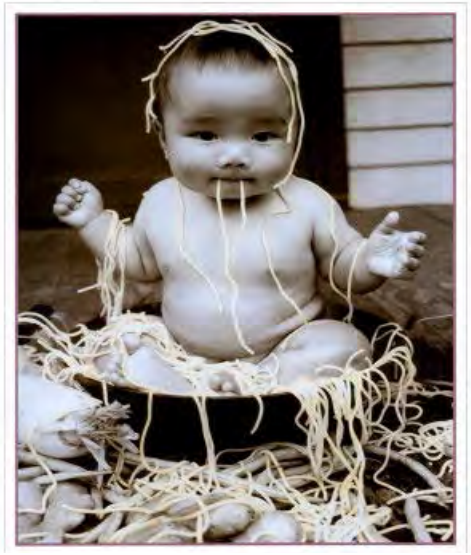

Basilio Malamisura

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Ospedale "Sacro Cuore di Gesù", Fatebenefratelli
UOC PEDIATRIA-NEONATOLOGIA-UTIN

JOURNAL CLUB
of Pediatrics
in Benevento

incontri monotematici
ospedale - territorio
per la elaborazione
di linee guida comuni

Febbraio
Dicembre 2015

Centro Congressi
Ospedale Sacro Cuore di Gesù
Fatebenefratelli, Benevento

Responsabili Scientifici:
Iride Dello Iacono
Carmen Verga

Weath:
friend or foe?

Gluten-related disorders:
"Beyond celiac disease"

BMC Medicine

OPINION Open Access

Spectrum of gluten-related disorders: consensus on new nomenclature and classification

Anna Sapone[1,2], Julio C Bai[3], Carolina Ciacci[4], Jernej Dolinsek[5], Peter HR Green[6], Marios Hadjivassiliou[7], Katri Kaukinen[8], Kamran Rostami[9], David S Sanders[10], Michael Schumann[11], Reiner Ullrich[11], Danilo Villalta[12], Umberto Volta[13], Carlo Catassi[1,14] and Alessio Fasano[1*]

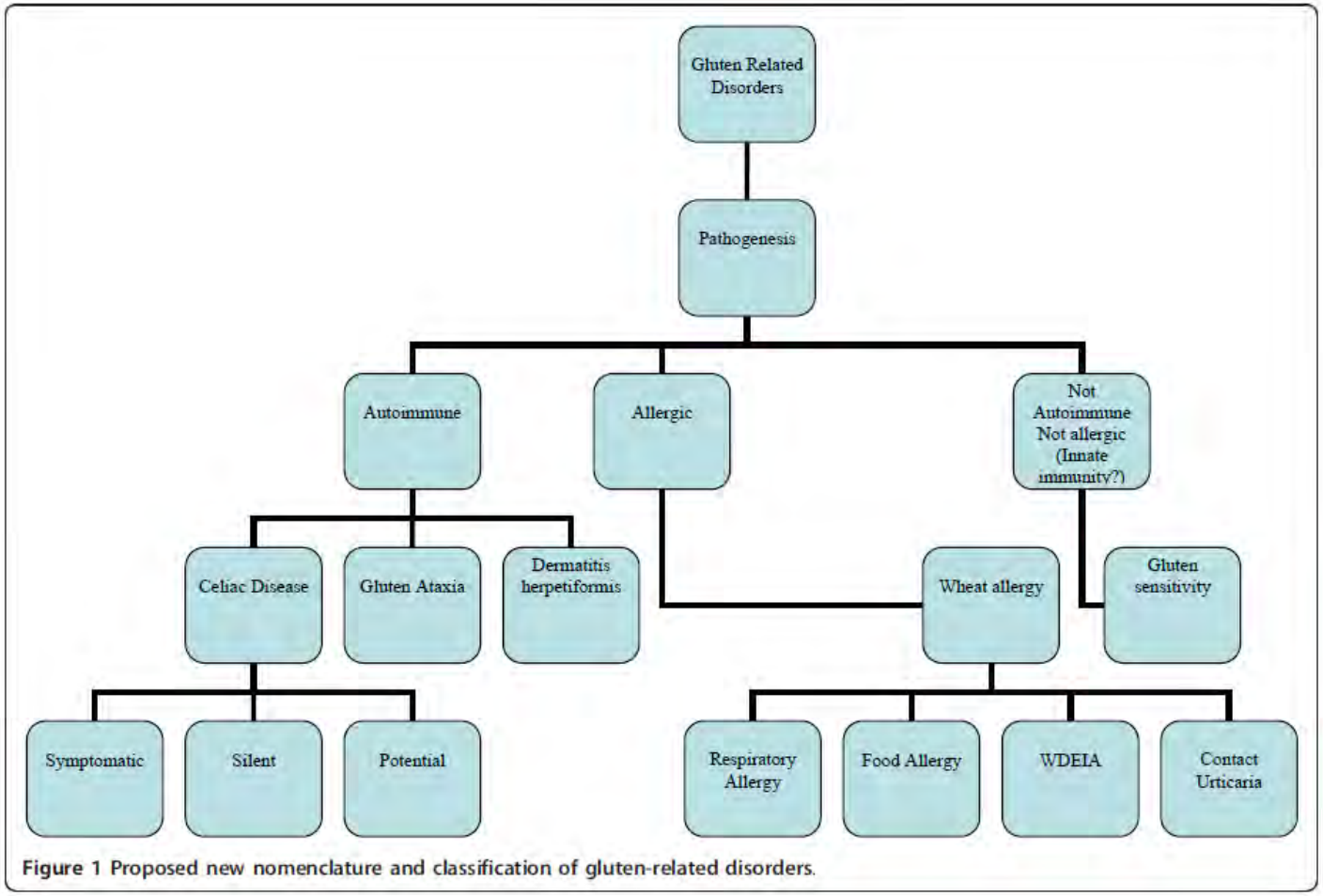


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

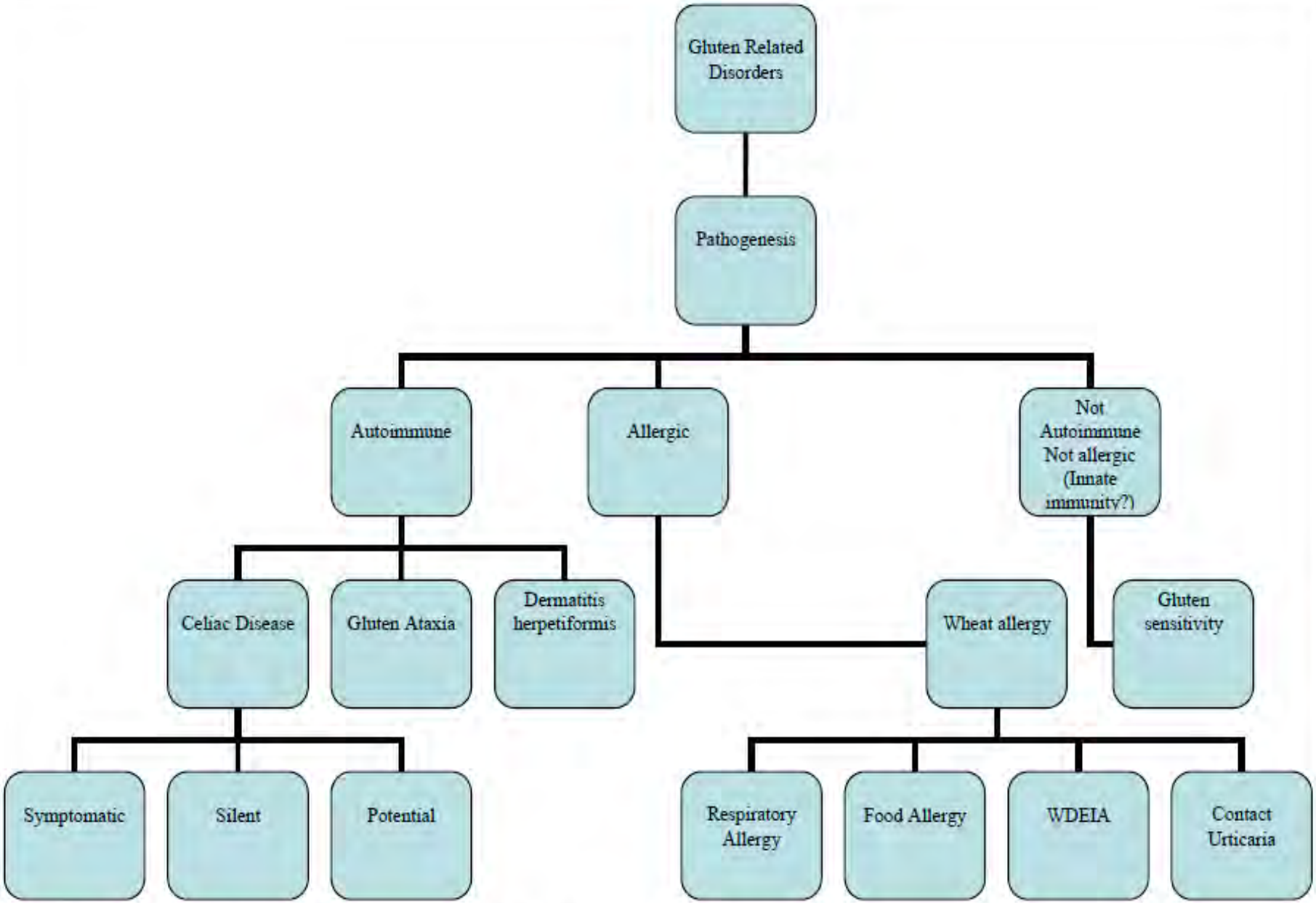


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

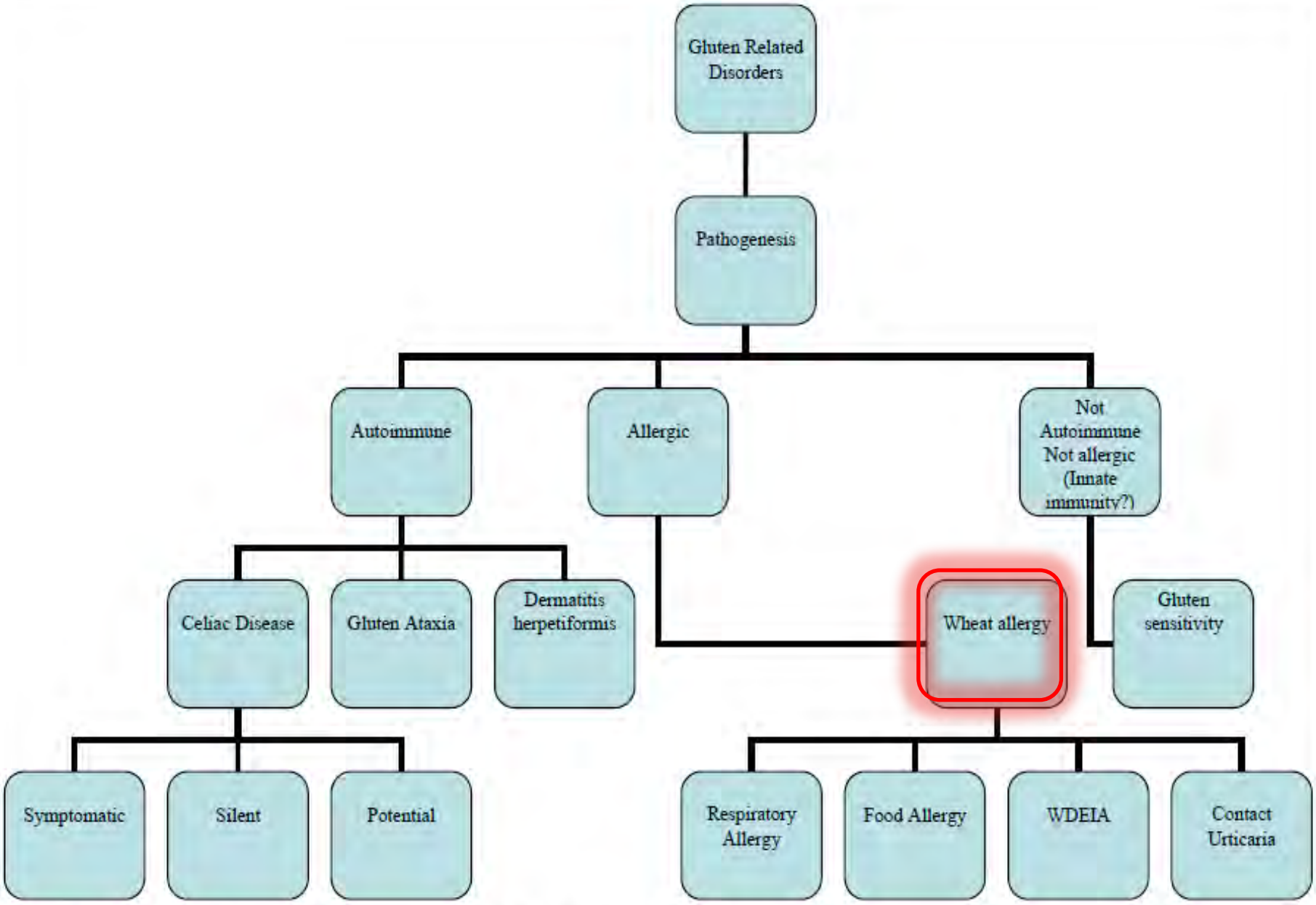


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

Wheat Allergy is defined as an adverse immunologic reaction to wheat proteins.

Depending on the route of allergen exposure and the underlying immunologic mechanisms, WA is classified into:

1. **classic food allergy** affecting the skin, gastrointestinal tract or respiratory tract;
2. **wheat-dependent-exercise-induced-anaphylaxis** (WDEIA);
3. **occupational asthma** (baker's asthma) **and rhinitis**
4. **contact urticaria**

IgE antibodies play a central role in the pathogenesis of these diseases.

Wheat allergy

Contact urticaria

Respiratory allergy

baker's asthma

rhinitis

Food allergy

- Gastrointestinal symptoms
- Urticaria/angioedema
- Bronchial obstruction
- Worsening of atopic dermatitis

In adults wheat-dependent exercise-induced anaphylaxis (WDEIA)

Baker's asthma

- **One of the most common causes of occupational asthma**
  - Second most common in Great Britain
  - Most common in France
- **incidence: 1 -10 cases per 1000 bakery workers/yr (bakers, confectioners, assistants)**
- **prevalence: 4 – 8% (8-12% allergic rhinitis)**
- **Many wheat allergens involved**

Baker's asthma

Allergic responses to the inhalation of wheat and cereal flours and dusts.
Chest respiratory symptoms ascribed to baker's asthma were observed in 4.2% of bakery apprentices after only one year and in 8.6% after two years.
The corresponding values for allergic rhinitis were 8.4% and 12.5%, respectively.

Diagnosis is usually based on skin prick tests and the demonstration of specific IgE antibodies (for example, anti-wheat, -barley and -rye flour IgE as well as anti-a-amylase IgE in serum).

Tatham AS, Shewry PR. Clin Experiment Aller 2008
Walusiak J et al. Allergy 2004.

