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# 2nd International Expert Meeting on Gluten Sensitivity

Munich, December 1st 2012

## **NON CELIAC GLUTEN SENSITIVITY IN ADULTS: CLINICAL AND SEROLOGICAL ASPECTS**

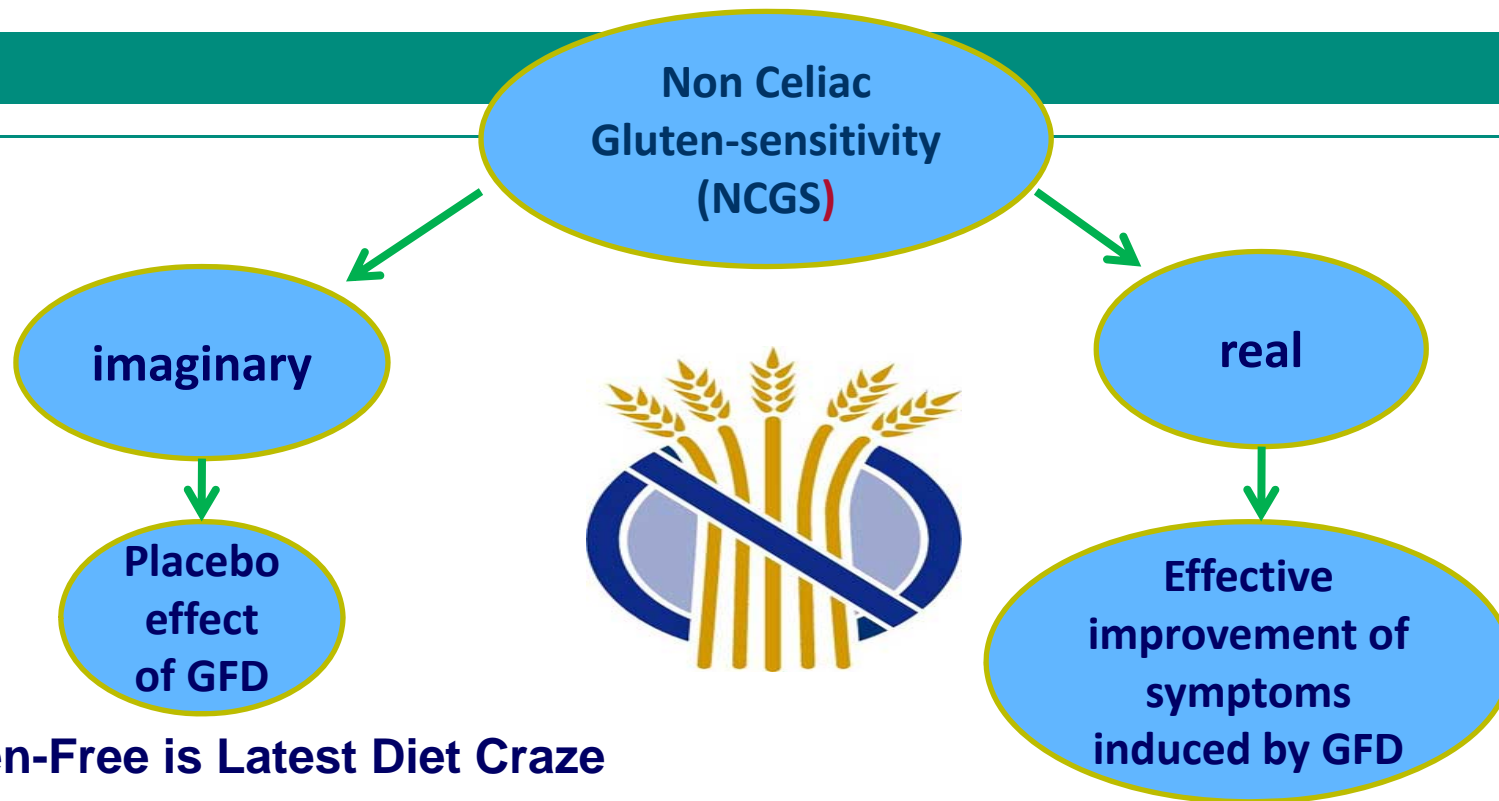
*Umberto Volta*

*Coeliac Disease and Malabsorption Unit*

*St.Orsola-Malpighi Hospital*

*AIC Board Coordinator*





### Gluten-Free is Latest Diet Craze

Gwyneth Paltrow said she got rid of gluten to lose her extra “holiday” and Lady Gaga is the latest celebrity to embrace a gluten-free diet.



**NCGS is still a debatable entity because of the difficulty of objectively demonstrating this diagnosis which remains highly presumptive**

**USA TODAY  
2008**



A market survey has evidenced that 15-25% of the U.S. population (i.e., from 40 to 70 millions) think that to eat gluten-free is a food regimen for staying healthy



**The Washington Post  
2011**



The American press has hypothesized that 17 millions of U.S. citizens (i.e., 6% of the U.S. people) complain of gluten sensitivity although evidence-based data on its prevalence are lacking.



Gluten-free market is in a great expansion in U.S.

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## NCGS: an Internet problem or an emerging clinical entity?

### Media hype

The ratio between Google and PubMed citations for NCGS is higher than 5000:1

The number of Internet citations is more than 10 times higher than that for breast cancer, Alzheimer disease and gastric cancer

### Scientific production

In the last 2 years papers on NCGS in IF journals are rapidly increasing

However, most of them are reviews or commentaries with only a few clinical studies on series of NCGS patients



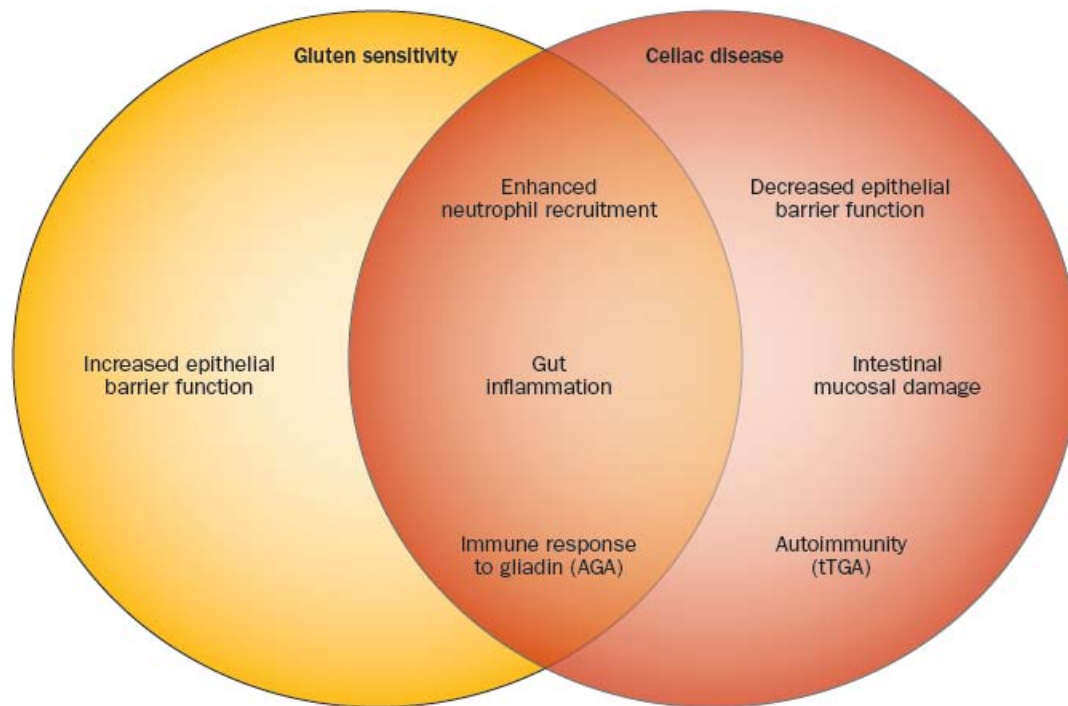
## THE FIRST DEMONSTRATION OF GLUTEN SENSITIVITY

Gluten-sensitive diarrhea without evidence of celiac disease  
Cooper BT, Holmes GKT et al Gastroenterology 1980

- Six of eight adult female patients suffering from abdominal pain and chronic diarrhea had dramatic relief on a GFD and return of symptoms after a double-blind cross-over challenge
- Previous attempts of treatment including a milk-free diet were ineffective
- Duodenal biopsy showed minor abnormalities (no villous atrophy)
- No immunological abnormalities were found in these subjects
- These 6 patients were diagnosed as having gluten-sensitive diarrhea without evidence of celiac disease



# New Understanding in Gluten Sensitivity



Which is/are the toxic component/s?

**gluten or wheat fractions (wheat amylase/trypsin inhibitor)**

**Unknown pathogenic mechanisms, including:**

**innate immunity, low-grade inflammation, starch carbohydrate malabsorption, etc..**



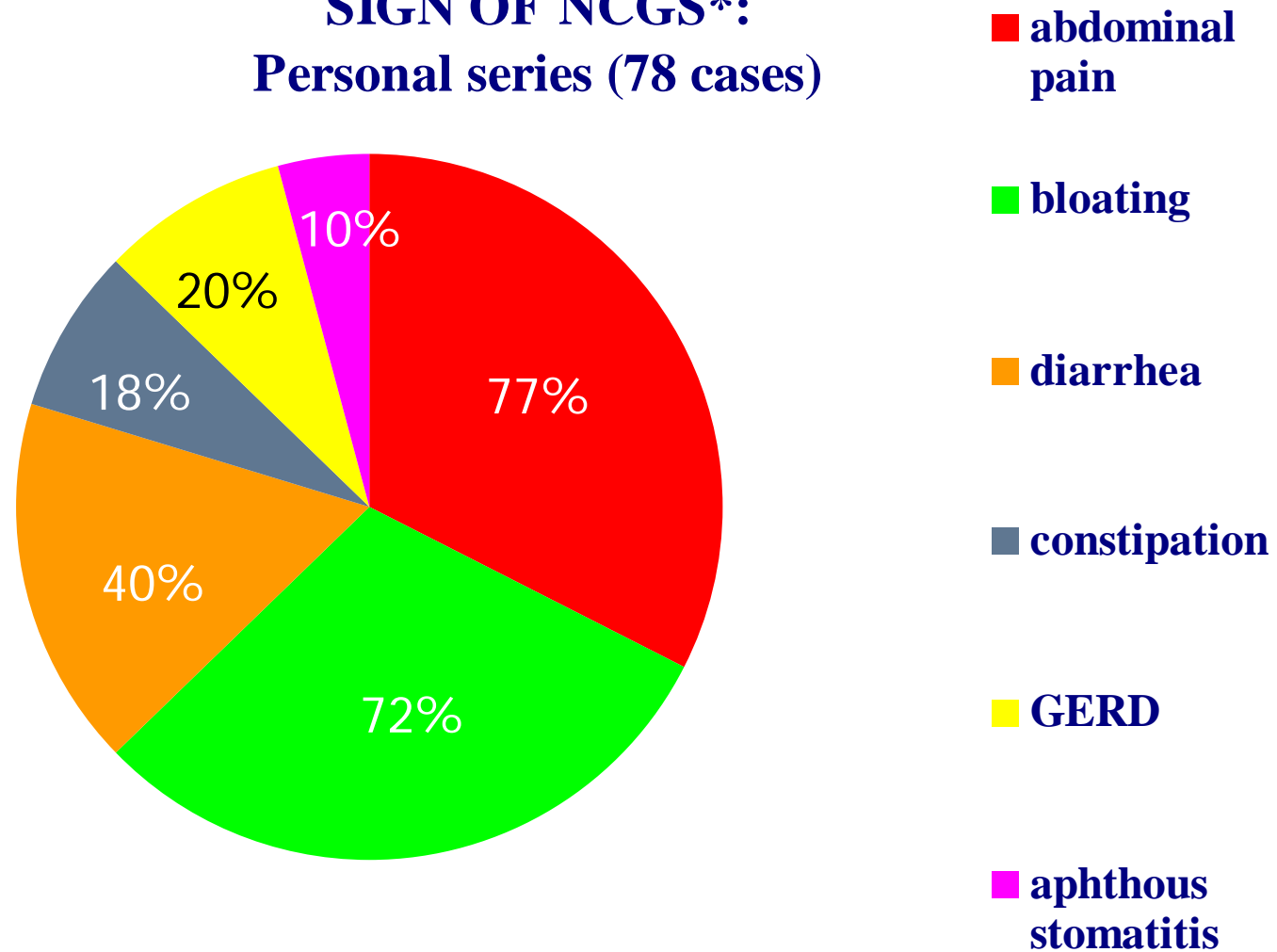
## Non Celiac Gluten Sensitivity(NCGS): Bologna experience

