GLUTEN SENSITIVITY

Symptoms…

may appear **after hours or even days** after gluten ingestion

symptoms withdraw after gluten-free diet

Non-Celiac Gluten Sensitivity and Celiac Disease Comorbidity For Autoimmune Diseases

	Type 1 Diabetes	Autoimmune Thyroiditis
Non-Celiac Gluten sensitivity	0	1%
Celiac Disease	5-10%	12.5%

Volta U, J Clin Gastroenterol 2011

Outcome della Gluten Sensitivity

Ipotizzata assenza di comorbimidità autoimmune (?)

Ipotizzata assenza di evoluzione in linfoma ed adenocarcinoma del tenue (?)

Non esisterebbe il problema della contaminazione

Intestinal, Systemic And Oral Gluten-related Alterations In Patients With Non-celiac Gluten Sensitivity

Study: 60 NCGS patients, 20 untreated CD, 20 treated CD and 20 healthy volunteers were recruited. The differential diagnosis among gluten-related disorders was performed by serological, allergy and histological tools. NCGS patients were also subjected to anti-gliadin antibody (AGA) detection and HLA typing. All participants underwent oral mucosa patch test for gluten (GOMPT), while oral provocation test (OPT) for gluten was performed in 26 NCGS patients.

Results: 6/60 (10%) NCGS patients showed IgG AGA positive results, while 45/60 (75%) carried HLA-DQ2 and/or -DQ8 genes. GOMPT showed positive results in 45/60 (75%) NCGS patients, 3/20 (15%) untreated CD, 5/20 (25%) treated CD and in no healthy volunteer. No significant difference was found between the severity of symptoms reported by NCGS patients subjected to OPT with gluten-containing croissants and those who underwent OPT with gluten-free croissants.

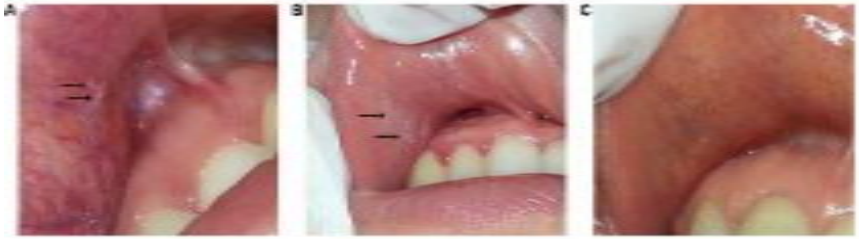


Figure 1 – Local lesions at 2 hours from the application of GOMPT
Blisters of the upper lip mucosa (arrows) after administration of GOMPT in two NCGS patients [A,B]. No lesion of the upper lip mucosa after application of GOMPT in a healthy control [C].

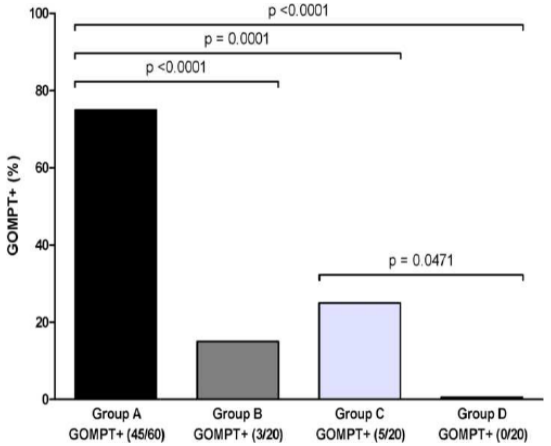


Figure 2 – GOMPT results in the four studied groups

Group A: NCGS pts
Group B: untreated CD pts
Group C: treated CD pts
Group D: healthy pts

Conclusions: GOMPT seems to be a specific tool for NCGS diagnosis, although further investigations are needed to overcome limits due to the small population studied and to contextualize GOMPT false positive results.