Wheat food allergy

- No sure data on the prevalence of wheat food allergy

Allergy 2008: 63: 418–424

DOI: 10.1111/j.1398-9995.2007.01575.x

Original article

Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children

Ostblom et al. Allergy 2008

2336 children
Aged <4yr

Table 1. Prevalence of sensitisation* to common food allergens in a cohort of 2336 4-year-old children without and with food hypersensitivity (FHS)

Allergens	Total (N = 2336), n (%)	No FHS (N = 2052), n (%)	FHS (N = 284), n (%)
Any food**	305 (13)	218 (11)	87 (31)
Animal origin			
Cow's milk	197 (8)	151 (7)	46 (16)
Hen's egg	112 (5)	70 (3)	42 (15)
Cod fish	17 (1)	7 (0)	10 (4)
Plant origin			
Peanut	125 (5)	63 (3)	62 (22)
Soy bean	70 (3)	31 (2)	39 (14)
Wheat	88 (4)	54 (3)	34 (12)

4%

*Allergen-specific IgE-antibodies ≥ 0.35 kU_A/l.
**Allergen-specific IgE-antibodies ≥ 0.35 kU_A/l to at least one of the foods tested.

Clin Exp Allergy 2008

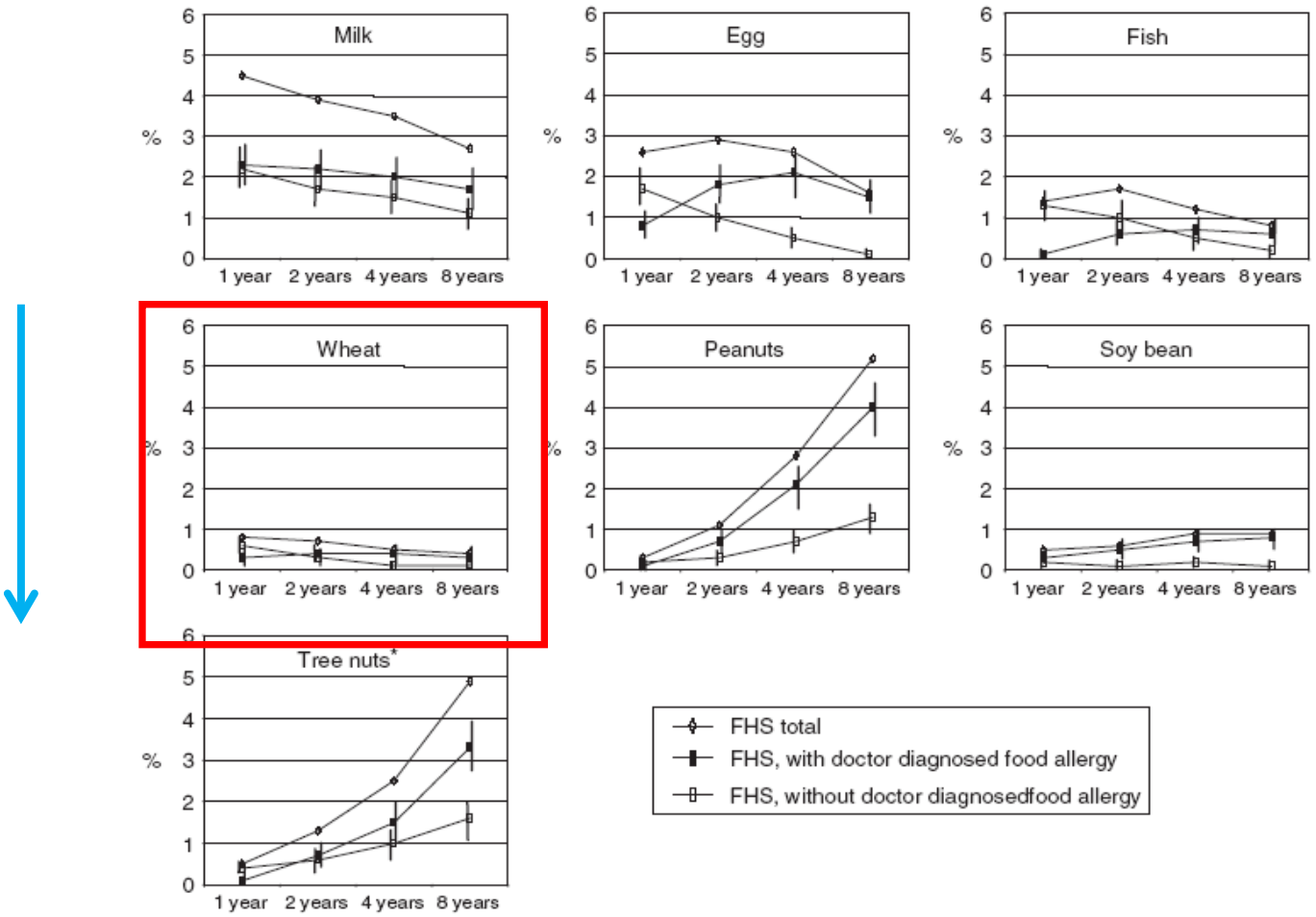


Fig. 1. Prevalence of reported food hypersensitivity (FHS) and 95% confidence intervals to specific foods divided by reported diagnosis of food allergy at a certain age in a birth cohort of 3104 children.

Another, longitudinal, study of 273 children from ages two to ten years reached contrary conclusions, showing that the prevalence of IgE to wheat progressively increased with age, from 2% to 9%

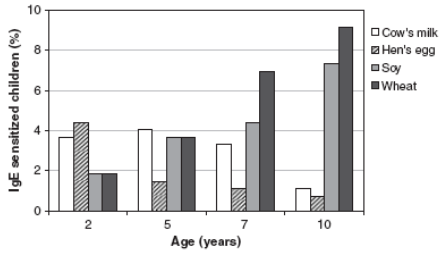


Fig. 1. Prevalence of sensitization from birth to 10 years. Point prevalence of IgE sensitization (cut-off 1 kU/L) to four common food allergens from birth to 10 years in 273 children participating in MAS. *P*-values for trend in sensitization at age 2, 5, 7, 10 years are the following: cow's milk $P = 0.037$; hen's egg $P = 0.001$; soy $P < 0.001$; wheat $P < 0.001$. MAS, Multi-Centre Allergy Study.

Matricardi PM et al
Primary versus secondary immunoglobulin E sensitization to soy and wheat in the Multi-Centre Allergy Study cohort.
Clin Exp Allergy 2008, 38:493-500.

In adults, the prevalence of sensitization to wheat (assessed by IgE) was higher (> 3% in several studies) than perceived (< 1%).

Zuidmeer L et al.
The prevalence of plant food allergies: a systematic review.
J Aller Clin Immunol 2008

Food allergy to wheat

Cow's milk

Hen's egg

Soy

Peanut

Fish

Wheat →

90% of food allergies in children

12% (Ostblom Allergy 2008)

SPT wheal > 5 mm

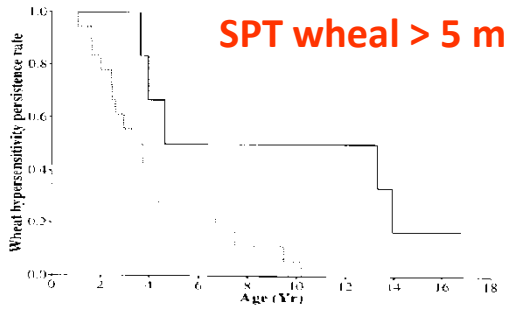
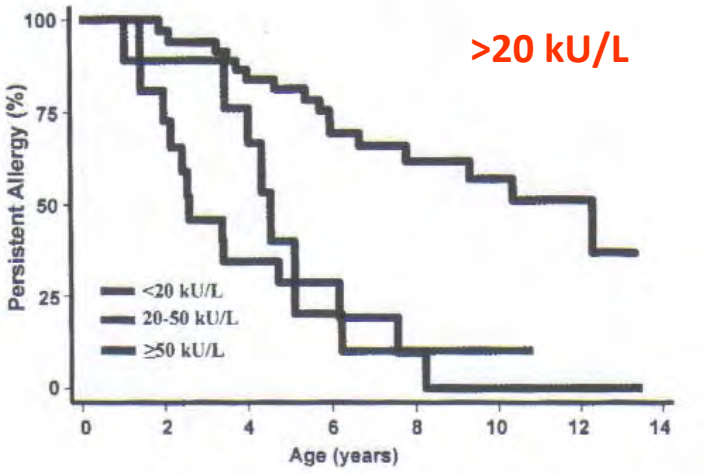


Fig. 1. Proportion of children with persistent wheat hypersensitivity by age: sensitization to gliadin with a SPT wheal of ≥5 mm (——) (n = 6) was linked to the slower recovery from wheat hypersensitivity when compared with sensitization to gliadin with a SPT wheal of <5 mm (- - -) (n = 18) (p = 0.019).

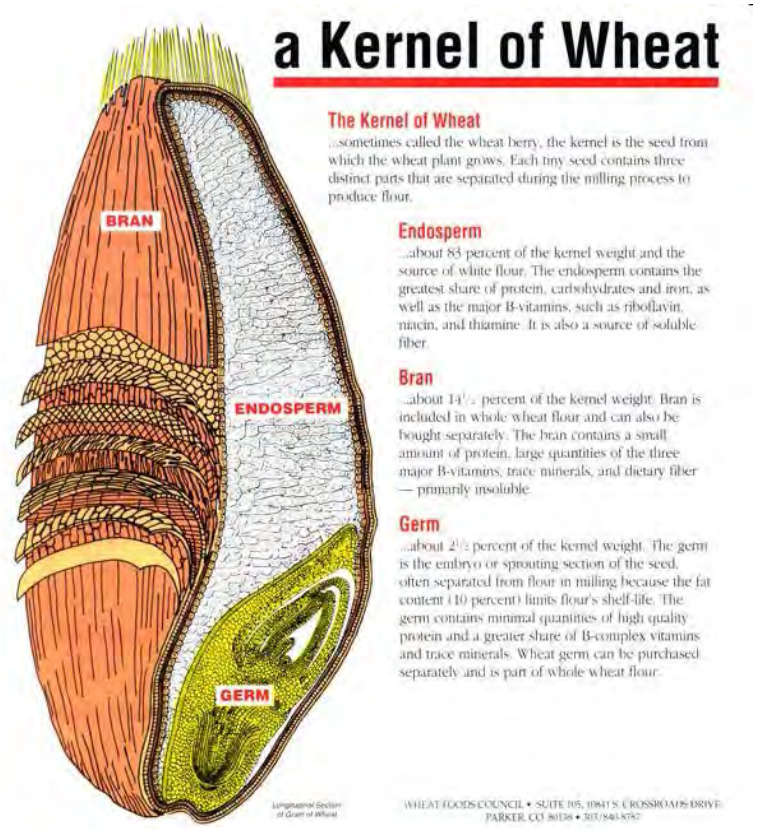
Totaniemi-Syrjänen et al. Pediatr Allergy Immunol 2010

>20 kU/L



Keet CA et al Ann Allergy Clin Immunol 2009

Totally: 0.4 – 1% of children

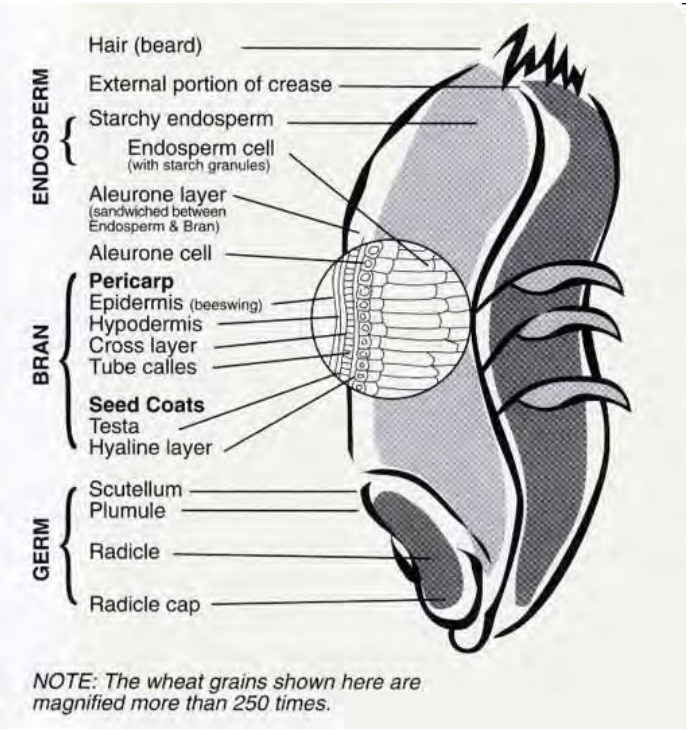


The proteins that are responsible for a **dietary allergy in wheat** are also less clearly defined than those contributing to **baker's asthma**, but recent studies indicate that there are intriguing similarities and differences between the two conditions.

Tatham AS, Shewry PR. Clin Experiment Aller 2008
Walusiak J et al. Allergy 2004.

More recent studies have identified individual proteins, which are recognized by IgE from patients' sera.

It is clear that one group of wheat proteins contains the most important allergens, the **alfa amylase inhibitors**.
However, a number of other proteins present in wheat, including **germ agglutinin**, **peroxidase** and **non-specific lipid transfer proteins (LTPs)**, have been reported to bind to IgE from **patients with baker's asthma.**



It is of interest that both peroxidase and LTP have also been reported to be active in food allergy to wheat.

Tatham AS, Shewry PR. Clin Experiment Aller 2008

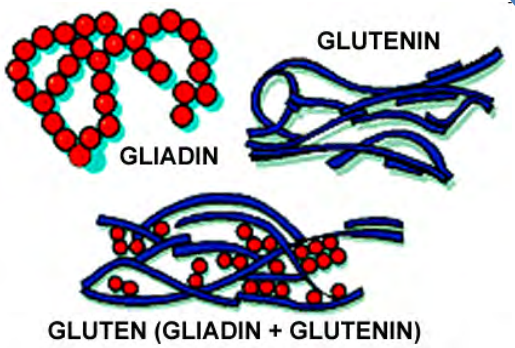
Wheat proteins

Functions based classification (80% major storage protein)

Osborne classification

- Albumins (water extraction)
- Globulins (saline extraction)
- Prolamins (alchol/water mixture extraction)
- Glutenins (dilute acid extraction)

Gluten proteins



Monomeric gliadins

Polymeric glutenins

α/β

γ

ω

HMW

LMW

Gliadin groups based on electrophoretic mobility of native proteins at low pH

Groups of glutenin subunits separated by SDS-PAGE after reduction of disulphide bonds

ELSEVIER

Journal of Cereal Science 42 (2005) 109–117

Journal of CEREAL SCIENCE

www.elsevier.com/locate/jnlabr/yjcrs

Food allergy to wheat: differences in immunoglobulin E-binding proteins as a function of age or symptoms

Fabrice Battais[a], Philippe Courcoux[b], Yves Popineau[a], Gisèle Kanny[c], Denise Anne Moneret-Vautrin[c], Sandra Denery-Papini[a,*]

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[c]Department of Internal Medicine, Clinical Immunology and Allergology University Hospital, 29 Avenue de Lattre de Tassigny, 54035 Nancy, France

Table 1

Frequencies of IgE antibodies to different wheat protein fractions obtained by F-ELISA for children and adult patients with food allergy to wheat and *p*-values calculated by chi-square tests to analyze relationships between these frequencies and patient age

Protein fraction	60 sera	31 children	29 adults	*p*-Values
Overall positivity	90%	87%	93%	
Albumins/globulins	72%	84%	59%	0.0301
LTP	28%	35%	21%	0.2038
Prolamins	67%	55%	79%	
α-Gliadins	23%	39%	7%	0.0036
β-Gliadins	18%	29%	7%	0.0268
γ-Gliadins	13%	23%	3%	0.0294
ω_5-gliadins	37%	26%	48%	0.0711
$\omega_{1,2}$-gliadins	22%	29%	14%	0.1522
LMW glutenins	30%	29%	31%	0.8657
HMW glutenins	28%	26%	31%	0.6534

Gluten proteins

Food allergy to wheat: identification of immunogloglin E and immunoglobulin G-binding proteins with sequential extracts and purified proteins from wheat flour

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*INRA, Unité de Recherche sur les Protéines Végétales et leurs Interactions, Nantes, †CHU, Immunologie Clinique et Allergologie, Nancy and ‡Laboratoire Allerbio, Varennes en Argonne, France

Clin Exp Allergy 2003;33:962-70

Patients with food allergy to wheat (children and adults)

Table 2. Comparison of percentages of sera giving positive results for IgE or IgG binding to different wheat proteins by ELISA, RAST or immunoblotting

					ω-gliadin				
	Techniques used	α-gliadin	β-gliadin	γ-gliadin	Fast ω-gliadin	Slow ω-gliadin	HMW glutenin	LMW glutenin	Alb/Glob
IgE									
$n=27$	RAST	60%	60%	55%	48%		26%	60%	ND
$n=27$	Immunoblotting	7%	20%	7%	20%	0%	15%	52%	67%
IgG									
$n=25$	ELISA	64%		36%	32%		16%	40%	ND

ND, not determined.