- Seventy-eight patients (56 females e 22 males – F/M = 2.5 : 1, median age 38 years, range 17-63) were diagnosed as having NCGS in the Coeliac Disease Unit of Bologna University between January 2009 and June 2011
- In all the 78 pts NCGS was suspected on the basis of intestinal and/or extraintestinal symptoms with an early onset (a few hours or days) after gluten ingestion. In all of them coeliac disease (CD) and wheat allergy were excluded by means of CD serology (EmA and tTGA), duodenal biopsy and and specific IgE/Prick tests to wheat.
- NCGS was confirmed by a trial of strict GFD for 6 months with a quick disappearance of symptoms, followed by an open gluten challenge of 1 month with an immediate relapse of the clinical picture
- All the 78 NCGS patients were tested for antibodies to gliadin of first (AGA) and second generation (DGP) as well as for HLA typing; total serum IgA were determined in order to exclude an IgA deficiency
- Antibody and genetic results obtained in the 78 NCGS patients were compared with those found in 80 CD patients



## GASTROINTESTINAL SYMPTOMS AS A SIGN OF NCGS\*:

Personal series (78 cases)



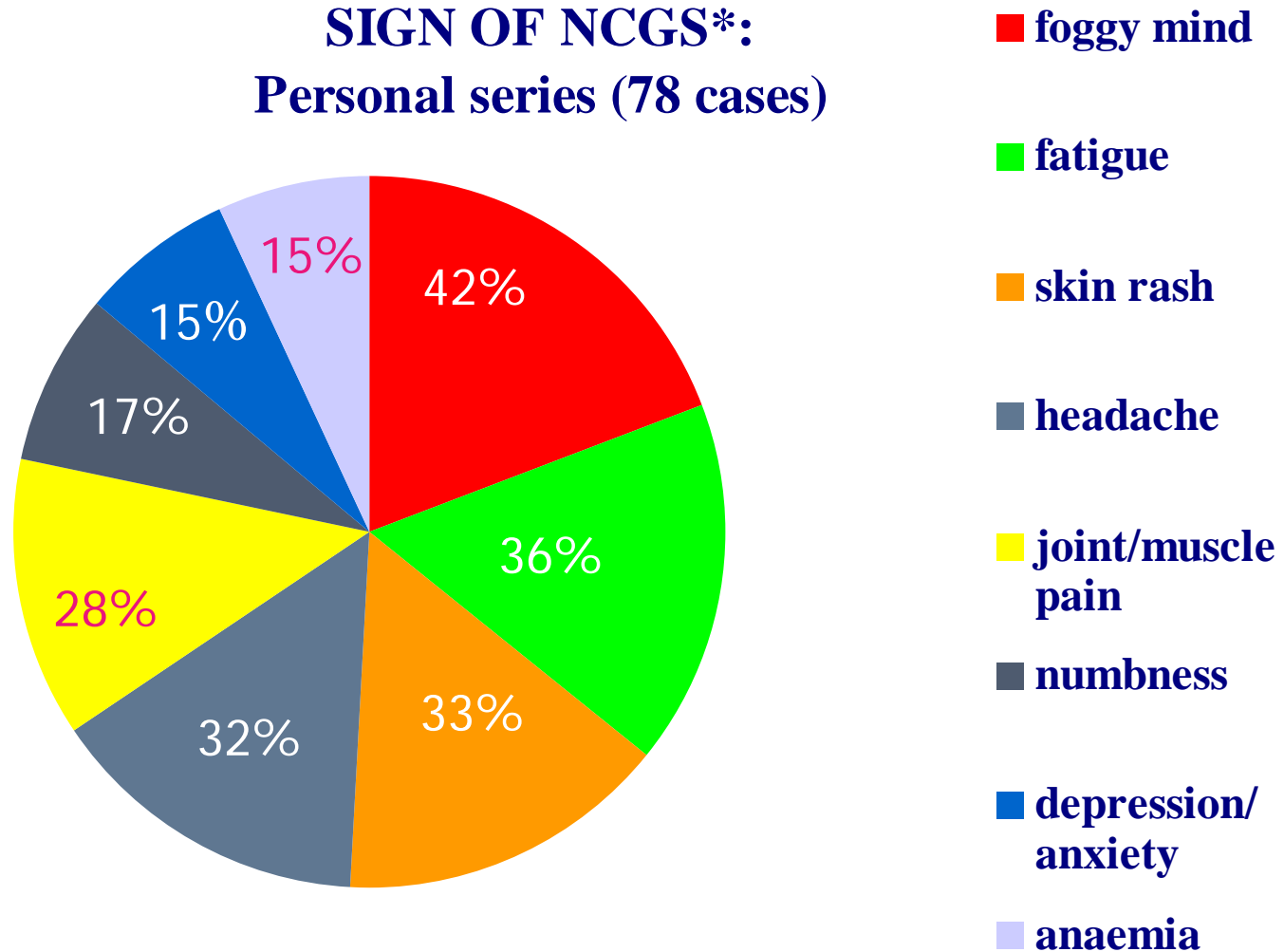
\*The majority of patients displayed more than 2 symptoms