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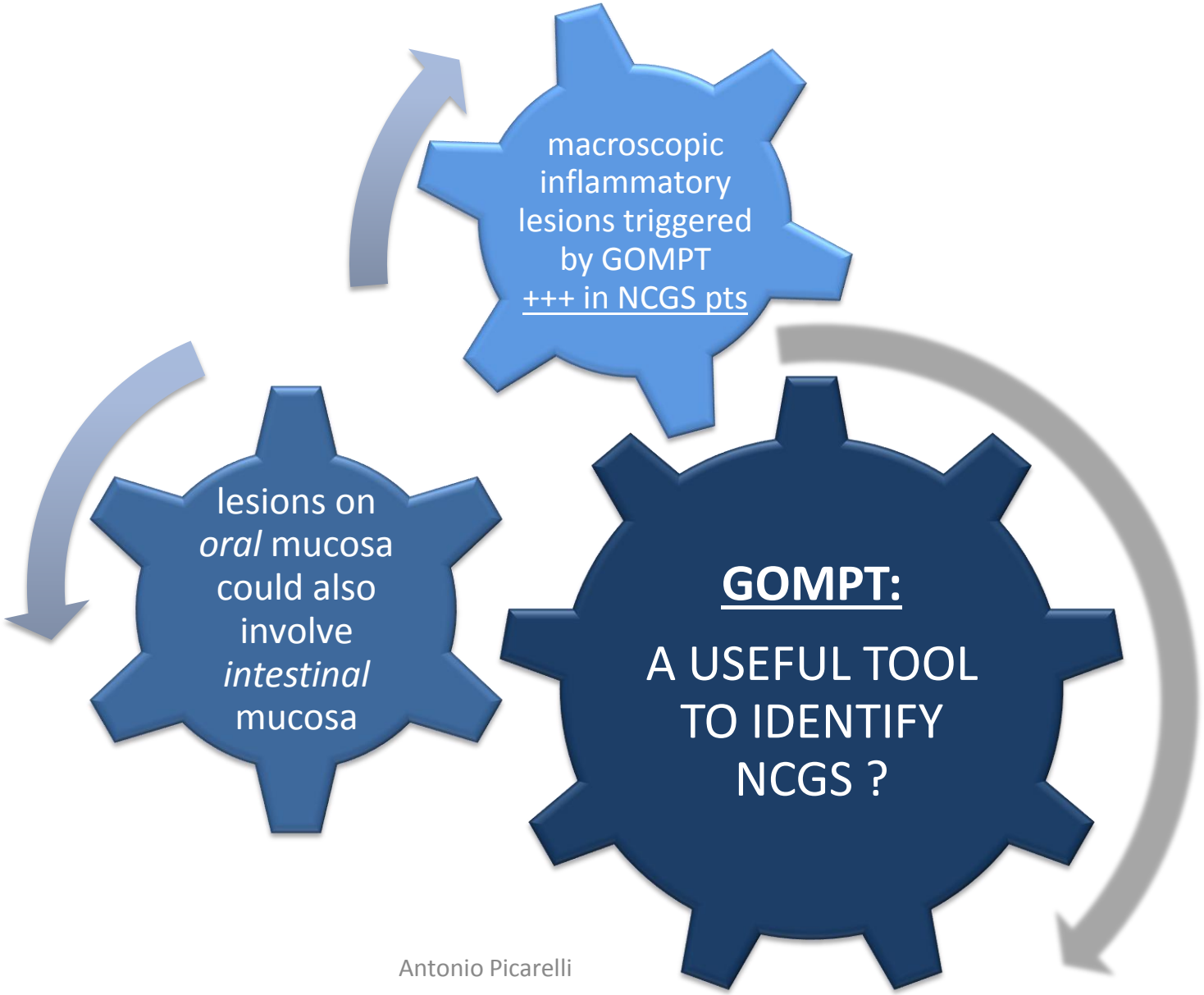
Picarelli A, et al. J Clin Gastroenterol 2016

…and DISCUSSION



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