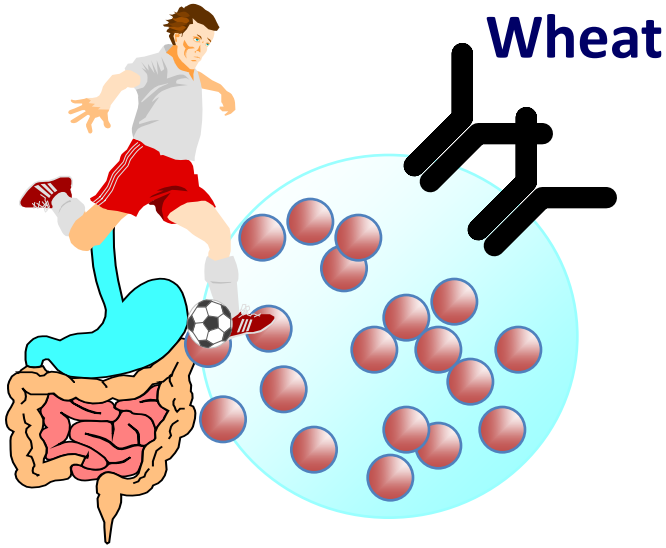
80% of sera reacted with al least four antigens simultaneously - numerous sequence homologies exist between prolamins

Clinical presentations

Dietary allergy to wheat, which in its extreme form may lead to anaphylaxis and death, is probably less widespread in the general population versus respiratory allergy.

Allergic responses to the ingestion of wheat can be divided into two types.

Wheat-dependent exercise-induced anaphylaxis



WDEIA is a well-defined syndrome that is caused by a specific type of grain protein, **ω5-gliadins**.

Patients with WDEIA display a range of clinical symptoms, from generalized urticaria to severe allergic reactions including anaphylaxis.

Wheat-dependent, exercise-induced anaphylaxis (WDEIA)

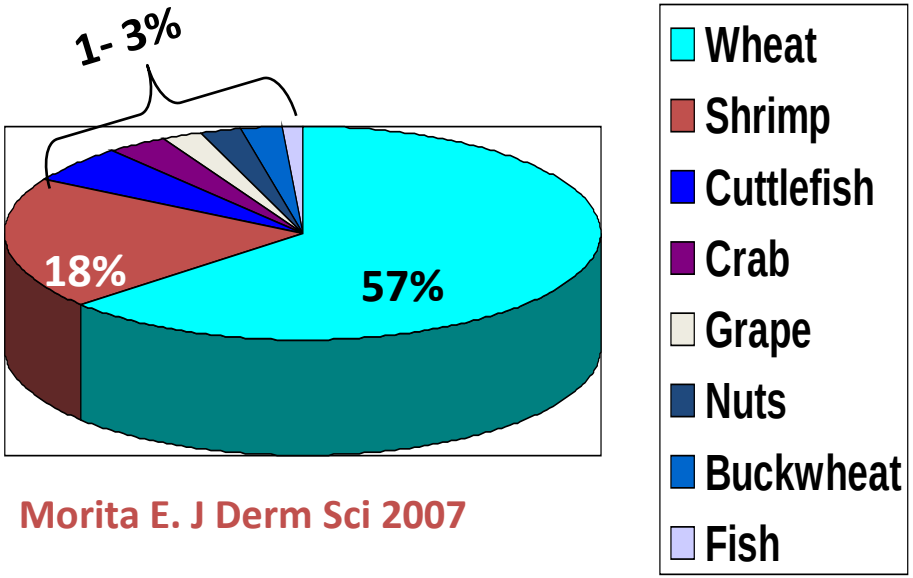
-**FDEIA: - 0.06% of the elementary school students**

- 0.21% of the high school students

- peak incidence in the second decade

- M/F = 2:1

Tanaka S 1994



Morita E. J Derm Sci 2007

Triggering factors
Foods (amount, sort and combination)
Exercise (strength, type, duration and timing after meal)
General conditions (cold, stress, menstruation, etc)
Alcohol
Drugs (aspirin and NSAIDs)

Other allergic responses include **atopic dermatitis, urticaria and anaphylaxis** and appear to be related to a range of wheat proteins.

They may vary between populations and be related to age and symptoms.

Studies with purified proteins using IgE specific assays with patients' sera showed that **had IgE:**

- **60%** **to a-gliadins, b-gliadins and low molecular weight subunits,**
- **55%** **to g-gliadins,**
- **48%** **to ω-gliadins,**
- **26%** **to high molecular weight subunits.**

100% of patients with anaphylaxis or WDEIA and 55% of those with urticaria had IgE to ω5-gliadins.

Tatham AS, Shewry PR. Clin Experiment Aller 2008

Diagnostic tests for wheat allergy

- Skin prick tests (SPTs)
- In vitro IgE assays (plus molecular tests)
- atopy patch testing (APT)

- Spirometry (improvement in periods away from work)
- Specific bronchial challenge

} Baker's asthma

- Food elimination diet
- Double-blind, placedo-controlled food challenge (DBPCFC)

} Food allergy

- Basophil histamine release/activation assays

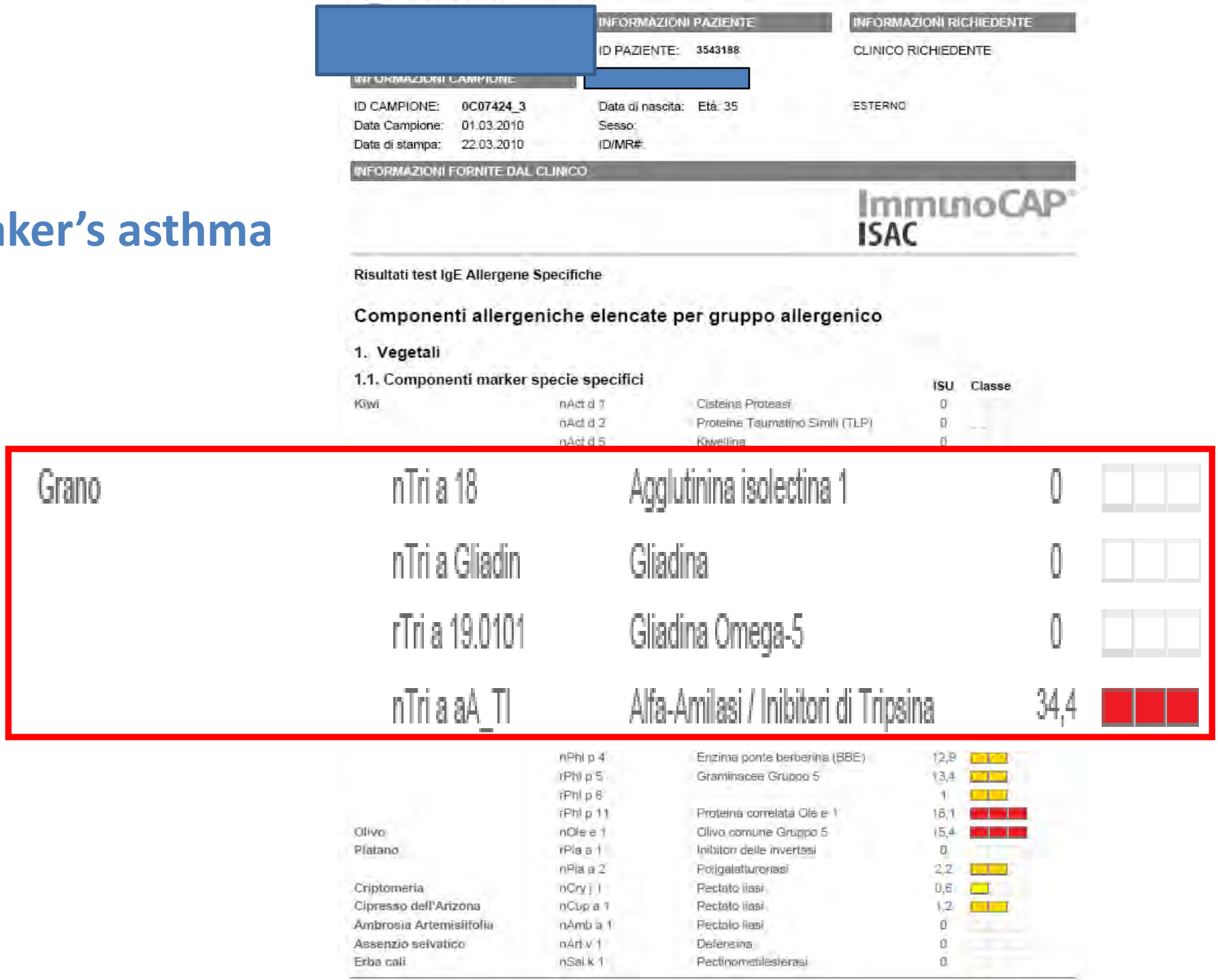
SPTs: low sensitivity (many commercial reagents are mixtures of water/soluble wheat proteins, lacking insoluble gli… fraction

…NSATISFACTORY

IgE assays: … reactivity … …lin and polle…

There is no evidence that identifying serum-IgG antibodies to wheat or gliadin indicates the presence of disease.

baker's asthma



INFORMAZIONI PAZIENTE
ID PAZIENTE: 3543188

INFORMAZIONI RICHIEDENTE
CLINICO RICHIEDENTE

INFORMAZIONI CAMPIONE
ID CAMPIONE: 0C07424_3
Data Campione: 01.03.2010
Data di stampa: 22.03.2010

Data di nascita: Età: 35
Sesso:
ID/MR#:

ESTERNO

INFORMAZIONI FORNITE DAL CLINICO

ImmunoCAP ISAC

Risultati test IgE Allergene Specifiche

Componenti allergeniche elencate per gruppo allergenico

1. Vegetali

1.1. Componenti marker specie specifici

			ISU	Classe
Kiwi	nAct d 1	Cisteina Proteasi	0	
	nAct d 2	Proteine Taumatino Simili (TLP)	0	
	nAct d 5	Kiwellina	0	
Grano	nTri a 18	Agglutinina isolectina 1	0	
	nTri a Gliadin	Gliadina	0	
	rTri a 19.0101	Gliadina Omega-5	0	
	nTri a aA_TI	Alfa-Amilasi / Inibitori di Tripsina	34,4	
	nPhl p 4	Enzima ponte berberina (BBE)	12,9	
	rPhl p 5	Graminacee Gruppo 5	13,4	
	rPhl p 6		1	
	rPhl p 11	Proteina correlata Ole e 1	18,1	
Olivo	nOle e 1	Olivo comune Gruppo 5	15,4	
Platano	rPla a 1	Inibitori delle invertasi	0	
	nPla a 2	Poligalatturonasi	2,2	
Criptomeria	nCry j 1	Pectato liasi	0,6	
Cipresso dell'Arizona	nCup a 1	Pectato liasi	1,2	
Ambrosia Artemisiifolia	nAmb a 1	Pectato liasi	0	
Assenzio selvatico	nArt v 1	Defensina	0	
Erba cali	nSal k 1	Pectinometilesterasi	0	

[redacted]

ImmunoCAP ISAC

INFORMAZIONI CAMPIONE		INFORMAZIONI PAZIENTE			
ID Campione:	1E80927_1	ID Paziente:	4247562		
Data Campione:	07.12.2011	Nome:	[redacted]		
Stato di approvazione:	Measured	Data di nascita:	10/12/1972	Età:	38
Data di stampa:	09.12.2011	ID/MR#:		Sesso:	
Curva di calibrazione:	CTR02 30/11/2011 14.40.00				

INFORMAZIONI RICHIEDENTE	
Clinico richiedente:	ESTERNI
Address:	

baker's asthma

1. Riassunto dei risultati IgE positivi

Componenti alimentari principalmente specie-specifiche				
Noce	nJug r 2	Proteina di deposito, 7S globulina	0,4 ISU-E	
Grano	rTri a 14	Proteina di trasferimento lipidico (LTP)	1,7 ISU-E	

WDEIA

[redacted]

INFORMAZIONI PAZIENTE

ID PAZIENTE: 3845920

INFORMAZIONI RICHIEDENTE

CLINICO RICHIEDENTE

INFORMAZIONI CAMPIONE

ID CAMPIONE: 0O00324_2
Data Campione: 21.12.2010
Data di stampa: 11.01.2011

Data di nascita: Età: 45
Sesso:
ID/MR#:

ESTERNO

INFORMAZIONI FORNITE DAL CLINICO

ImmunoCAP ISAC

Risultati test IgE Allergene Specifiche

Componenti allergeniche elencate per gruppo allergenico

1. Vegetali

1.1. Componenti marker specie specifici

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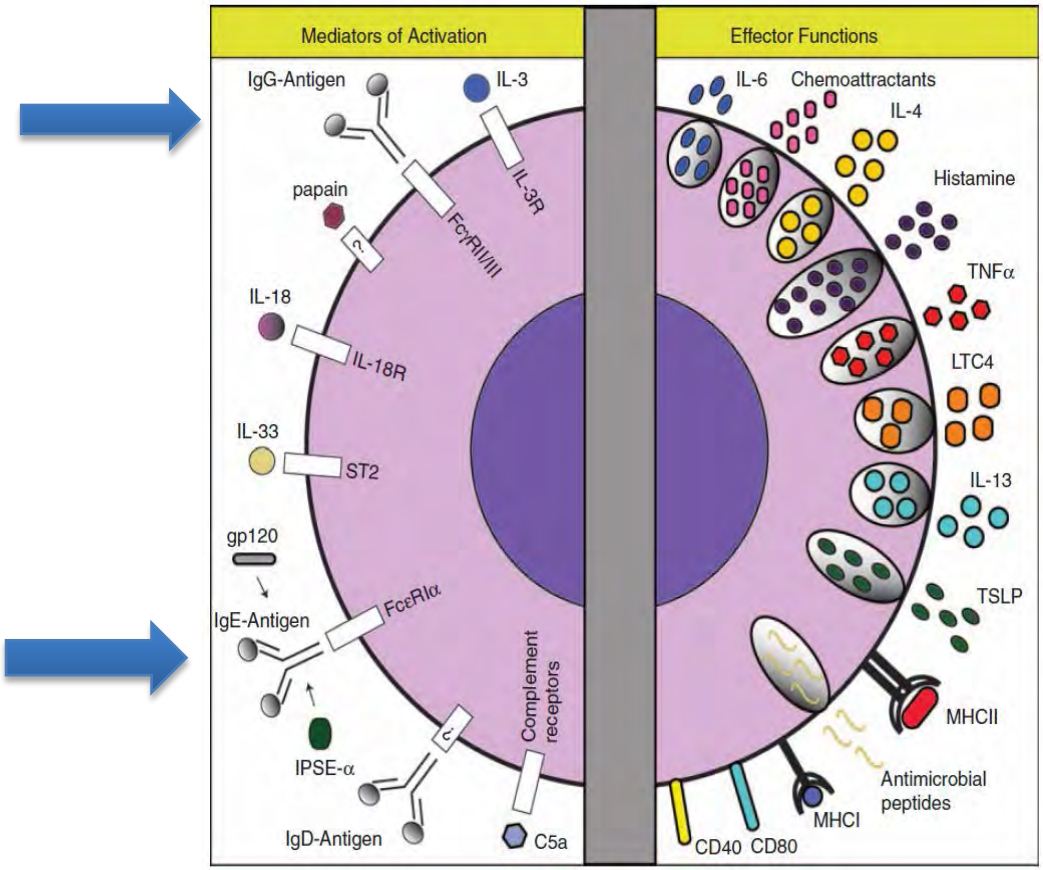
	nAct d 2	Proteine Taumatino Simili (TLP)	0	
	nAct d 5	Kiwellina	0	
Grano	nTri a 18	Agglutinina isolectina 1	0	
	nTri a Gliadin	Gliadina	0	
	rTri a 19.0101	Gliadina Omega-5	2,6	
	nTri a aA_TI	Alfa-Amilasi / Inibitori di Tripsina	0	
Erba canina	nCyn d 1	Graminacee Gruppo 1	0	
Coda di topo	rPhl p 1	Graminacee Gruppo 1	0	
	rPhl p 2	Graminacee Gruppo 2	0	
	nPhl p 4	Enzima ponte berberina (BBE)	0	
	rPhl p 5	Graminacee Gruppo 5	0	
	rPhl p 6		0	
	rPhl p 11	Proteina correlata Ole e 1	0	
Olivo	nOle e 1	Olivo comune Gruppo 5	0	
Platano	rPla a 1	Inibitori delle invertasi	0	
	nPla a 2	Poligalatturonasi	0	
Criptomeria	nCry j 1	Pectato liasi	0	
Cipresso dell'Arizona	nCup a 1	Pectato liasi	0,6	
Ambrosia Artemisiifolia	nAmb a 1	Pectato liasi	0	
Assenzio selvatico	nArt v 1	Defensina	0	
Erba cali	nSal k 1	Pectinometilesterasi	0	

TEST DI ATTIVAZIONE DEI BASOFILI (BAT)

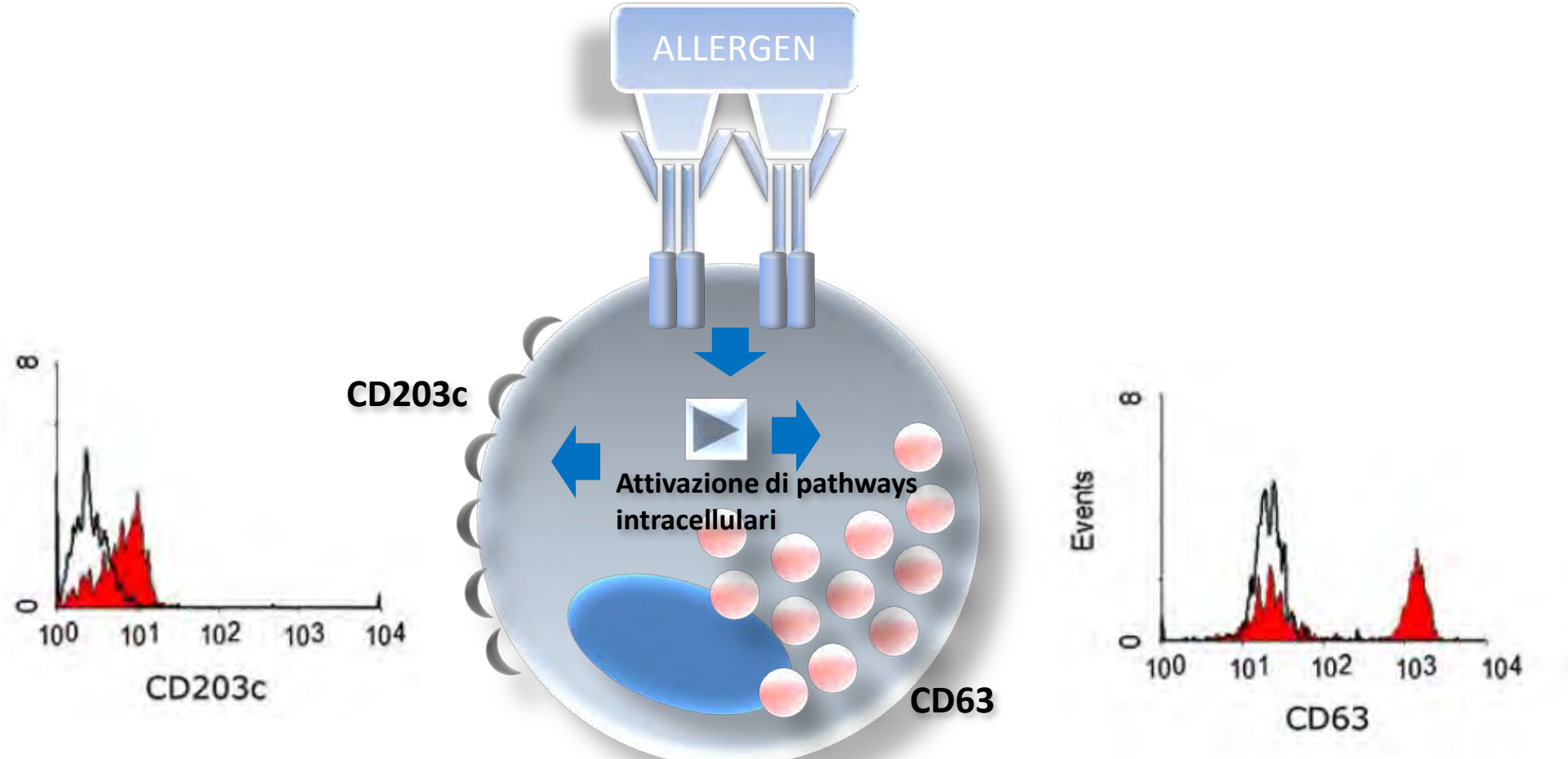
È un test funzionale che ci permette di studiare «*in vitro*» la capacità dei basofili di attivarsi e degranulare, dopo esposizione ad uno specifico allergene

Basophil activation test



Il Test di Attivazione dei Basofili (BAT) rileva "in vivo" l'espressione di particolari molecole di superficie (CD63/CD203c/CRTH2) del basofilo, coinvolte nelle reazioni allergiche, a seguito del contatto con l'allergene responsabile e conseguente liberazione di istamina.

Principi del BAT
(Basophil Activation Test)



Take home messages

- **Wheat is an important allergen source and is one of the causes of baker's asthma and food allergy**
- **Wheat allergy is one of the most common food allergies**
- **Wheat allergy is involved in 50-60% of patients with FDEIA (amount of wheat ingested as well as the degree of exercise needed vary greatly)**
- **Although it is probable that the full range of wheat proteins responsable for BA & FA has not been identified, it is likely that the major component have been characterized (α-amylase inhibitors; nsLTP, ω-5 gliadin, glutenins)**
- **Management: removal from wheat flour exposure (BA) and dietary avoidance (FA)**

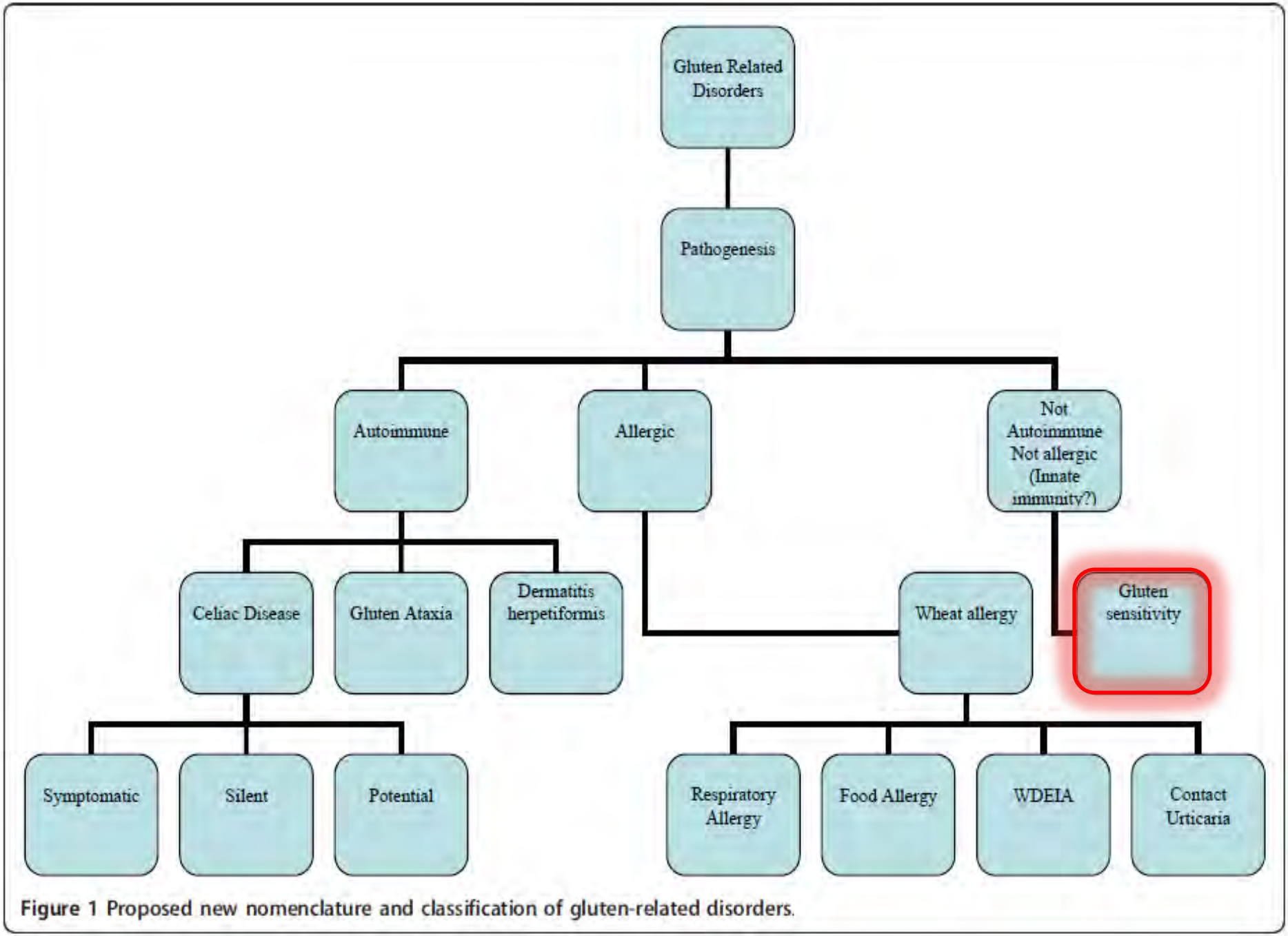


Figure 1 Proposed new nomenclature and classification of gluten-related disorders.

Gluten Sensitivity (NCGS): Facts Consensus Conferences to Define NCGS

Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, Kaukinen K, Rostami K, Sanders DS, Schumann M, Ullrich R, Villalta D, Volta U, Catassi C, Fasano A. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med. 2012 Feb 7;10:13

Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C. The Oslo definitions for coeliac disease and related terms. Gut. 2013 Jan;62(1):43-52

Catassi C, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zevallos V, Sapone A, Fasano A. Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. Nutrients. 2013 Sep 26;5(10):3839-53.

DEFINIZIONE ED EPIDEMIOLOGIA

La “gluten sensitivity”, o più precisamente “**non celiac gluten sensitivity** (NCGS)”, è una sindrome caratterizzata da sintomi intestinali ed extra-intestinali correlati all’ingestione di alimenti contenenti glutine, in soggetti non affetti da malattia celiaca (CD) né allergici al grano.

Catassi C, Bai JC, Bonaz B et al.
Non-Celiac Gluten sensitivity:
the new frontier of gluten related disorders.
Nutrients. 2013

Per quanto sia inclusa nei disordini correlati all'ingestione di glutine, molti aspetti epidemiologici e patogenetici sono ancora poco chiari.

In effetti questa entità è conosciuta da decenni: già negli anni '80 si individuarono gruppi di pazienti non celiaci con diarrea cronica, la cui sintomatologia migliorava dopo eliminazione del glutine dalla dieta, e peggiorava dopo la sua reintroduzione.

Gluten Sensitivity (NCGS): Facts
Definition

Cases of reaction to ingestion of gluten-containing grains in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion criteria)

- Triggered by the ingestion of gluten-containing grains;
- Negative immuno-allergy tests to wheat;
- Negative CD serology (EMA and/or tTG) and in which IgA deficiency has been ruled out;
- Negative duodenal histopathology;
- Possible presence of biomarkers of gluten immune-reaction (AGA+);
- Presence of clinical symptoms that can overlap with CD or wheat allergy symptomatology;
- Resolution of the symptoms following implementation of a GFD and relapse after re-exposure to gluten-containing grains (double blind)

Sapone A. et al BMC Med 2012, Ludvigsson JF et al Gut 2013, Catassi C. Et al, Nutrients 2013

La prevalenza della NCGS

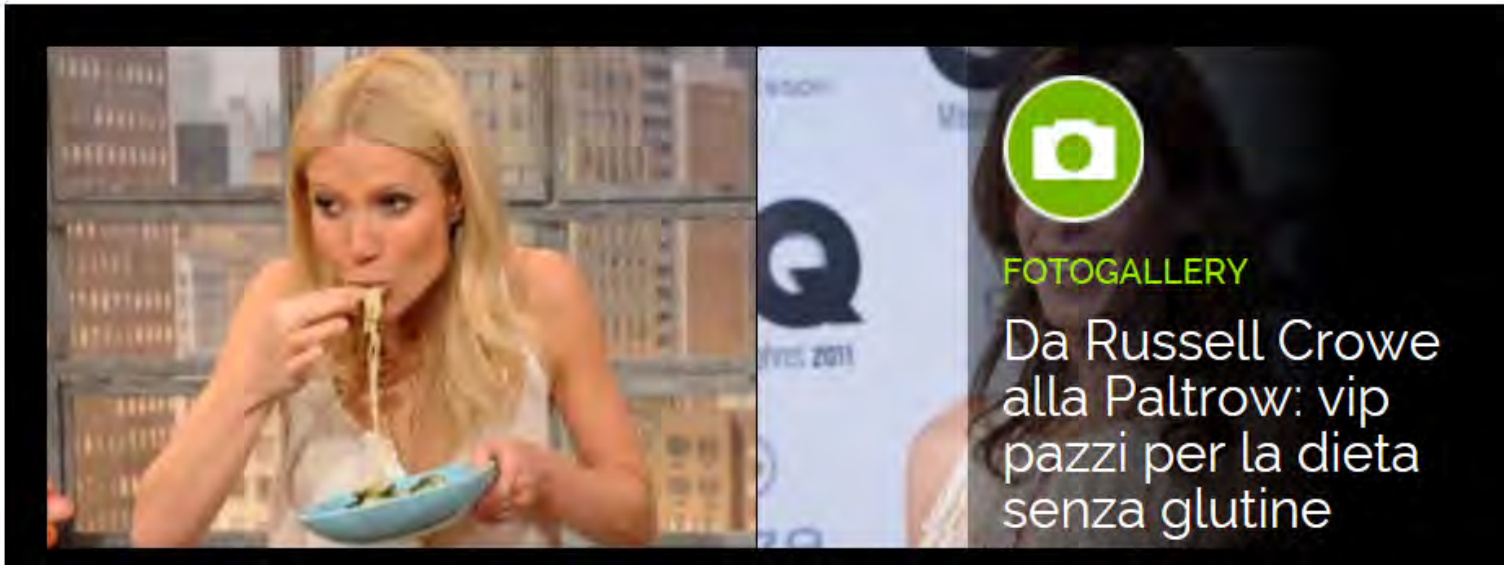
La prevalenza nella popolazione generale è difficilmente stimabile.