Volta U et al, J Clin Gastroenterol 2012





## EXTRAIESTINAL SYMPTOMS AS A SIGN OF NCGS\*: Personal series (78 cases)

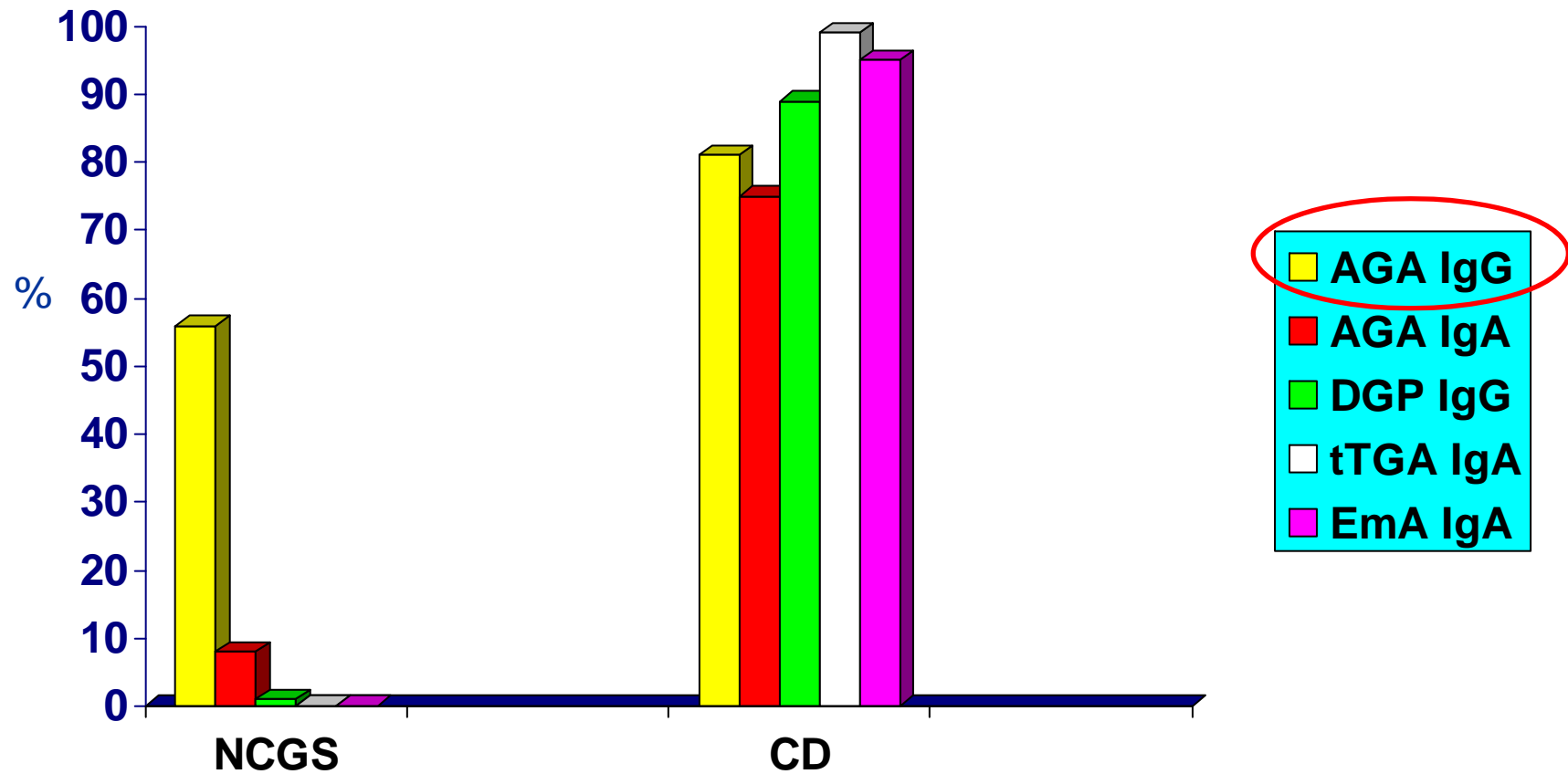


\*The majority of patients displayed more than 2 symptoms

Volta U et al, J Clin Gastroenterol 2012



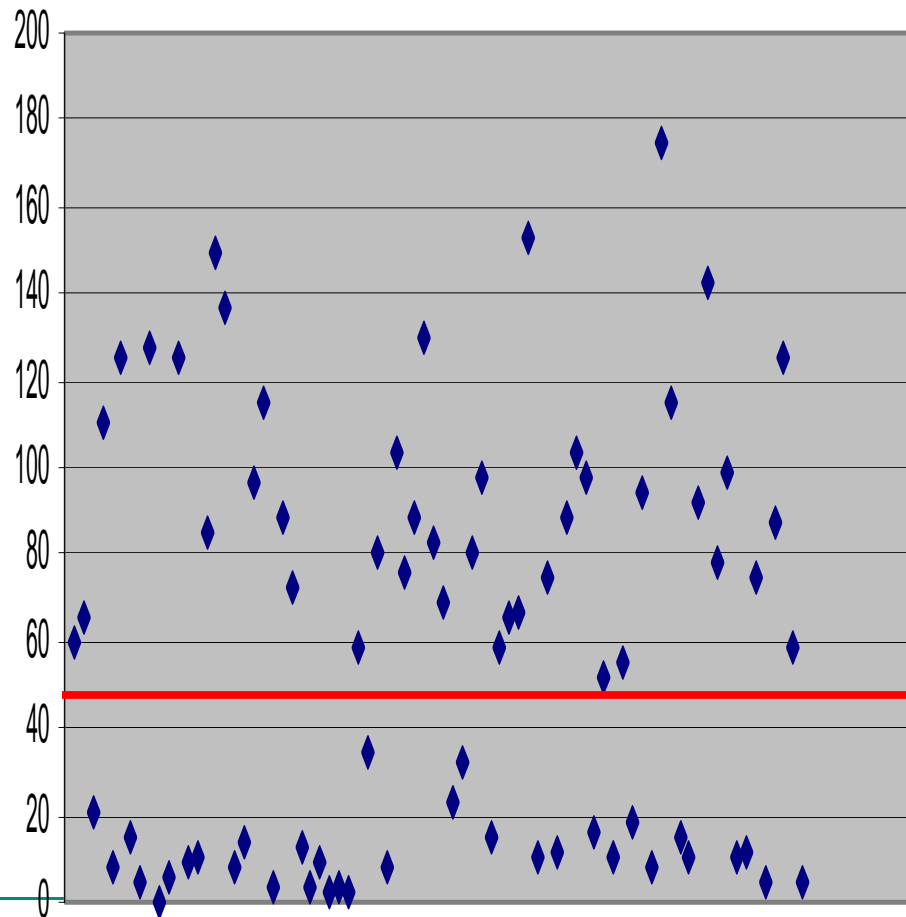
## Serology in non celiac gluten sensitivity (NCGS) and in celiac disease (CD)



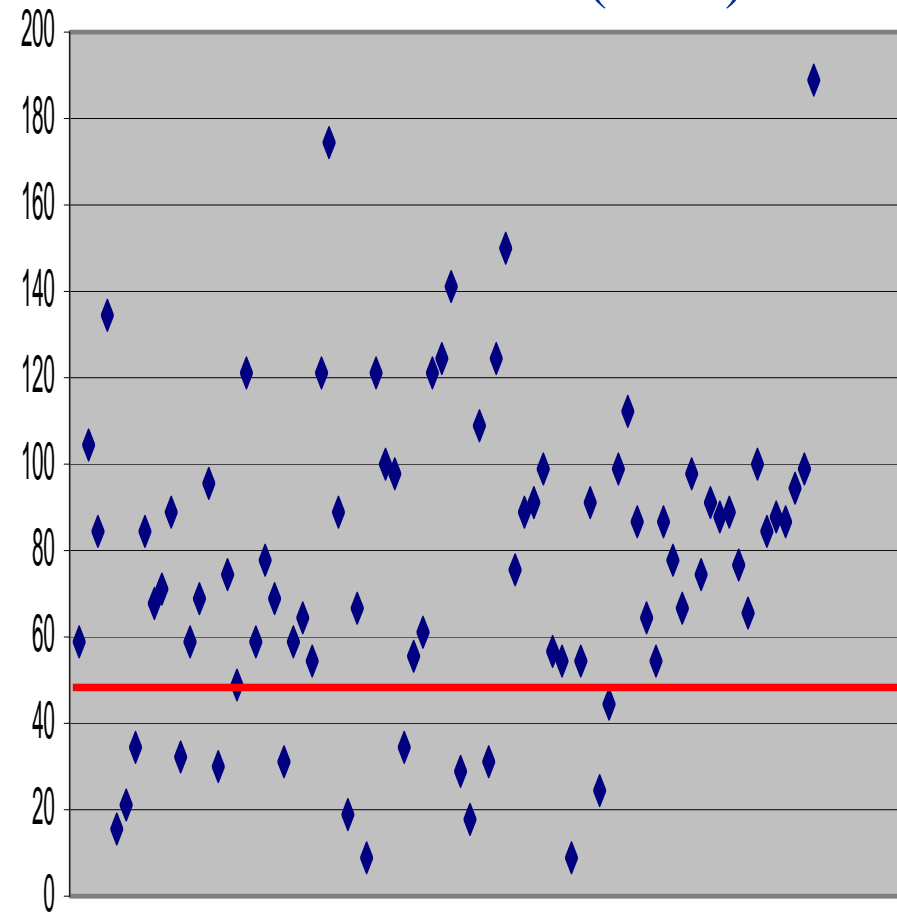


# AGA IgG (cut-off 50 AU)

**NCGS**  
Pos. 44/78 (56%)



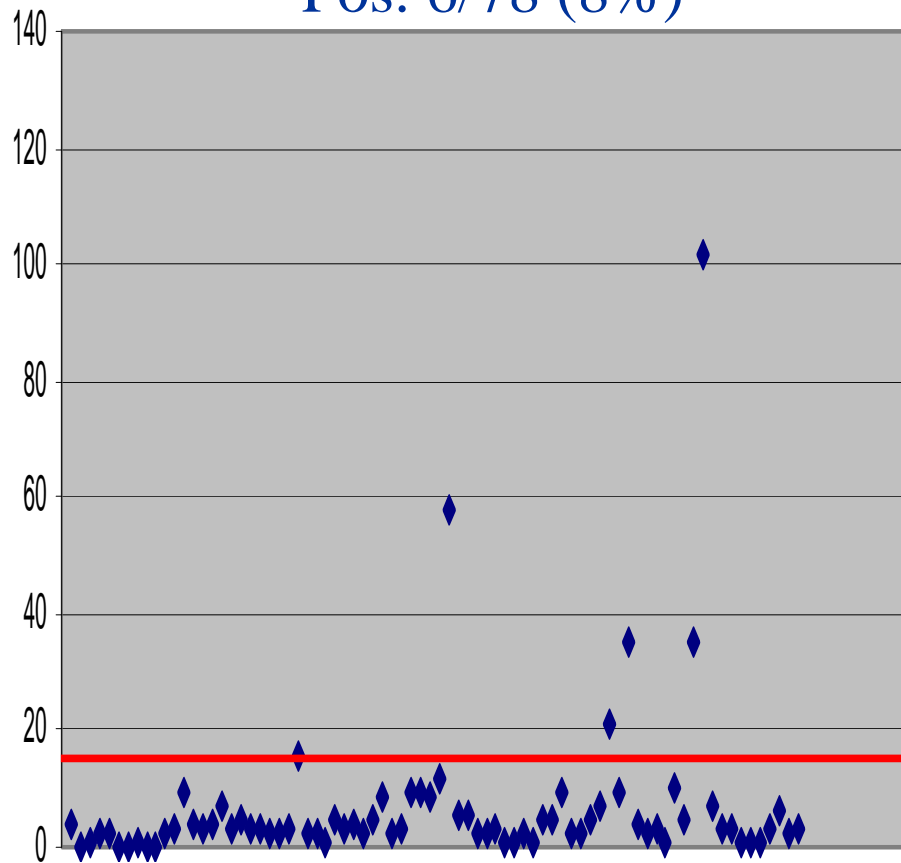
**Celiac Disease**  
Pos. 65/80 (81%)



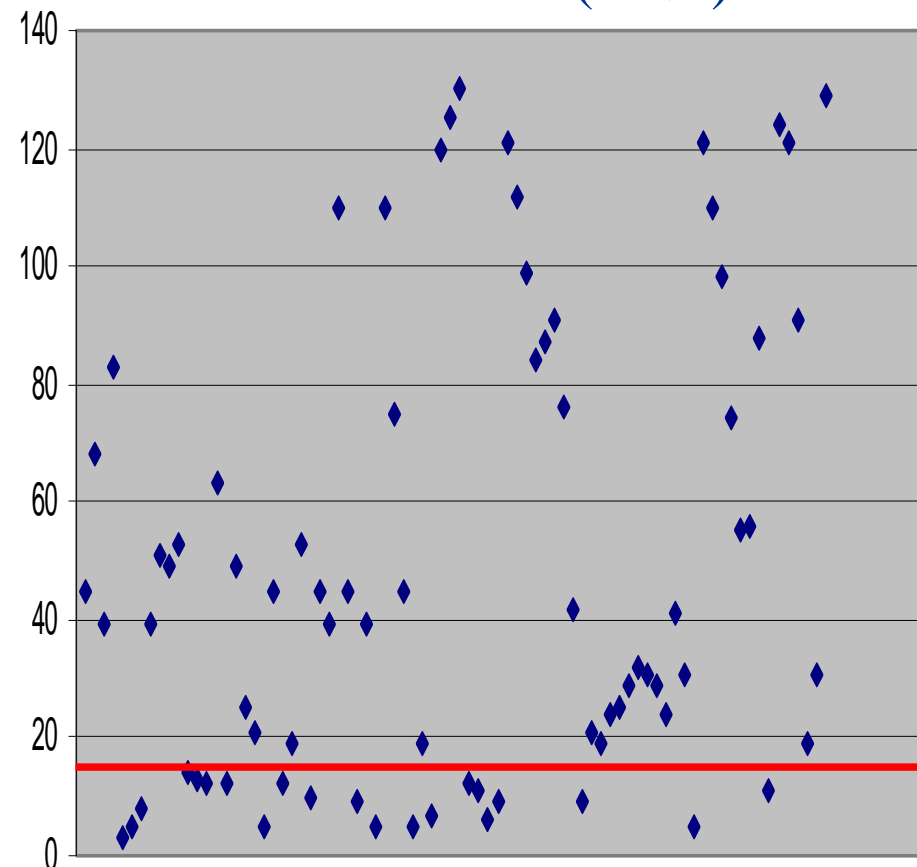


# AGA IgA (Cut-off 15 AU)

NCGS  
Pos. 6/78 (8%)



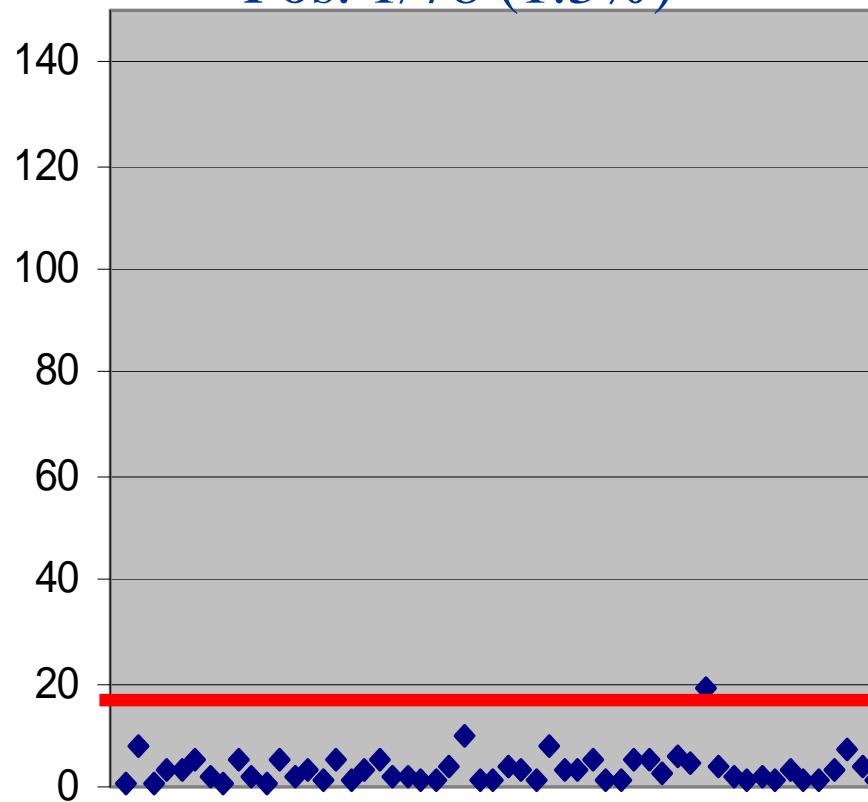
Celiac Disease  
Pos. 60/80 (75%)



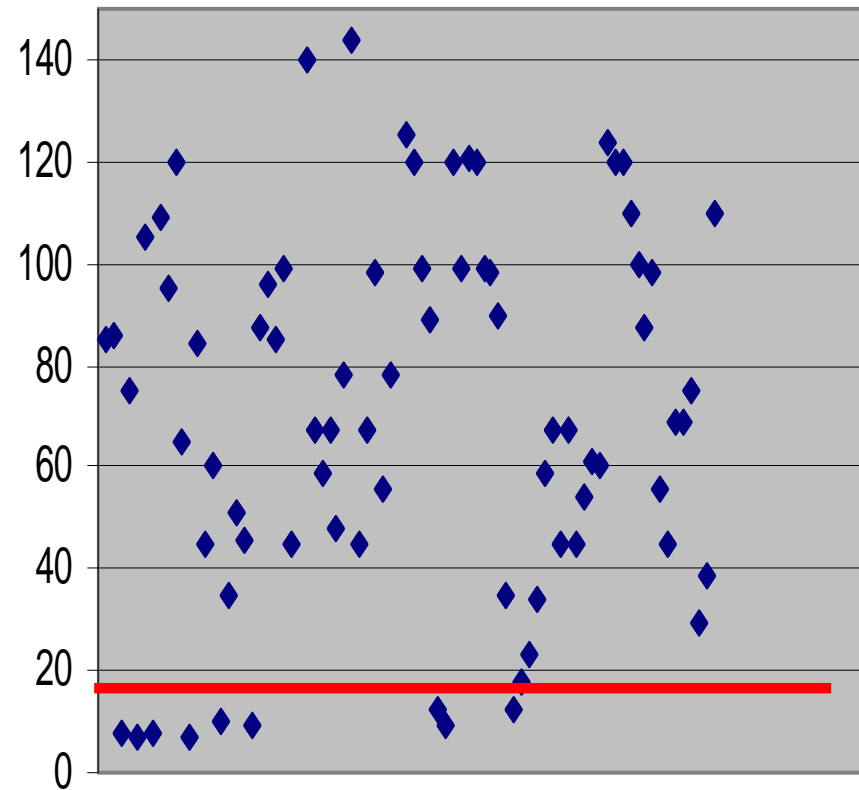
# DGP IgG (Cut-off 16AU)



NCGS  
Pos. 1/78 (1.3%)



Celiac Disease  
Pos. 72/80 (89%)



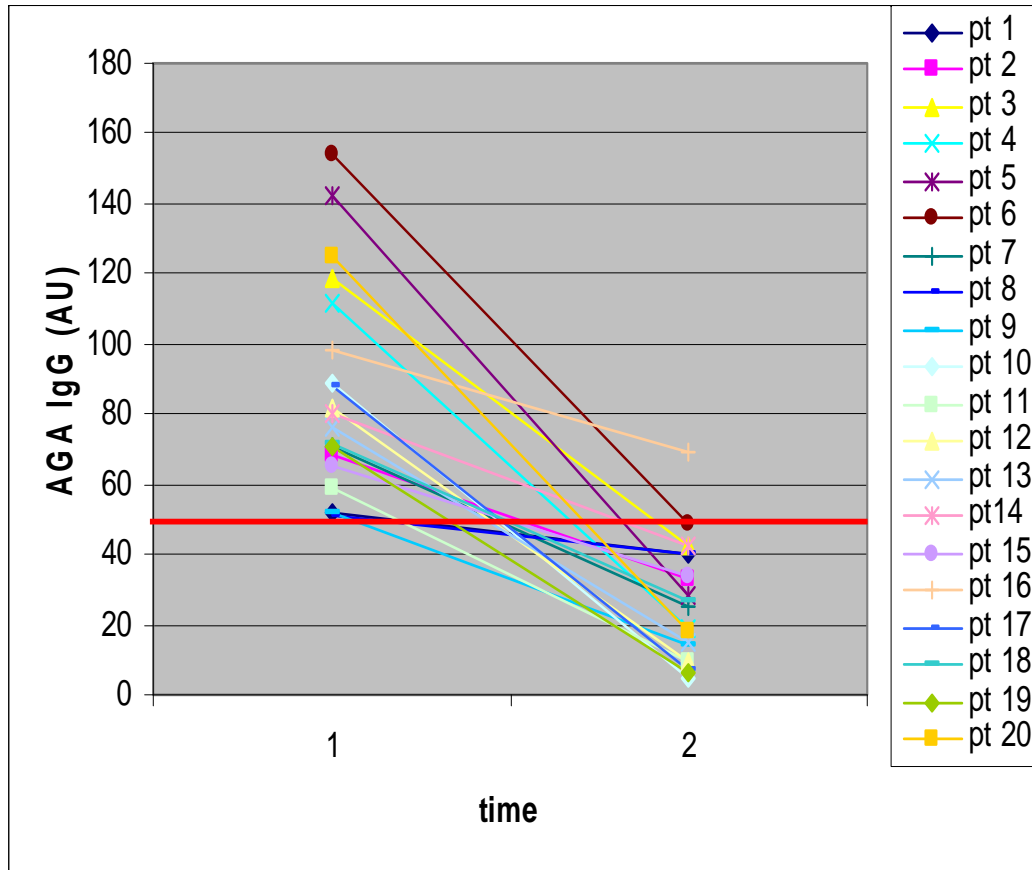
## AGA prevalence in other diseases and healthy controls

- Connective tissue disorders 9%
- Irritable bowel syndrome (IBS) 20%
- Autoimmune liver diseases 21%
- Blood donors 2%

AGA IgG is not a marker neither specific nor highly sensitive for NCGS, but for the time being its positivity (especially at a high titer) in patients with suspected NCGS can contribute to this diagnosis



# AGA IgG in Non Celiac Gluten Sensitivity (NCGS) before and after GFD



**Digestion**  
Editor-in-Chief: W. Creutzfeldt, Göttingen

**Reprint**  
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## IgA Antigliadin Antibodies and Persistence of Jejunal Lesions in Adult Coeliac Disease

U. Volta, G.R. Corazza, M. Frisoni, R.A. Valentini<sup>1</sup>, N. Molinaro, F.B. Bianchi, G. Gasbarrini

I Patologia Medica e Cattedra di Semeiotica Medica, Istituto di Clinica Medica Generale e Terapia Medica dell'Università di Bologna, Policlinico S. Orsola, Bologna, Italia

**Table 1.** Prevalence of IgA and IgG AGA in coeliac patients and disease controls

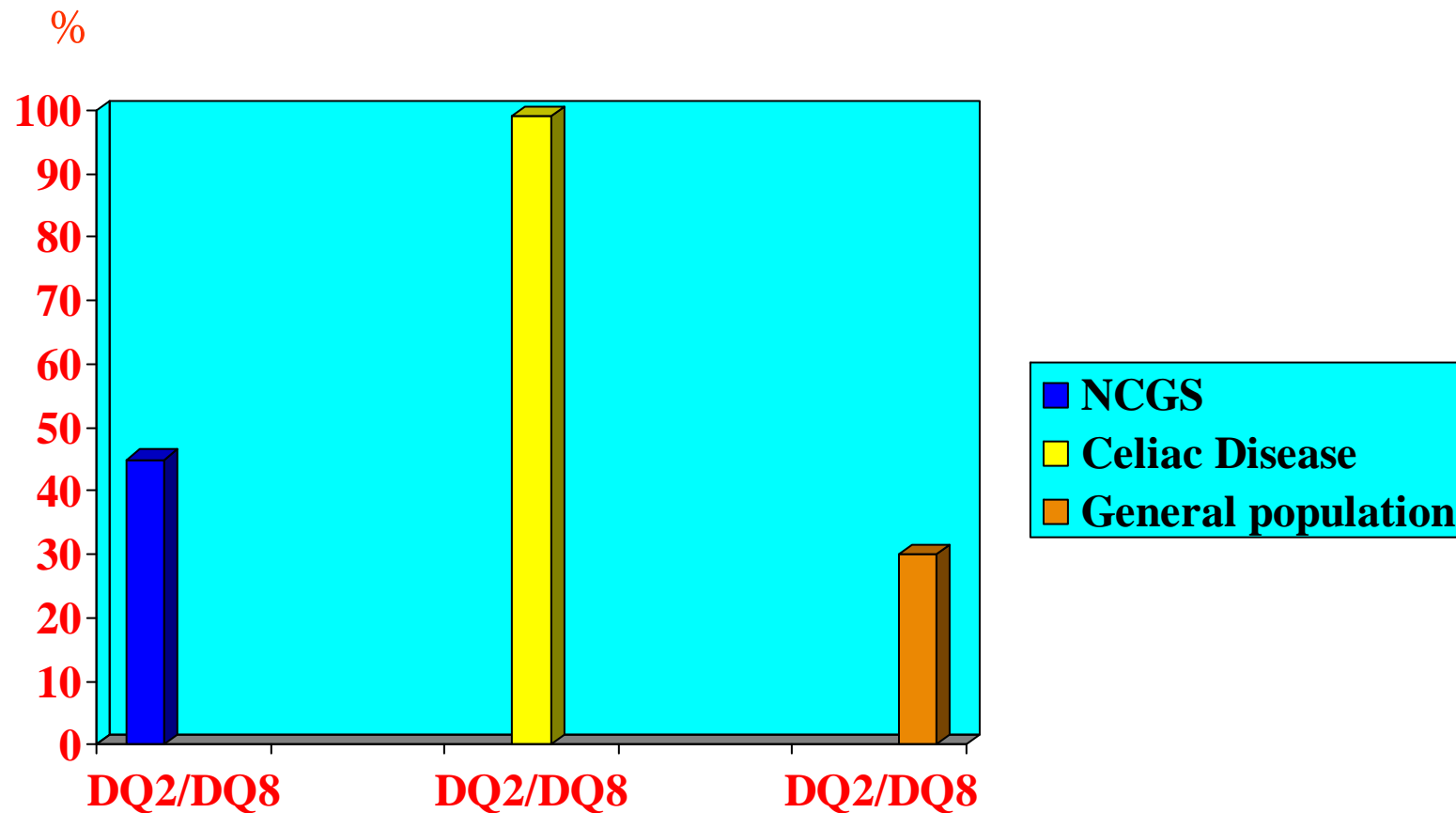
	IgA and/ or IgG	IgA	IgG
<b>Coeliac patients (n = 46)</b>			
Before GFD	41 (89%)	23 (50%)	40 (87%)
<u>After GFD</u>	21 (46%)	4 (9%)	<u>21 (46%)</u>
<b>Disease controls (n = 36)</b>			
5 (14%)	-	5 (14%)	