Aumento dei pazienti “self-diagnosed” per disturbi attribuiti al glutine che hanno iniziato la dieta senza glutine (DSG) senza indicazione medica.

La dieta senza glutine: i falsi miti della nuova mania dei vip

Dalla Paltrow a Crowe diversi attori hanno abbracciato questo regime alimentare. Ma non è tutto oro ciò che luccica

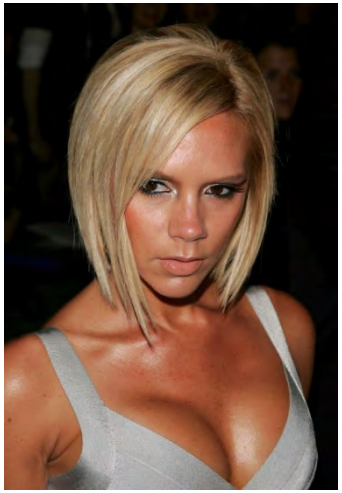
Pubblicato il **16 ottobre 2013**



•Dichiarazioni in cui si celebrano i benefici di una scelta così radicale, non dettata da un obbligo di salute come per chi è affetto da **celiachia**, ma dall'esigenza di dimagrire.

•**Falsi miti**.

•Nessuna correlazione tra alimentazione senza glutine e perdita di peso.



•I cibi senza glutine non sono dimagranti.

•Sostituire un prodotto con il glutine con uno *gluten-free*, molto spesso ricco di grassi non sposta l'ago della bilancia.

•Esiste una grande varietà di cibo senza glutine.

•Rischia di filtrare , erroneamente, il messaggio che i nutraceutici senza glutine siano più sani.

•Solo gli alimenti naturali che vengono consumati in una dieta senza glutine sono notoriamente sani: **carne, pesce, uova, formaggi, latte, verdure, frutta, riso, patate**.

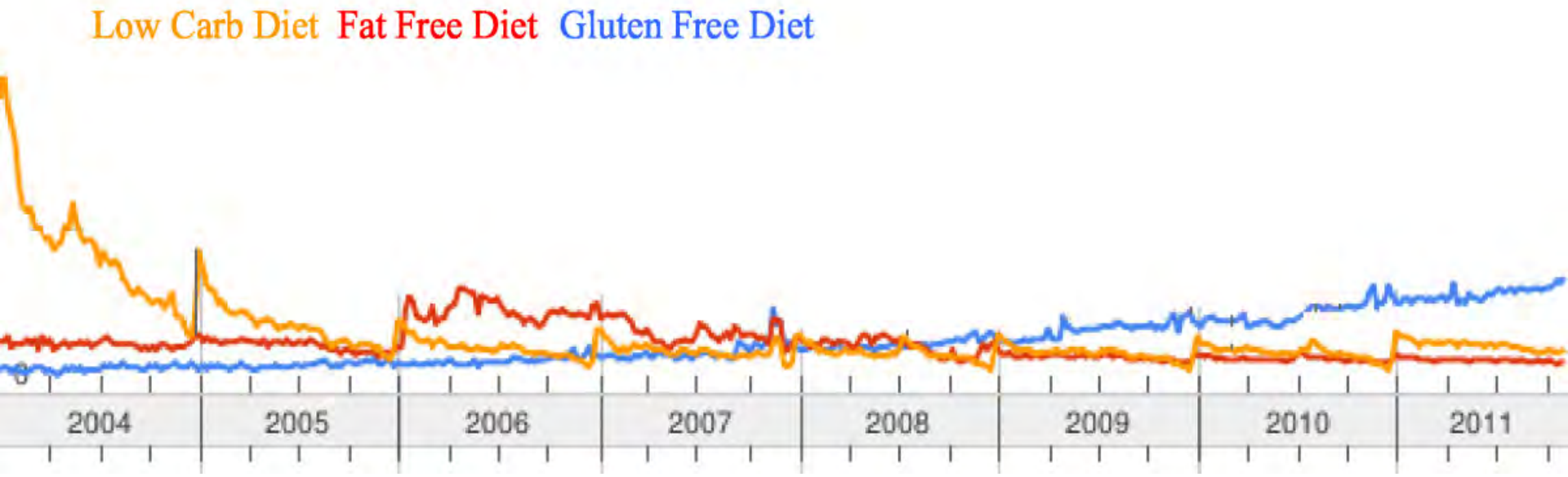
Hype?!


Daily Mail, Tuesday, October 1, 2013
Good Health
Feeling bloated? Always tired? You may be a victim of a hidden epidemic
How one in ten could be wheat intolerant – but not even know
THE SUNDAY TIMES
thesundaytimes.co.uk/news
28.10.12
9
Stars' diet is free of gluten but full of fat
Celebrities claim to lose weight with wheat-free food, but it is often full of calories – and pricy, writes Kathryn Cooper
House price rise gathers pace

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
THE CHALLENGE OF NON-COELIAC GLUTEN SENSITIVITY

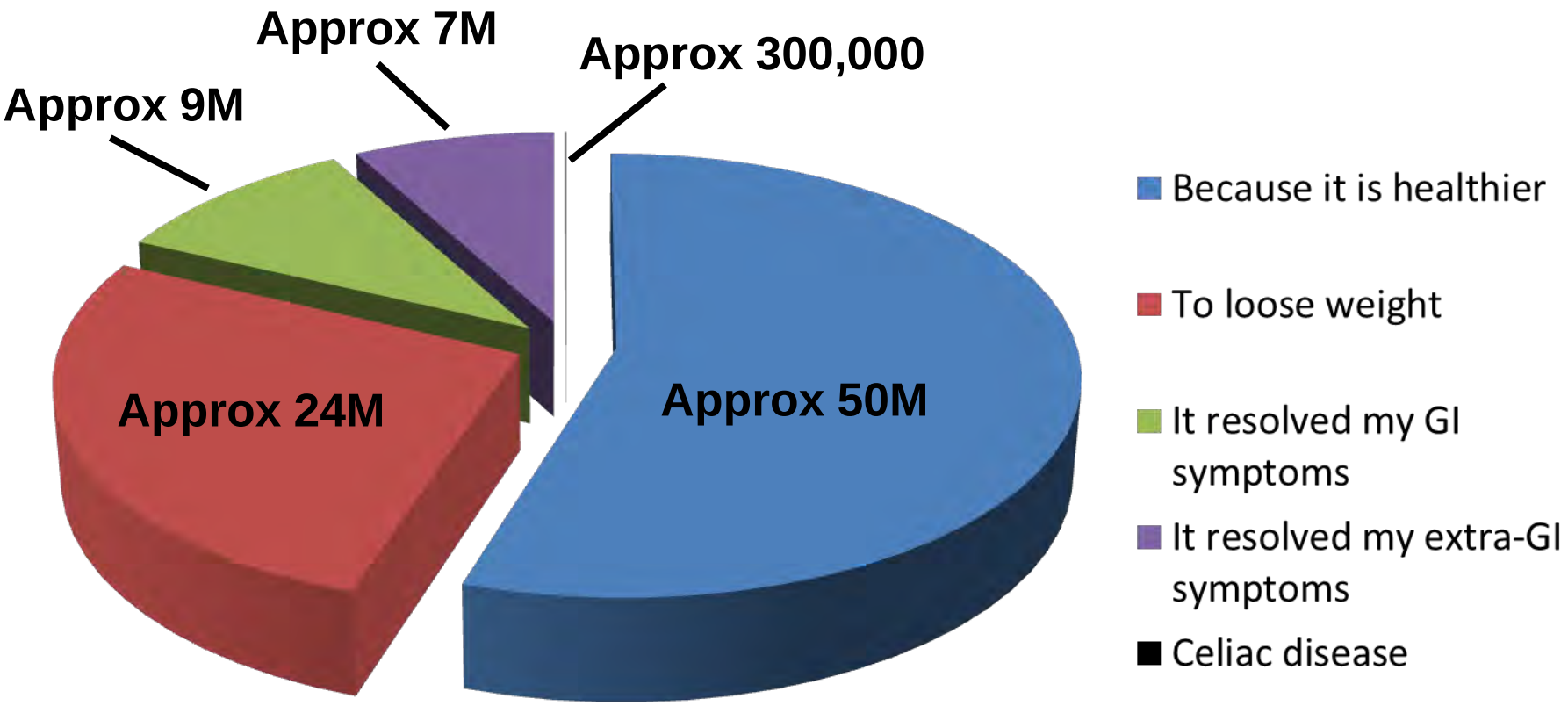
Gluten Free Market



For the American general population adopting a gluten-free diet is becoming an increasingly popular solution. The market for gluten-free food and beverage products grew at a compound annual growth rate of 28 percent/year from 2004 to 2011, to finish with almost $6.7 billion in retail sales last year. By the end of 2014 the market is expected to reach about $10.2 billion in sales.

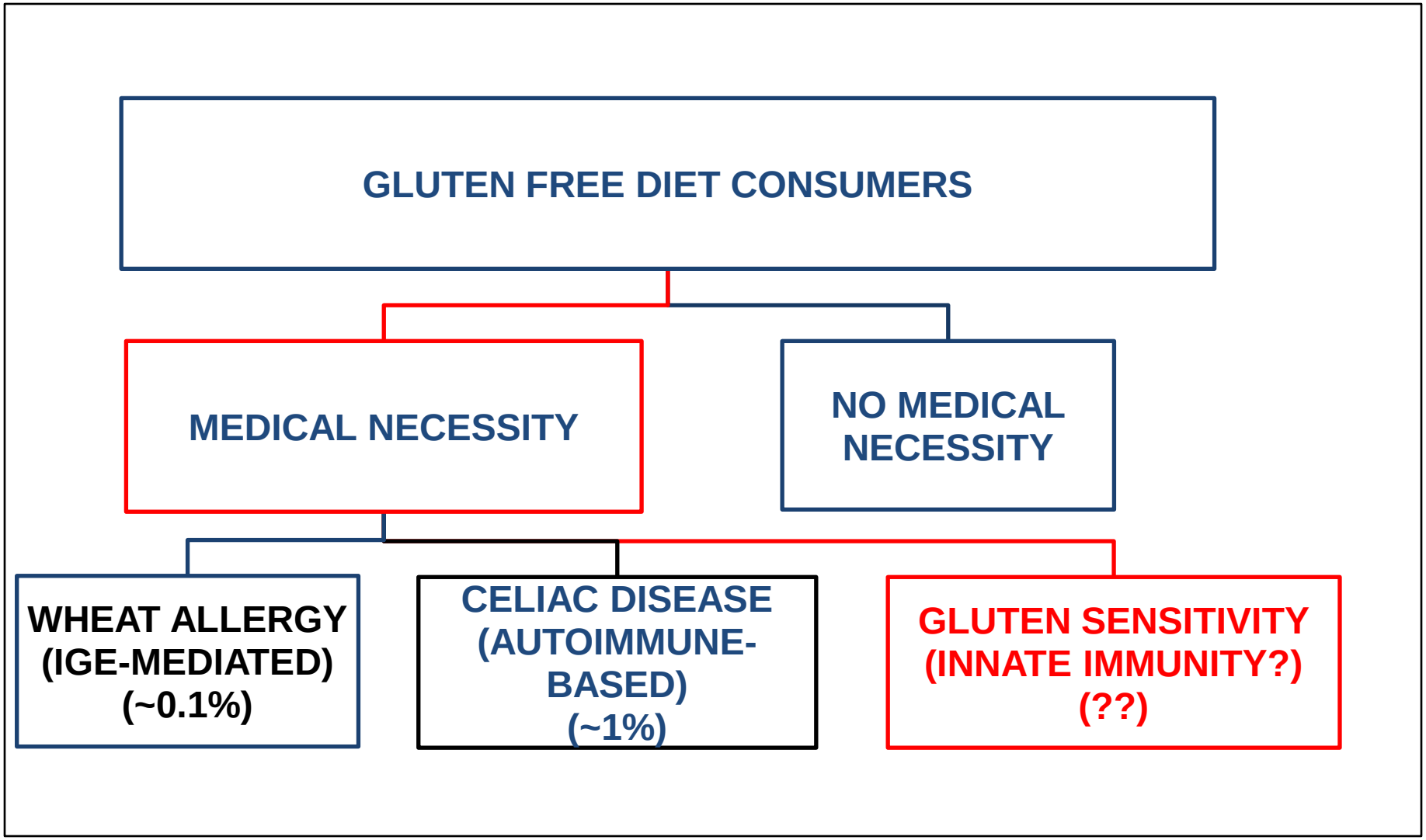
The fact that approximately 3 million Americans suffer from celiac disease and only a fraction of these patients have been diagnosed **implies that patients suffering of other forms of proven gluten reaction, including gluten sensitivity and wheat allergy, contribute to this market growth.** *The rest of the market is filled by people affected by maladies claimed to be affected by gluten exposure, including autism, ADHD, multiple sclerosis, IBS, and ADHD.*

Why People in the US Embrace a GFD?



Based on internet interview users age 18y+ who eats GF food

The Gluten Free Diet:
Not Only Celiac Disease



La prevalenza della NCGS

La NCGS sembrerebbe un disturbo piuttosto comune: in uno studio statunitense, condotto su 7.762 persone (> 6 anni di vita) coinvolte nel "National Health and Nutrition Examination Survey" (NHANES), è stata stimata una percentuale dello **0,55%** di pazienti a DSG auto-prescritta, con una prevalenza più alta nelle donne e nei pazienti adulti.

Sapone A et al: Int Arch Allergy Immunol 2010

La prevalenza della NCGS

Altri studi hanno mostrato **prevalenze variabili tra lo 0,6% e il 6%.**

Gli importanti limiti di queste stime è che si tratta di dati spesso provenienti dai centri specialistici e in ogni caso la relazione tra sintomi gastrointestinali e l'intake di glutine non è stata adeguatamente esplorata.

Sapone A et al: BMC Med 2011

DBPC

Gold standard diagnosi è il challenge con glutine in doppio cieco controllato con placebo (double-blind placebo-controlled challenge, DBPC), con comparsa di sintomi intestinali ed extraintestinali direttamente correlabili all'ingestione di glutine e la loro scomparsa con l'eliminazione dello stesso dalla dieta.

Biesiekierski JR et al:
Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial.
Am J Gastroenterol 2011

DBPC

non è di facile esecuzione nella pratica clinica

In pochissimi studi i pazienti sono stati correttamente diagnosticati e ciò rappresenta un importante limite per molte delle informazioni disponibili circa la clinica e la patogenesi di questa condizione.

La conferma diagnostica basata sulla risoluzione dei sintomi con dieta aglutinata è confondente…

(anche i pazienti con IBS e normale biopsia o con altre patologie si giovano della dieta)

Esteve M et al. Gut 2006

Dietary beliefs of people with ulcerative colitis and their effect on relapse and nutrient intake.