The duration of GFD was: < 6 months in 11 coeliacs; > 6 and < 12 months in 21 coeliacs, and > 12 months in 14 coeliacs.

time 1 : on a gluten-containing diet; time 2: after 6 months of GFD



## GENETICS (HLA typing)



Absence of correlation between NCGS and HLA-DQ2 and/or -DQ8

Volta U et al, J Clin Gastroenterol 2012





## Duodenal biopsy in NCGS

- A normal small bowel mucosa was observed in 58% of 78 NCGS patients studied (V/C ratio  $\geq 3:1$ , IEL  $< 25\%$ , normal villi, i.e. Marsh-Oberhübler type 0)
- In the remaining 42% of NCGS patients a slight IEL increase (between 25% and 40%) was observed (Marsh-Oberhübler type 1)
- No increase of  $\gamma/\delta^+$  T lymphocytes when determined

## Clinical features of NonCeliac Gluten Sensitivity (NCGS)

- NCGS is rare in infancy being more frequent in adults and in females than in males.
- Symptoms related to gluten ingestion (previously absent) appear some months or years before the diagnosis.
- Frequent coexistence of other food intolerances, i.e. lactose and fructose intolerance.
- Differently from coeliac patients, subjects with NCGS usually lose weight after GFD.
- A subgroup of NCGS patients does not improve by consuming commercially available gluten-free products and needs naturally gluten free foods.
- It is not known if NCGS patients are at risk for associated autoimmunity and complications like coeliacs.
- NCGS is frequently observed in 1<sup>st</sup> degree relatives of coeliac disease patients.



*Pierre Auguste Renoir, The two sisters 1881*



Non Celiac Gluten  
Sensitivity and Coeliac  
Disease are like two sisters  
with similar features, but  
with substantial differences

It is not rare to find NCGS  
cases among first degree  
relatives of celiacs

About 12% of NCGS  
cases of our study  
were 1st degree relatives  
of celiacs



## PROSPECTIVE AIC-FC SURVEY IN PATIENTS WITH SUSPECTED NCGS

The aim of this project is to have a picture of NCGS in Italy through a questionnaire which will be employed to collect prospectively data of pts with suspected NCGS in Italian Centers for gluten-related disorders in the period September 1<sup>st</sup> 2012-February 28 2013.

The NCGS form will allow to collect data about:

1)symptoms and signs of clinical presentation 2)frequency and timing of symptoms 3)duration of symptoms before diagnosis 4)who was the first to think about it 5)associated disorders; 6) familiarity for coeliac disease (CD) and HLA typing 7) 1st and 2nd generation gliadin antibodies 8)duodenal biopsy (if performed).

Moreover, another relevant aim is to verify the ratio between NCGS/CD cases during the 6 months of the study.

**Inclusion criteria:** symptoms elicited by gluten ingestion

**Exclusion criteria:** lack of correlation symptoms/gluten ingestion; tTG or EmA positivity.



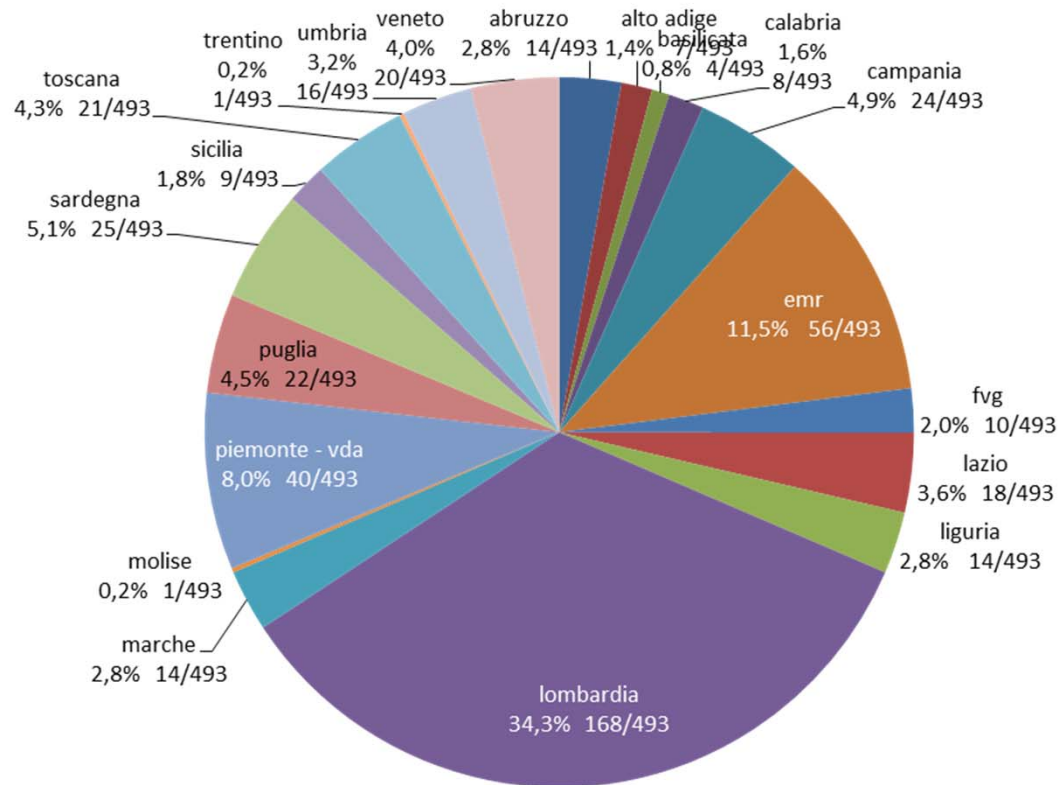
### Scientific Board for Non Celiac Gluten Sensitivity (NCGS)

**Coordinators:** U. Volta, G.R. Corazza, E. Tosi (President AIC), O. Lovello (President F.C.)


**Members** M.T. Bardella, A. Calabrò, G.R. Corazza, C. Corposanto, O. Lovello, C. Pilo, A. Pucci, E. Tosi, R. Troncone, U. Volta

# Geographical distribution of the 493 Italian Centres for Coeliac Disease diagnosis invited to participate

	493
abruzzo	14
alto adige	7
basilicata	4
calabria	8
campania	24
emr	56
fvg	10
lazio	18
liguria	14
lombardia	169
marche	14
molise	1
piemonte - vda	40
puglia	22
sardegna	25
sicilia	9
toscana	21
trentino	1
umbria	16
veneto	20

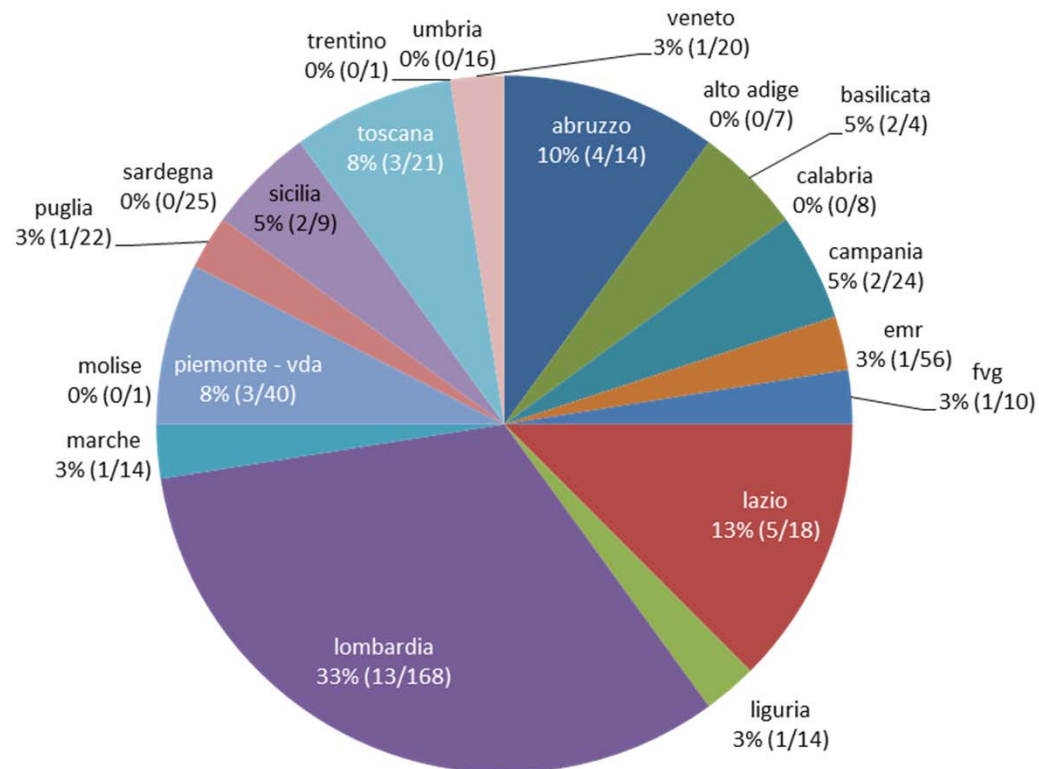


## CENTRES PARTICIPATING IN THE PROJECT BY THE END OF OCT. 2012

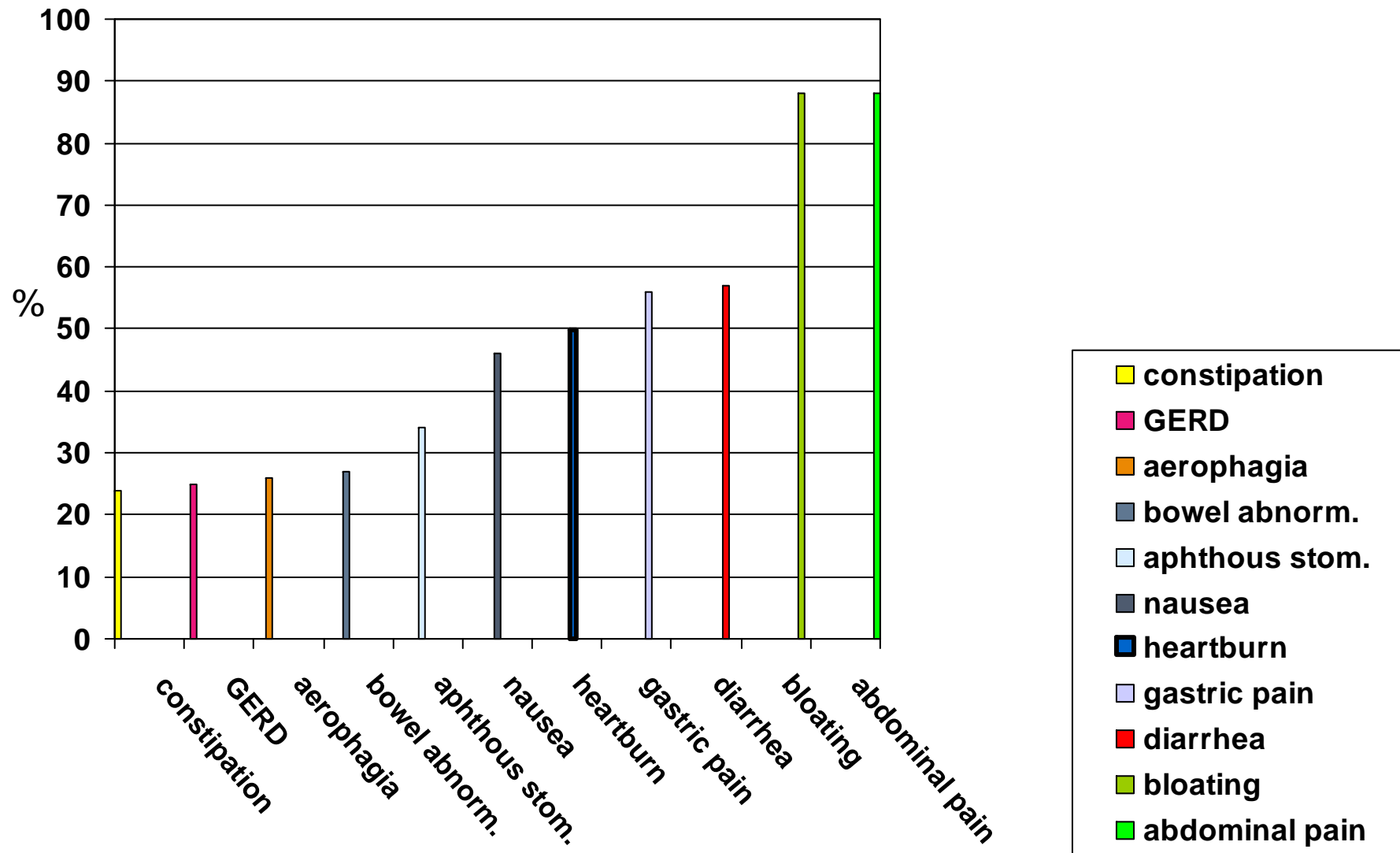

**in 2 months only 40 centres out of the 493 invited (8%) agreed to participate. Up to the end of October 2012, 115 cases, median age 60 years, range 18-80 yrs, ratio F/M: 5.5:1, were enrolled.**

### centri aderenti rispetto al N di centri nella regione

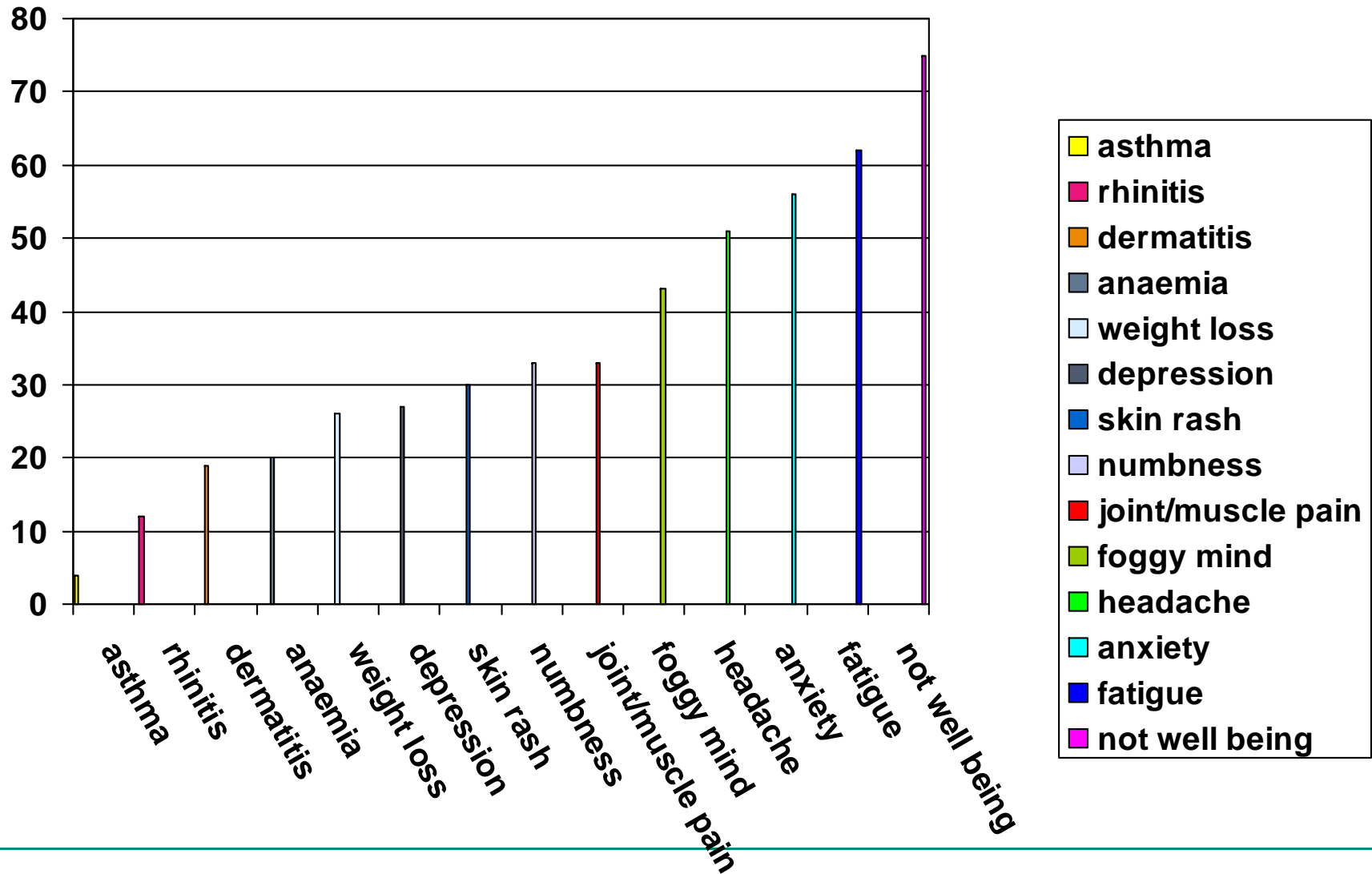
4/14 abruzzo	28,6%
0/7 alto adige	0,0%
2/4 basilicata	50,0%
0/8 calabria	0,0%
2/24 campania	8,3%
1/56 emila	1,8%
1/10 friuli	10,0%
5/18 lazio	27,8%
1/14 liguria	7,1%
13/168 lombardia	7,7%
1/14 marche	7,1%
0/1 molise	0,0%
3/40 piemonte	7,5%
1/22 puglia	4,5%
0/25 sardegna	0,0%
2/9 sicilia	22,2%
3/21 toscana	14,3%
0/1 trentino	0,0%
0/16 umbria	0,0%
1/20 veneto	5%