Jowett SL, Seal CJ, Phillips E, Gregory W, Barton JR, Welfare MR. Clin Nutr. 2004 Apr;23(2):161-70.

BACKGROUND & AIMS:

Ulcerative colitis usually follows a relapsing and remitting course. Patients believe that dietary factors are important. We wished to determine the nature of and reasons for patients' dietary beliefs and their effect on relapse and nutrient intake.

RESULTS:

One hundred and eighty-three patients were studied and 52% relapsed. Sixty-eight per cent held dietary beliefs and reported modifying their intake accordingly. The most common reported behaviour was the avoidance of milk and dairy products. Food beliefs were more common amongst those who had received dietary advice. No reported behaviour reduced the risk of relapse, but patients who avoided dairy products had a significantly lower intake of calcium. Folate intake was below UK recommended levels in 13% of patients.

CONCLUSIONS:

Patients with ulcerative colitis believe that many foods are harmful or helpful to their disease activity.

Commonly held beliefs do not modify the risk of relapse, but do adversely affect nutrient intake.

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

Effects of enteral nutrition on Crohn's disease: clues to the impact of diet on disease pathogenesis.

Levine A, Wine E. Inflamm Bowel Dis. 2013 May;19(6):1322-9

Crohn's disease is a complex inherited disorder of unknown pathogenesis with environmental, genetic, and microbial factors involved in the development of the disease. A remarkable feature of this disease, especially, but not limited to childhood, is the effective response to exclusive enteral nutrition therapy and the observed benefit from exclusion of normal diet (principle of exclusivity). We reviewed the ***possible mechanisms of action of enteral nutrition*** for induction of remission and provided a ***hypothetical model*** (herein termed bacterial penetration cycle) that integrates dietary components, bacteria, susceptibility genes, and the innate immune response in the pathogenesis of Crohn's disease.

Existing dietary guidelines for Crohn's disease and ulcerative colitis.

Brown AC, Rampertab SD, Mullin GE.

Expert Rev Gastroenterol Hepatol. 2011 Jun;5(3):411-25

Patients with inflammatory bowel disease (IBD) often question their doctors about diet. The objectives of this article are to provide clinicians with existing dietary advice by presenting the dietary information proposed by medical societies in the form of clinical practice guidelines as it relates to IBD; listing dietary guidelines from patient-centered IBD-related organizations; and creating a new 'global practice guideline' that attempts to consolidate the existing information regarding diet and IBD. The dietary suggestions derived from sources found in this article include nutritional deficiency screening, avoiding foods that worsen symptoms, eating smaller meals at more frequent intervals, drinking adequate fluids, avoiding caffeine and alcohol, taking vitamin/mineral supplementation, eliminating dairy if lactose intolerant, limiting excess fat, reducing carbohydrates and **reducing high-fiber foods during flares.** Mixed advice exists regarding probiotics. Enteral nutrition is recommended for Crohn's disease patients in Japan, which differs from practices in the USA.

A "global" clinical practice guideline summarizing dietary advice for IBD patients
(ADA, WGO, ASPEN, ESPEN, CCFA, Japanese Society for PGHN)

- Screen all IBD patients for nutritional deficiencies, expecially children. Consider suggesting a vitamin/mineral supplement and/or specific supplementation based on individual patient history.
- Dietary suggestion my include to eat smaller, more frequent meals, consume sufficient liquids (water), decrease exess saturated fat, decrease exess sugars (dysaccharides and polysaccharides) and decrease high fibr foods during flares.
- Educate IBD patients about possible food sensitivities and consider 2-week trial elimination diet for their detection ***(consider casein and gluten as the two top offenders)***
- Educate CD patients about the benefits of eteral or oral elemental supplementation options.

Brown aC, et al. Expert Rev Gastroenterol hepatol 2011; 5:411-425

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

Effect of gluten-free diet on preventing recurrence of gastroesophageal reflux disease-related symptoms in adult celiac patients with nonerosive reflux disease.

Usai P et al

J Gastroenterol Hepatol 2008 Sep;23(9):1368-72.

BACKGROUND AND AIM:

In celiac disease (CD) the role of a gluten-free diet (GFD) on gastroesophageal reflux disease-related symptoms (GERD-rs) is unclear. The aim of this study was to establish the recurrence of GERD-rs, in CD patients with nonerosive reflux disease (NERD).

METHODS:

29/105 CD patients who presented NERD. 30 non-CD patients with NERD as controls. Recurrence of GERD-rs after withdrawal of PPI for 8 weeks.

RESULTS:

GERD-rs were resolved in 25 (86.2%) CD patients and in 20 (66.7%) controls after 8 weeks of PPI treatment. In the CD group, recurrence of GERD-rs in 5/20 cases (20%) at 6 months but in none at 12, 18, and 24 months while in the control group recurrence was found in 6/20 controls (30%), in another six (12/20, 60%), in another three (15/20, 75%), and in another two (17/20, 85%) at 6, 12, 18, and 24 months follow-up respectively.

CONCLUSIONS:

The present study is the first to have evaluated the effect of a GFD in the nonerosive form of GERD in CD patients, by means of clinical long-term follow-up, suggesting that GFD could be a useful approach in reducing GERD symptoms and in the prevention of recurrence.

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Gastroesophageal reflux symptoms in patients with celiac disease and the effects of a gluten-free diet.

Nachman F et al.

Clin Gastroenterol Hepatol. 2011 Mar;9(3):214-9

BACKGROUND and AIMS:

To assess the prevalence of GERD symptoms at diagnosis of CD and to determine the impact of the gluten-free diet (GFD).

METHODS:

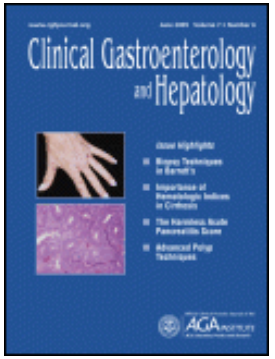
133 adult CD patients at diagnosis and 70 healthy controls. 53 patients completed the study.

RESULTS:

At diagnosis, celiac patients had a significantly higher reflux symptom mean score than healthy controls ($P < .001$). At baseline, 30.1% of CD patients had moderate to severe GERD (score >3) compared with 5.7% of controls ($P < .01$). A rapid improvement was evidenced at 3 months after initial treatment with a GFD ($P < .0001$) with reflux scores comparable to healthy controls from this time point onward.

CONCLUSIONS:

GERD symptoms are common in classically symptomatic untreated CD patients. The GFD is associated with a rapid and persistent improvement in reflux symptoms that resembles the healthy population.



Basilio Malamisura

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Does gluten cause gastrointestinal symptoms in subjects without coeliac disease?

Newnham ED

J Gastroenterol Hepatol. 2011 Apr;26 Suppl 3:132-4

AIM:

To determine the evidence for the effect of gluten ingestion on gastrointestinal symptoms, intestinal permeability and other indices of small intestinal injury in non-coeliac, gluten intolerant individuals.

CONCLUSIONS:

Non-coeliac gluten intolerance does exist.

Future studies need to identify issues of the dose of gluten needed and mechanisms of action.

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Homemade Gluten-Free Pasta Is as Well or Better Digested Than Gluten-Containing Pasta

G. Clemente and al.

Journal of Pediatric Gastroenterology and Nutrition 32:110–113 © January 2001

- 20 healthy medical students less than 30 years of age, body mass index less than 25 kg/m2.
- After a 15-hour fast, 100 g of home-made gluten-free pasta or ordinary gluten-containing pasta made with the best Italian durum wheat.

TABLE 1. *Nutritional values/100 g dry product*

	Gluten containing	Gluten free
KCal	366	347
Protein (%)	13.8 g	10.2 g
Fat (%)	5.0 g	5 g
Carbohydrate (%)	69.5 g	71 g

TABLE 2. *Self-perceived quality of the products tested: Median values from a score 0 to 4**

	With gluten	Without gluten	*P*†
Taste	3	3	0.57
Texture	3	2	0.0001
Fullness	3	2	0.0076
Satiety	3	2	0.018

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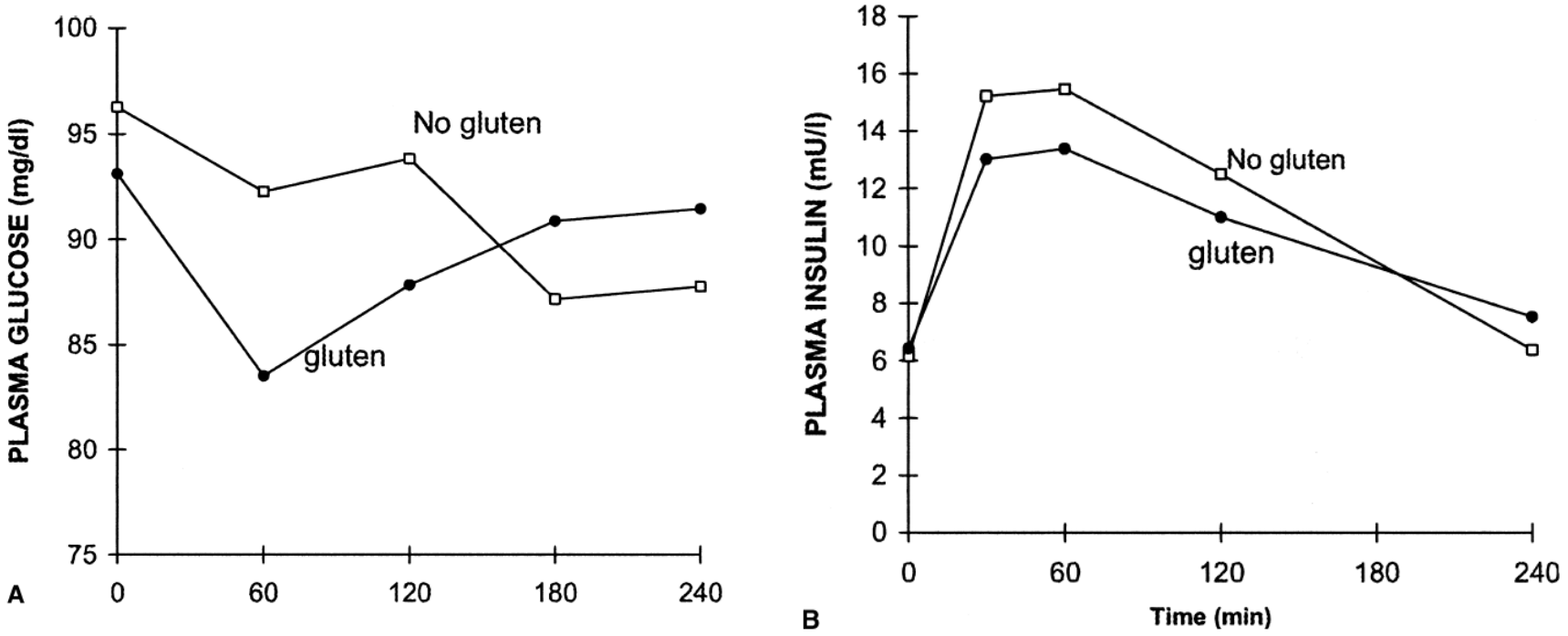

FIG. 1. Postprandial plasma glucose (**A**) and insulin (**B**) responses to the gluten-free pasta meal o and gluten-containing pasta meal l (*$P < 0.05$).

Homemade Gluten-Free Pasta Is as Well or Better Digested Than Gluten-Containing Pasta

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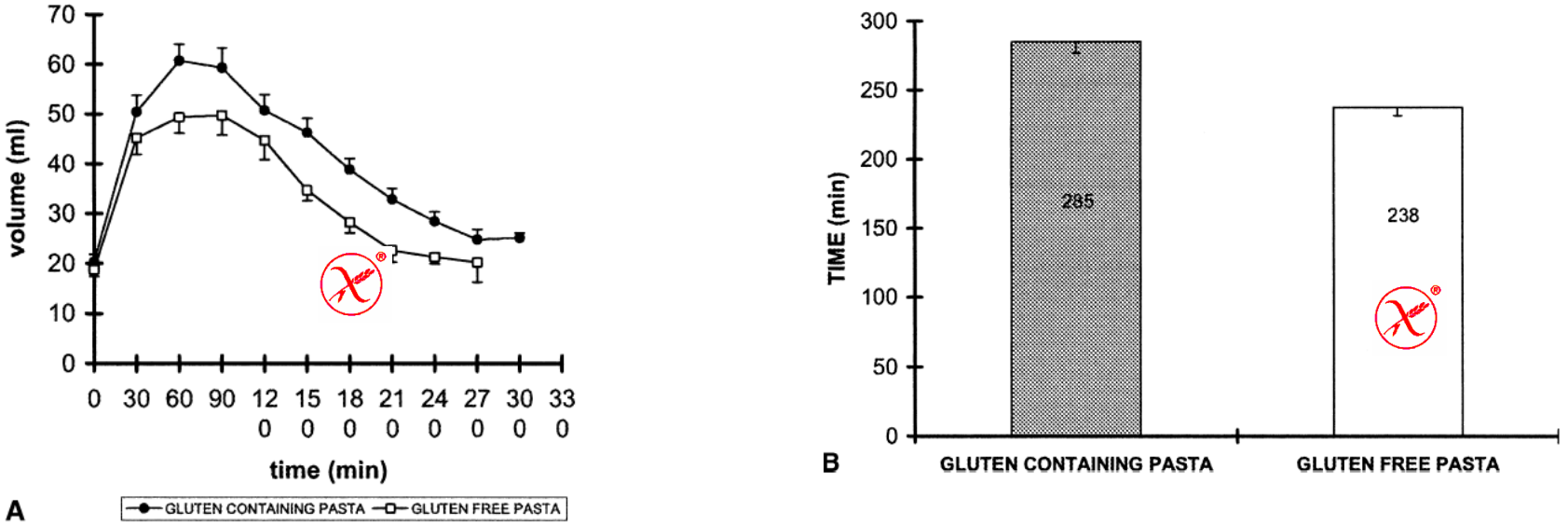
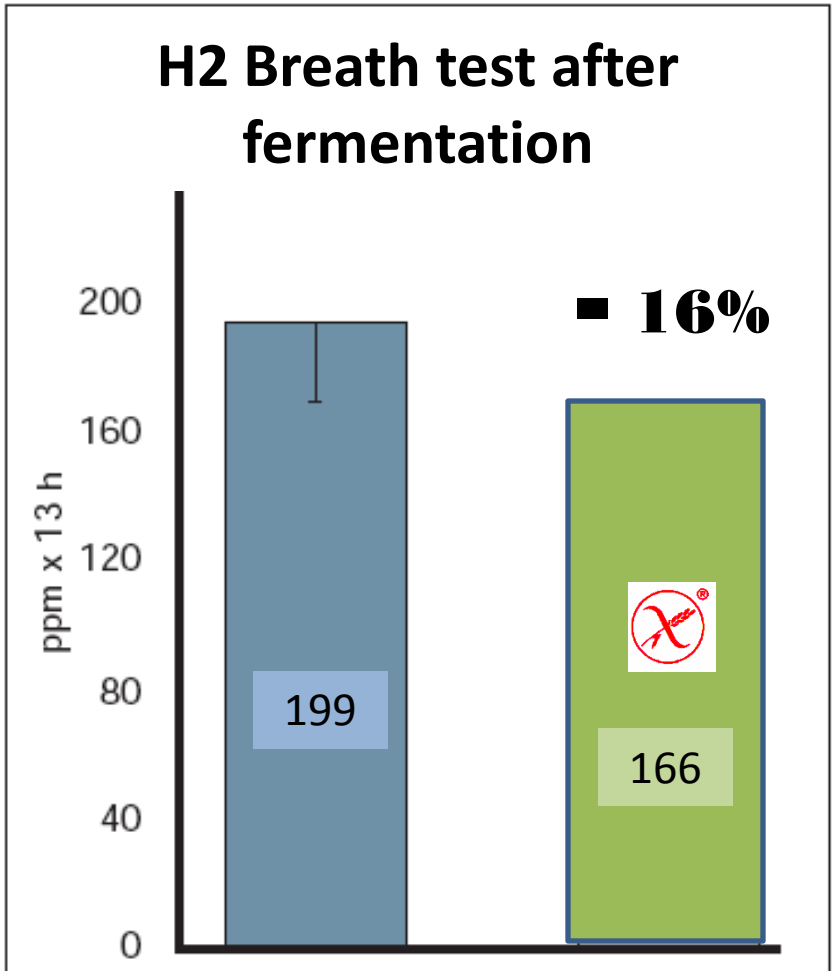


FIG. 2. Gastric antrum volume (**A**) and gastric emptying time (**B**) before and after the gluten-free pasta meal o and gluten-containing pasta meal l (*$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$).



Hydrogen production was minimal after both meals, but 199 ppm/hr hydrogen was produced after consumption of gluten-containing pasta; this valued peaked at 11 hours, corresponding to approximately 17.7 g of undigested carbohydrate (5 g lactulose produced 56 ppm hydrogen), which is significantly more than after consumption of gluten-free pasta (166 ppm/hr, corresponding to 14.8 g of undigested carbohydrate).

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Food: the forgotten factor in the irritable bowel syndrome.

Eswaran S, Tack J, Chey WD

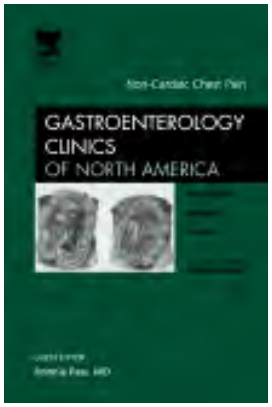
Gastroenterol Clin North Am 2011 Mar;40(1):141-62.

…evidence to suggest that **dietary constituents** at least **exacerbate symptoms and perhaps contribute to the pathogenesis of the irritable bowel syndrome (IBS)**

…**self-report food allergies** more often than the general population, the evidence suggests that true food allergies are relatively uncommon.

Less clearly defined **food intolerances may be an important contributor to symptoms in IBS patients.**

…supporting a **causal link between food and the symptoms of IBS** as well as the evidence supporting dietary interventions as a means of managing IBS symptoms.



AP&T Alimentary Pharmacology and Therapeutics

Personal view: food for thought – western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis

P. R. Gibson[1], S. J. Shepherd[2]

Issue

Alimentary Pharmacology & Therapeutics

Volume 21, Issue 12, pages 1399–1409, June 2005

Evidence supporting this hypothesis includes the increasing intake of FODMAPs in western societies, the association of increased intake of sugars in the development of Crohn's disease, and the previously documented effects of the ingestion of excessive FODMAPs on the bowel. This hypothesis provides potential for the design of preventive strategies and raises concern about current enthusiasm for putative health-promoting effects of FODMAPs.

Food choice as a key management strategy for functional gastrointestinal symptoms.

Gibson PR, Shepherd SJ. Am J Gastroenterol. 2012 May;107(5):657-66;

Recognition of food components that induce functional gut symptoms in patient's functional bowel disorders (FBD) has been challenging. Food directly or indirectly provides considerable afferent input into the enteric nervous system. There is an altered relationship between the afferent input and perception/efferent response in FBD. Defining the nature of food-related stimuli may provide a means of minimizing such an input and gut symptoms. Using this premise, reducing the intake of FODMAPs (fermentable oligo-, di-, and mono-saccharides and polyols)--poorly absorbed short-chain carbohydrates that, by virtue of their small molecular size and rapid fermentability, will distend the intestinal lumen with liquid and gas--improves symptoms in the majority of patients. Well-developed methodologies to deliver the diet via dietician-led education are available. Another abundant source of afferent input is natural and added food chemicals (such as salicylates, amines, and glutamates). Studies are needed to assess the efficacy of the low food chemical dietary approach. A recent placebo-controlled trial of FODMAP-poor gluten provided the first valid evidence that non-celiac gluten intolerance might actually exist, but its prevalence and underlying mechanisms require elucidation. **Food choice via the low FODMAP and potentially other dietary strategies is now a realistic and efficacious therapeutic approach for functional gut symptoms.**

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

F ermentable

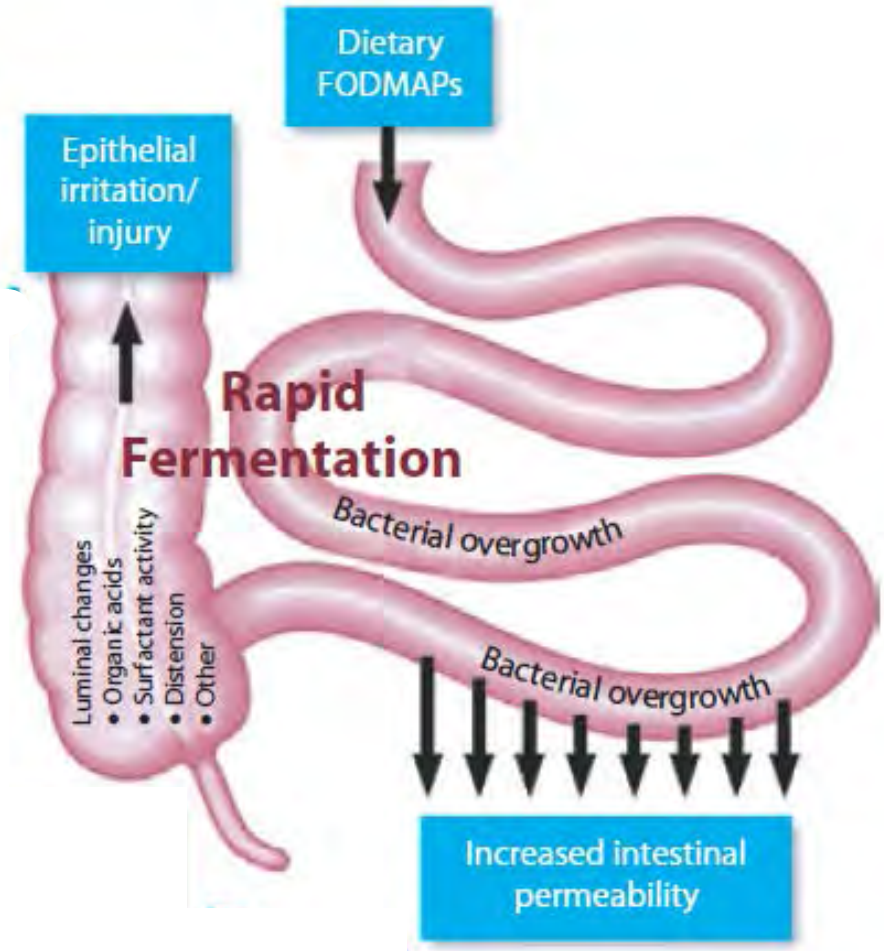
O ligosaccharide

D isaccharides

M onosaccharide

A nd

P olyols



Shepherd SJ, Am J Gast 2013;108(5):707–17

Gibson PR, Aliment Pharmacol Ther. 2005 Jun 15;21(12):1399-409.

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

Food sources of FODMAPs (where FODMAPs are problematic based on standard serving size) and suitable alternatives

FODMAP	Excess fructose	Lactose	Oligosaccharides (fructans and/or galactans)	Polyols
Problem high FODMAP food source	*Fruits:* apples, pears, nashi pears, clingstone peaches, mango, sugar snap peas, watermelon, tinned fruit in natural juice *Honey* *Sweeteners:* fructose, high fructose corn syrup *Large total fructose dose:* concentrated fruit sources; large serves of fruit, dried fruit, fruit juice	*Milk:* cow, goat and sheep (regular & low-fat), Ice cream *Yoghurt* (regular & low-fat) *Cheeses:* soft & fresh (e.g. ricotta, cottage)	*Vegetables:* artichokes, asparagus, beetroot, Brussels sprout, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots. *Cereals:* wheat & rye when eaten in large amounts (e.g. bread, pasta, couscous, crackers, biscuits) *Legumes*: chickpeas, lentils, red kidney beans, baked beans *Fruits:* watermelon, custard apple, white peaches, rambutan, persimmon	*Fruits:* apples, apricots, cherries, longon, lychee, nashi pears, nectarine, pears, peaches, plums, prunes, watermelon *Vegetables:* avocado, cauliflower, mushrooms, snow peas *Sweeteners:* sorbitol(420), mannitol(421), xylitol(967), maltitol (965), isomalt (953) & others ending in '-ol'
Suitable alternative low-FODMAP food source	*Fruit:* banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon, strawberry, tangelo. *Honey substitutes:* maple syrup, golden syrup *Sweeteners:* any except polyols	*Milk:* lactose-free, rice milk *Cheese:*'hard' cheeses including brie, camembert *Yoghurt:* lactose-free *Ice cream substitutes:* gelati, sorbet *Butter*	*Vegetables:* bamboo shoots, bok choy, carrot, celery, capsicum, choko, choy sum, corn, eggplant, green beans, lettuce, chives, parsnip, pumpkin, silverbeet, spring onion (green only), tomato *Onion/garlic substitutes:* garlic-infused oil *Cereals:* gluten-free & spelt bread/cereal products	*Fruits:* banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon *Sweeteners:* sugar (sucrose), glucose, other artificial sweeteners not ending in 'ol'

Gibson PR, Sheperd SJ. J Gastroenterol Hepatol. 2010;25:252-258

Therapeutic Advances in Gastroenterology
SAGE

Therap Adv Gastroenterol

Table 1.

FODMAP carbohydrates and their richest food sources.

FODMAP	Richest food sources
Fructo-oligosaccharides (fructans)	Wheat, rye, onions, garlic, artichokes, leek, barley
Galacto-oligosaccharides (GOS)	Legumes, nuts
Lactose	Milk
Fructose	Honey, apples, pears, watermelon, mango
Sorbitol	Apples, pears, stone fruits, sugar-free mints/gums
Mannitol	Mushrooms, cauliflower, sugar-free mints/gums, chicory, fennel

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

AJG The American Journal of GASTROENTEROLOGY

Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial

Biesiekierski JR et al

Am J Gastroenterol 201

Between 5-20% of IBS cases are due to NC-GS

OBJECTIVES:

To d

M

bowel syndrome. Celiac disease

RE

the study as per protocol. 56% had HLA-DQ2 and/or DQ8. 68% in the adequately controlled compared with 40% on placebo (P=0.0001). Patients were within 1 week for overall symptoms (P=0.047), pain (P=0.016), bloating (P=0.031), satisfaction sistency (P=0.024), and tiredness (P=0.001). No significant changes in fecal lactoferrin, levels of celiac ntibodies, highly sensitive C-reactive protein, or intestinal permeability.

CONCLUSIONS:

"Non-celiac gluten intolerance" may exist, but no clues to the mechanism were elucidated.

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

GLUTEN SENSITIVITY

- Does it occur only in adults or in children?
- How do we diagnose it?
- **Is it really gluten-induced?**

C 302 | JESSICA BIESIEKIERSKI

No evidence of gluten-induced gastrointestinal-symptoms in self-reported non-celiac gluten sensitivity: A randomized controlled evaluation

BIESIEKIERSKI JR | NEWNHAM ED | ROSELLA O | MUIR JG | GIBSON PR.

C 310 | ALBERTO LANZINI

"Non celiac gluten sensitivity" (NCGS) is uncommon in patients spontaneously adhering to gluten free diet (GFD), and is outnumbered by "FODMAPs sensitivity"

BARBARA ZANINI | ROBERTA BASCHÈ | ALICE FERRARESI | CHIARA RICCI | FRANCESCO LANZAROTTO | ALBERTO LANZINI

Il rapporto tra IBS e disturbi correlati al glutine è complesso e viene suggerito un legame tra IBS e NCGS.

La relazione tra sintomi IBS-like e dieta priva di glutine non può essere definita senza uno studio randomizzato e controllato.

Gastroenterology
OFFICIAL JOURNAL OF THE AGA INSTITUTE

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. GIBSON[2]

GASTROENTEROLOGY 2013;145:320–328

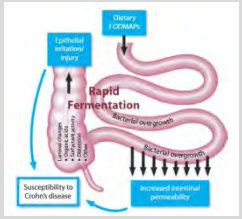
In questo studio non si evidenziano effetti specifici o dose-dipendenti del glutine, una volta esclusi i FODMAPs, in una coorte di pazienti con NCGS “autoriportata” e sintomi IBS-like.

Biesiekierski JR et al. No effects of gluten in patients with self-reported nonceliac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology. 2013 Aug

Design – RDBPCT (Crossover)

Low FODMAP diet

1 Week | **2 Weeks** | **1 Week** | **> 2 Weeks**



Screening

Run in / Low FODMAP diet

High gluten (16g)

Low Gluten (2g)

Placebo (0g)

Washout

Washout

Washout

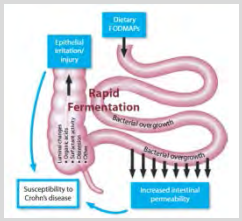
Gluten free diet

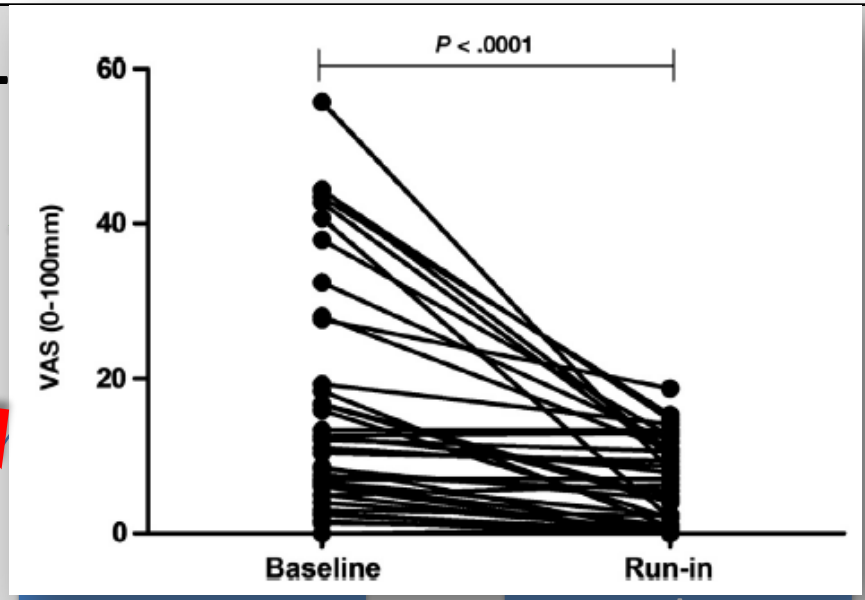
Design – RDBPCT (Crossover)