# GASTROINTESTINAL SYMPTOMS IN 115 NCGS CASES

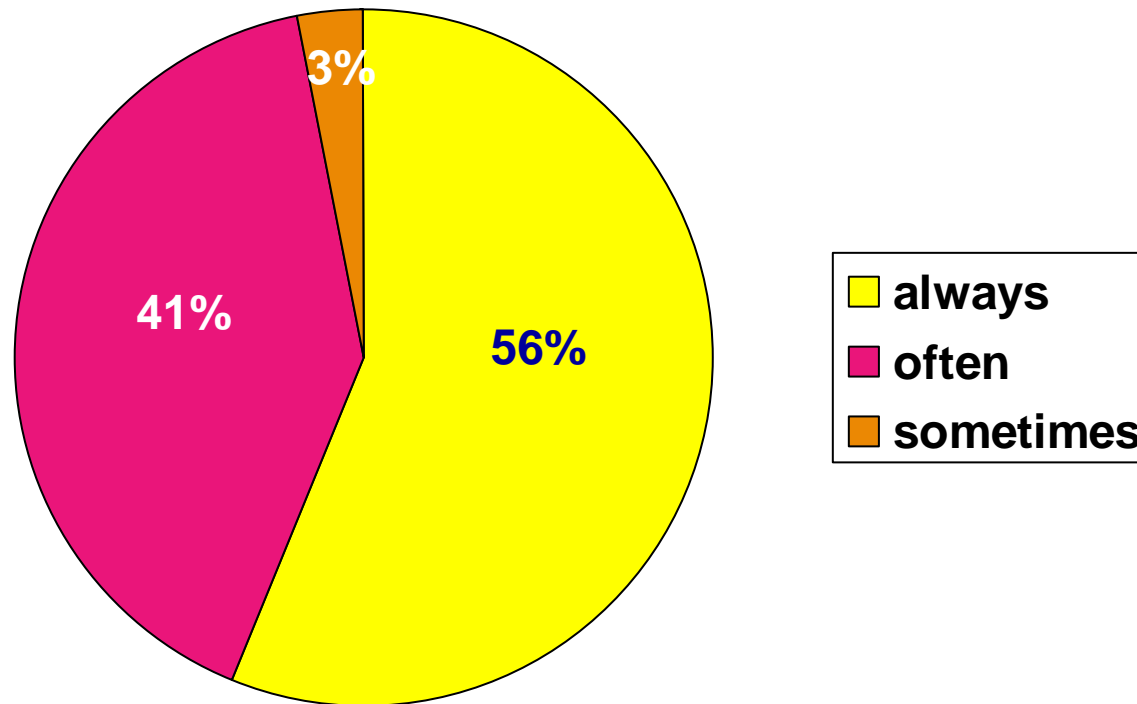


# EXTRAIESTINAL SYMPTOMS IN 115 NCGS CASES

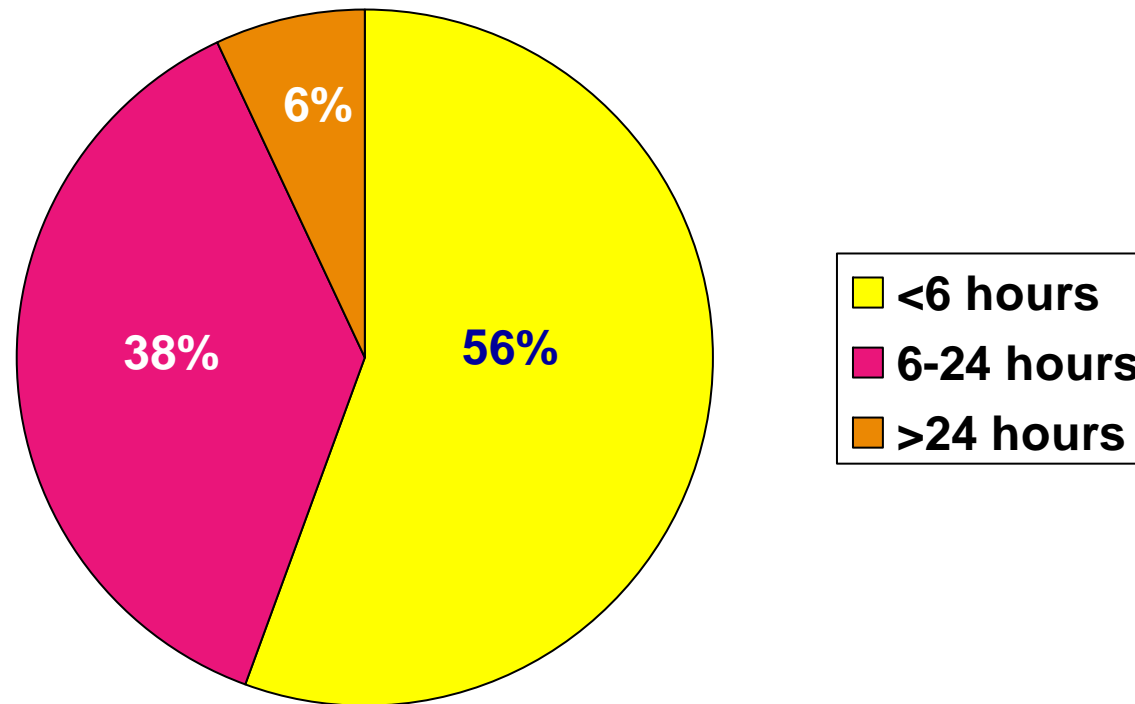




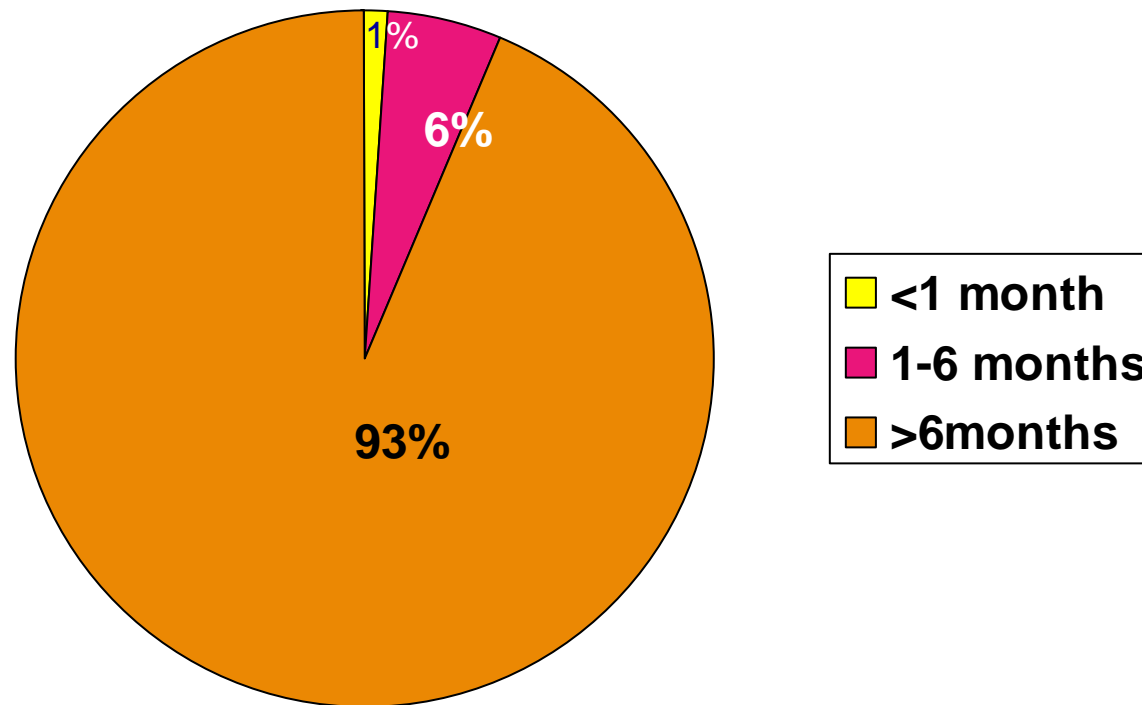
## FREQUENCY OF SYMPTOMS AFTER GLUTEN INGESTION



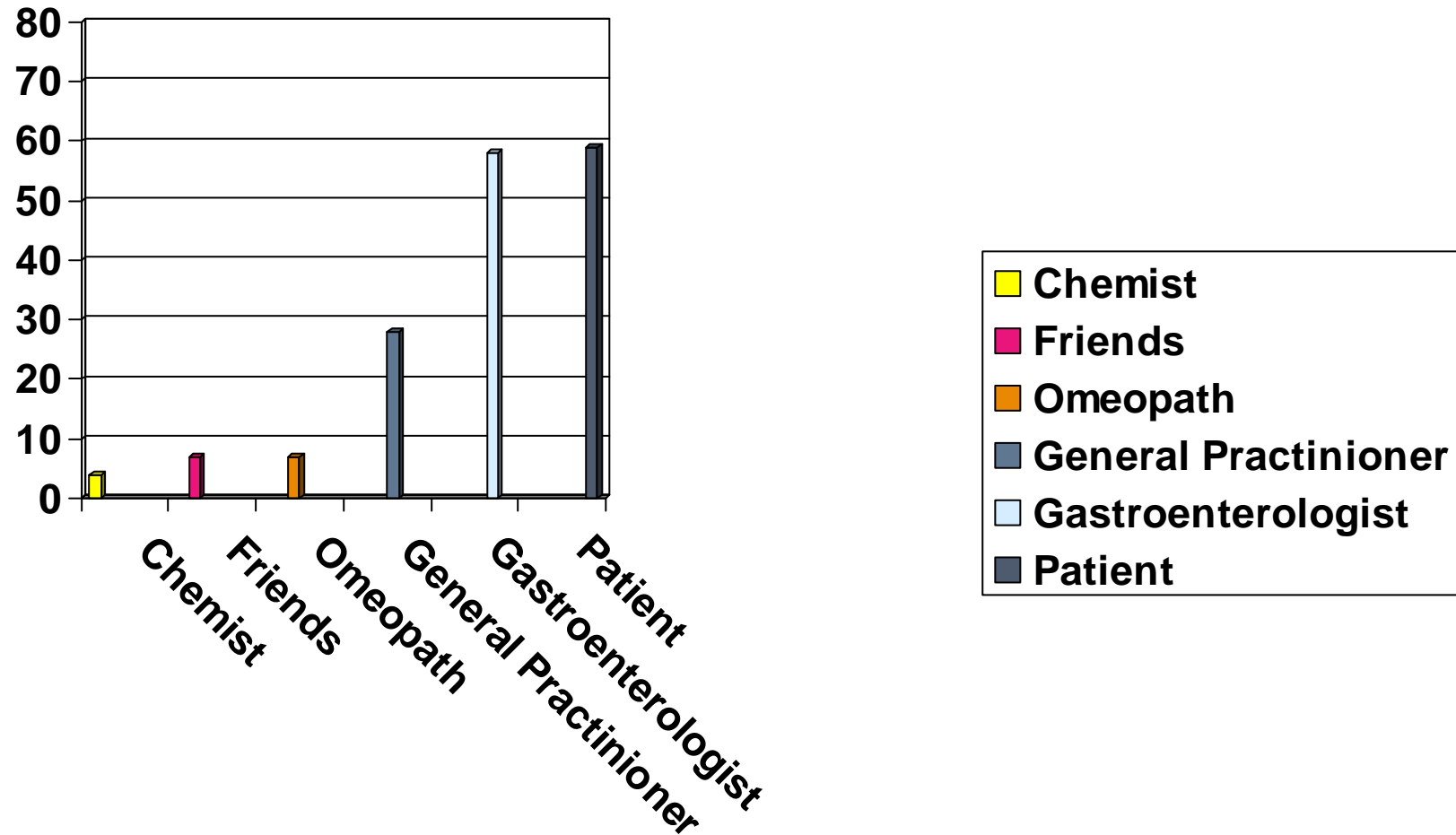
## TIMING OF SYMPTOM APPEARANCE AFTER GLUTEN INGESTION



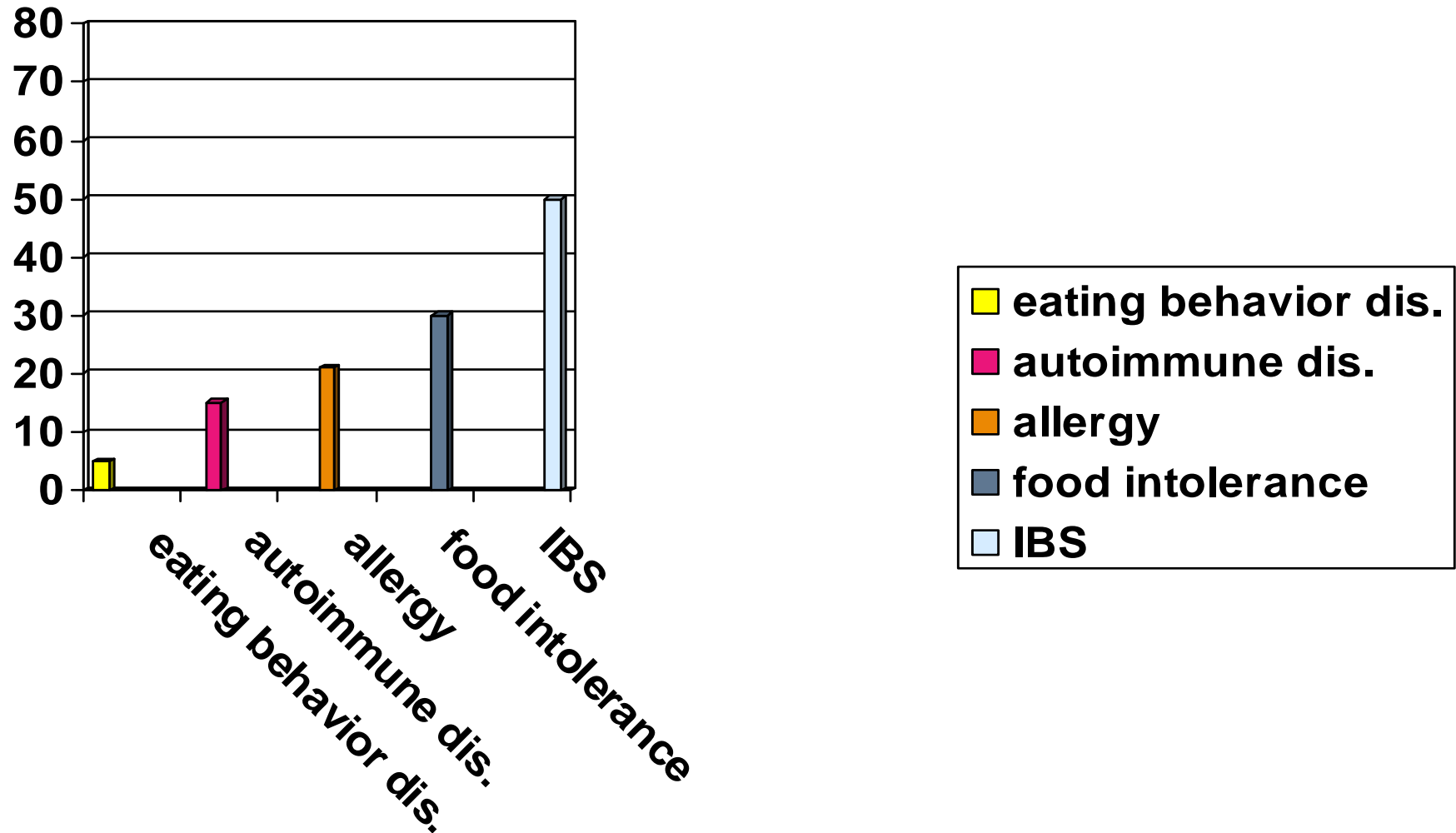
## DURATION OF SYMPTOMS BEFORE NCGS DIAGNOSIS



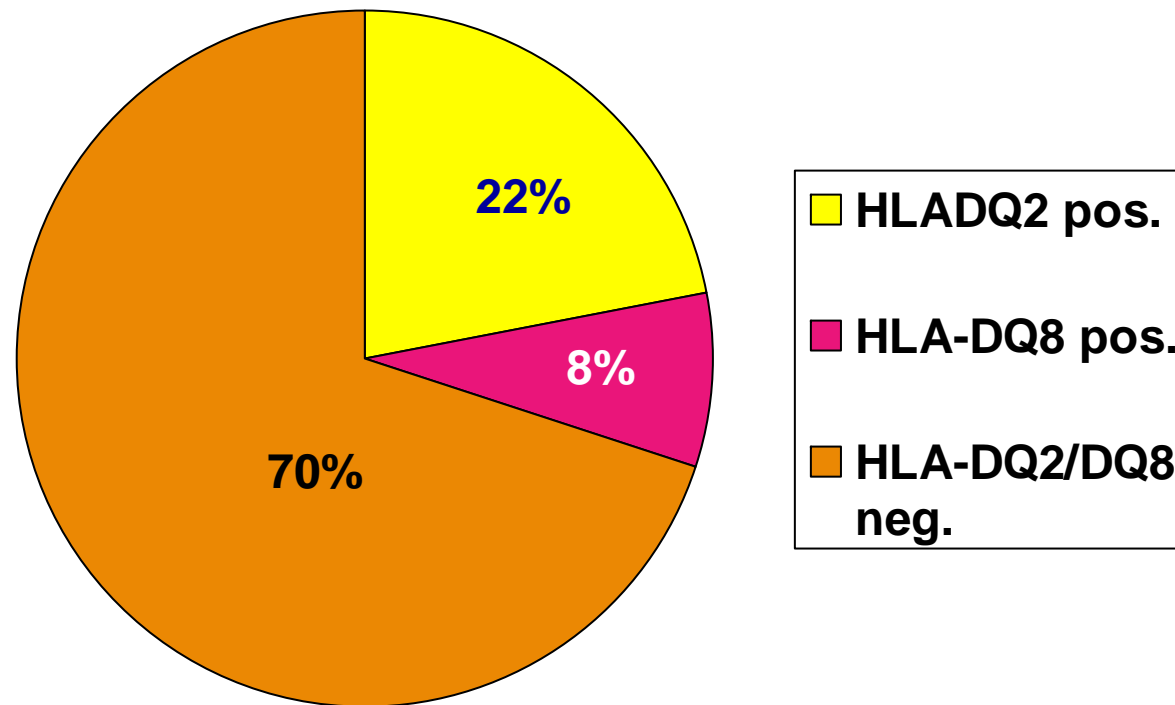
## WHO WAS THE FIRST TO THINK ABOUT NCGS



## ASSOCIATED DISORDERS IN NCGS PATIENTS



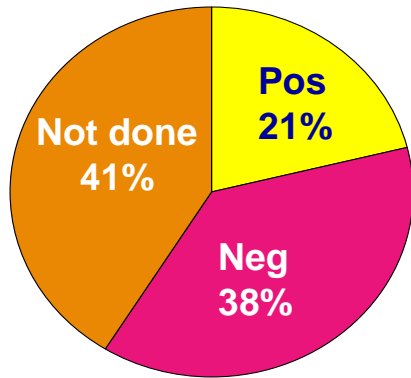
## FAMILIARITY FOR CD AND HLA TYPING IN NCGS



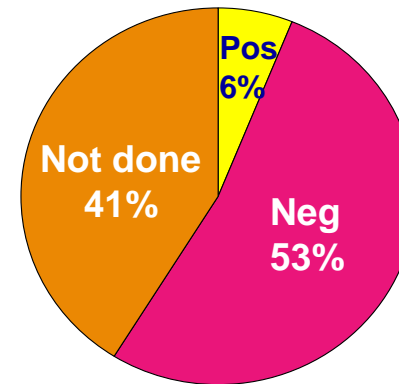
**16.5% of NCGS cases were 1<sup>st</sup> degree relatives of CD patients**

# 1<sup>st</sup> and 2<sup>nd</sup> GENERATION GLIADIN ANTIBODIES IN NCGS

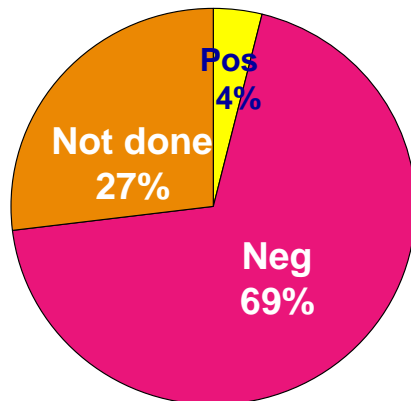
## AGA IgG



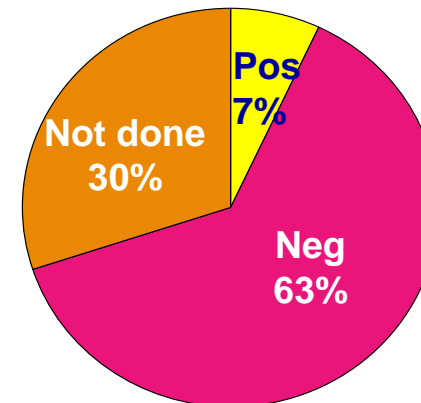
## AGA IgA



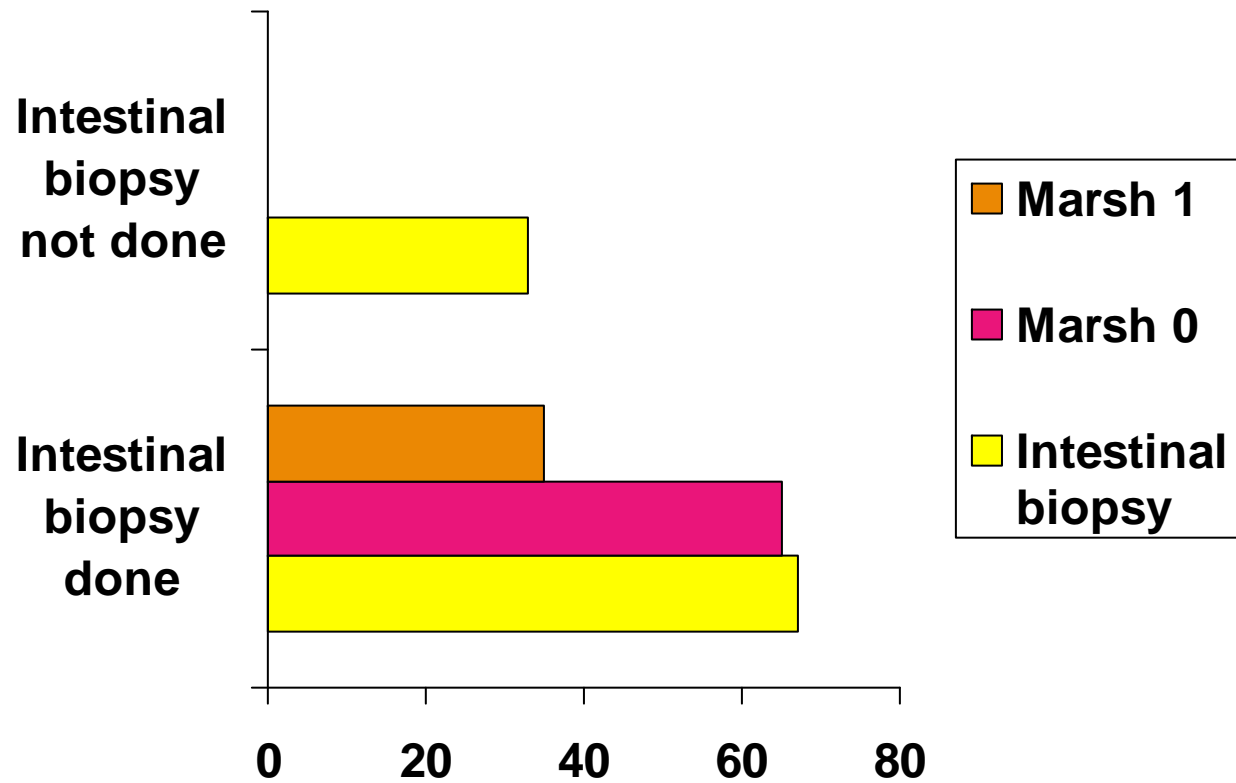
## DGP IgG



## DGP IgA



# INTESTINAL BIOPSY IN NCGS





## PROSPECTIVE SURVEY IN PATIENTS WITH SUSPECTED NCGS

- Results of our survey on NCGS are still preliminary (only two months of data collection and with a too few number of participating centers) and do not allow to draw any conclusion
- The participation of a higher number of centers will allow to have a more complete picture of NCGS in Italy and to extrapolate some data about its hypothetical prevalence related to new diagnosed CD cases in the same period