L

1 Week

2 Weeks





Screening

Run in / Low FODMAP diet

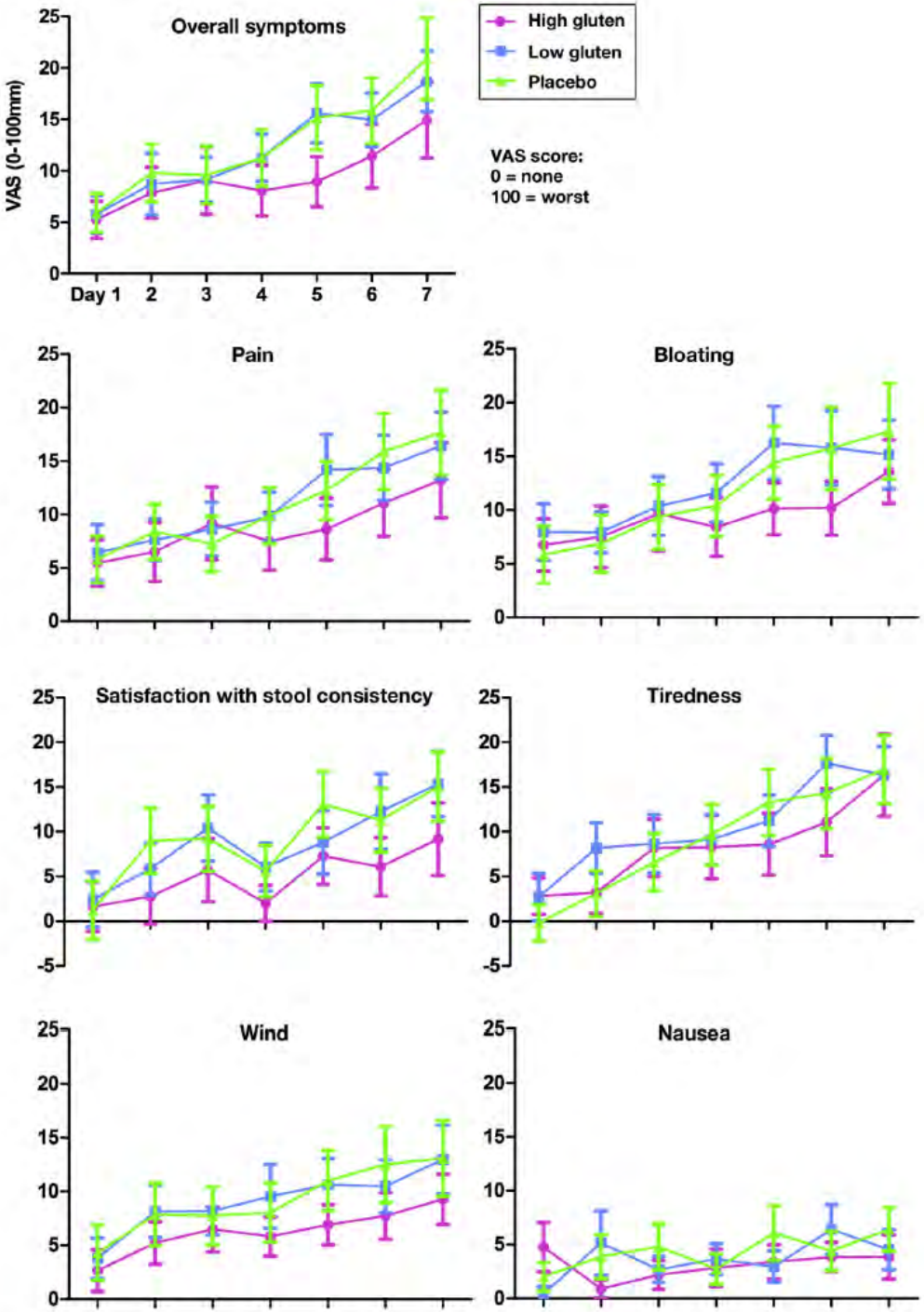
(2g)

Washout

Placebo (0g)

Washout

Gluten free diet



Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

Assessments (1)

- No difference
  - Symptoms
  - Biomarkers
  - Stool markers

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

Assessments (2)

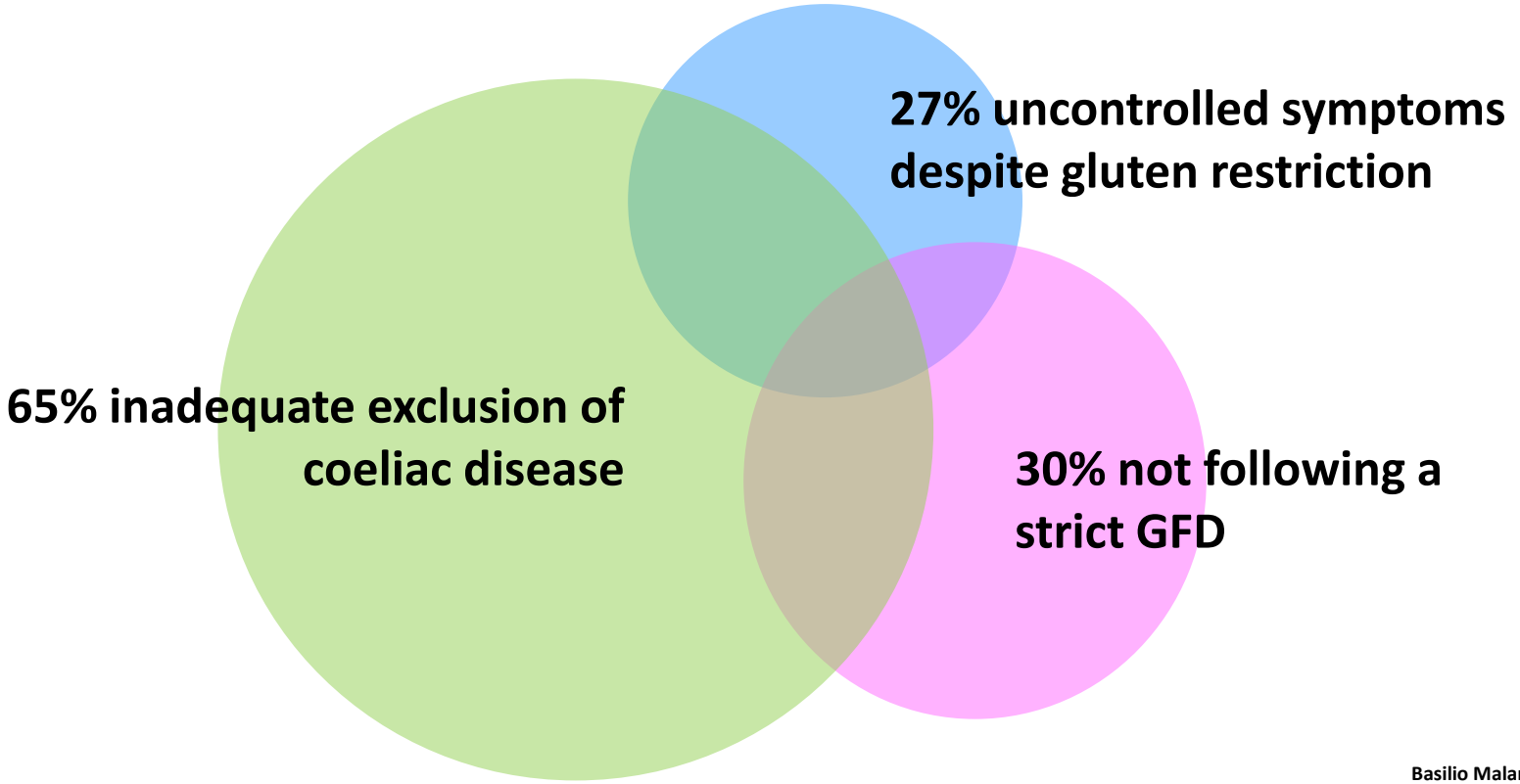
- In a placebo-controlled cross-over rechallenge study no evidence of specific or dose dependent effects of gluten in patients with NCGS placed diets low in FODMAPs
- Gluten specific effects were observed only in 8% of participants
- Therefore, NCGS does not exist !!!

- ***Permanent or transitory***
- ***Threshold of sensitivity***

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

Is it really NCGS?

- **71% (93/132) did not meet NCGS criteria:**



Biesiekierski JR, Newnham ED et al Submitted Aug 2013

Basilio Malamisura
Centro Diagnosi Celiachia - Cava de' Tirreni

Major raised issues

- The population study included IBS pts fulfilling ROME III criteria (recurrent abdominal pain or discomfort and a marked change in bowel habit) and no patient with NCGS
- The only extra-intestinal symptoms considerd were fatigue and sleep abnormalities
- What about the large panel of extra-intestinal symptoms of NCGS? (headache, arthro-myalgias, numbness, skin rash, foggy mind etc…)

Secondo questi autori, il ruolo del glutine nell'insorgenza dei sintomi della NCGS andrebbe ridimensionato, valorizzando invece il peso di altri nutrienti, in particolare gli oligo e monosaccaridi fermentabili e polioli (FODMAPs), presenti nel grano ma anche in altri alimenti come alcuni vegetali.

Biesiekierski JR et al. No effects of gluten in patients with self-reported nonceliac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology. 2013 Aug

Secondo altri sarebbe più corretto parlare di "sensibilità al grano non celiaca" (*Non Celiac Wheat Sensitivity - NCWS).*

NCGS or NCWS… that's the question!

Carroccio A, Mansueto P, Iacono G et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. Am J Gastroenterol. 2012

CARATTERISTICHE DEI PAZIENTI

Caratteristiche dei pazienti NCGS ancora poco chiare.

Studio prospettico multicentrico condotto in Italia

(38 centri - 4 ped). Durata 1 anno.

486 pazienti con NCGS, (comparsa di sintomi dopo assunzione di glutine, scomparsa in seguito all'eliminazione del glutine dalla dieta)

Esclusa CD e allergia al grano.

410 pazienti erano donne (84%) .

Età media 38 anni.

Volta U, et al.
An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. BMC Med. 2014 May;12:85.

Sintomi >2

Sintomi gastro-intestinali

Distensione addominale *
Dolore addominale *
Nausea
Sensazione di reflusso
Stomatite aftosa
Alvo diarroico (50%)
Costipazione (24%)
Alvo alterno (27%)

Sintomi extra-intestinali

Astenia
Sensazione di malessere
Dolore osteo-artro-muscolare
Perdita di peso
Anemia
Manifestazioni cutanee

Sintomi neuropsichiatrici

Cefalea
Ansia
Senso di mente annebiata
Depressione

Il 95% di questi pazienti riferiva insorgenza dei sintomi ogni volta o quasi che assumeva cibo contenente glutine.

Associazione con altre patologie

- ✓ **IBS (47%)**
- ✓ **Intolleranze alimentari (35%)**
- ✓ **Allergie ad inalanti, alimenti o metalli (20%)**

Confermata la mancanza di associazione con l'aplotipo HLA.

Marker immunitario contro la gliadina più frequentemente individuato:

anticorpi antigliadina IgG di I generazione (**AGA IgG**), (25% dei pazienti)

Biopsia duodenale (quando effettuata)

Marsh 0 (69%)

Marsh 1 (31%)

Rapporto nuove diagnosi di NCGS/celiachia

1,15:1

0,29:1 (solo ped)

Lo studio è interessante perché offre uno spaccato di come è percepita oggi la NCGS, ma va sottolineato come tutte queste informazioni provengano da ***pazienti non sottoposti ad adeguato DBPC.***

Volta U, et al.
An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. BMC Med. 2014 May;12:85.

Studio condotto su **popolazione adulta** nel 2012

(definizione **NCWS**)

276 pazienti - sintomi “IBS like” – diagnosi DBPC

Esclusione altre diagnosi (lab. Rx, endo)

DBPC anche per grano e latte.

Carroccio A, Mansueto P, Iacono G et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. Am J Gastroenterol. 2012

Questionario validato

Scala visiva analogica

Solo i pazienti positivi al challenge divisi in due gruppi:

1. **NCWS da sola**
2. **Ipersensibilità alimentari multiple**

Tutti i pazienti hanno mostrato un aumento della sintomatologia (gonfiore, dolore addominale, modifica della consistenza delle feci) in seguito all'assunzione di grano, ma nessuno ha mostrato aumento degli indici infiammatori.

Nessuno dei pazienti NCWS mostrava atrofia dei villi

Pazienti con HLA-DQ2 e/o DQ8 appartengono prevalentemente gruppo NCWS con infiltrazione linfocitaria maggiore rispetto a quelli HLA negativi.

Circa un terzo delle biopsie presentava la produzione di anticorpi antiendomisio (EMA) nel mezzo di coltura.

I pazienti del secondo gruppo mostravano frequentemente un infiltrato eosinofilo.

Tra i pazienti con sola NCWS maggior frequenza di anemia e perdita di peso rispetto ai pazienti con intolleranze multiple, mentre in questi ultimi era più frequente la coesistente storia di atopia.

Considerate le caratteristiche istologiche dei pazienti del primo gruppo, è possibile ipotizzare che alcuni pazienti con NCWS rientrino piuttosto nello spettro della CD.

Effetti del glutine su pazienti con IBS

45 pazienti affetti da IBS con fenotipo diarroico. Randomizzati in due gruppi per confrontare gli effetti della dieta con e senza glutine sulla motilità e permeabilità intestinale.

I pazienti HLA DQ2/8 positivi a dieta con glutine presentavano più movimenti intestinali, un aumento della permeabilità e un'alterazione dell'espressione delle proteine delle giunzioni cellulari.

Vazquez-Roque MI et al.
A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function.
Gastroenterology. 2013

Ci sono minori informazioni sulla popolazione pediatrica, anche se sembra che anche i bambini presentino come sintomi più frequenti dolore addominale, diarrea cronica, astenia e gonfiore, e spesso una positività degli AGA IgG.

Francavilla R, Cristofori F, Castellaneta S et al. Clinical, serologic, and histologic features of gluten sensitivity in children. J Pediatr. 2014

Pazienti “particolari”

DSG nella popolazione autistica.

Non provata da studi randomizzati e controllati.

140 bambini di cui 37 con autismo, 27 parenti sani di autistici e 76 controlli.

Autistici con livelli di AGA IgG significativamente più alti rispetto ai controlli sani e ai parenti

No differenze tra i markers sierologici CD né una chiara associazione tra livelli di AGA IgG e HLA.

I pazienti autistici con sintomi gastrointestinali associati presentavano livelli di AGA IgG significativamente più alti rispetto agli autistici senza sintomi gastrointestinali.

Lau NM, Green PH, Taylor AK et al. Markers of Celiac Disease and Gluten Sensitivity in Children with Autism. PLoS One. 2013

E’ possibile che nella popolazione autistica agisca un meccanismo immunitario coinvolgente la gliadina ma diverso dai processi coinvolti nella CD.

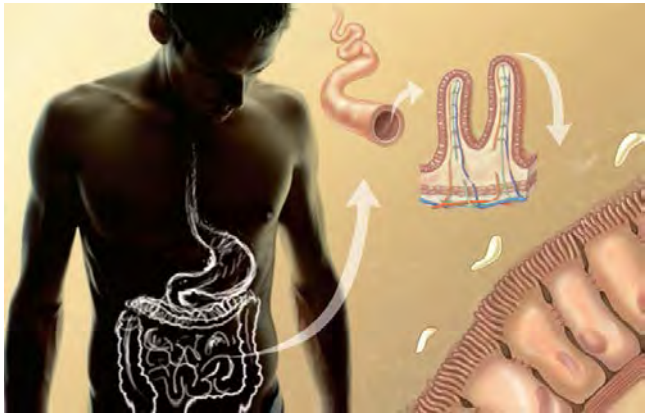
Per ammissione stessa degli autori, questi dati non necessariamente indicano la presenza di sensibilità al glutine nella popolazione autistica, ma piuttosto confermano l’assenza di correlazione tra CD e autismo.

Lau NM, Green PH, Taylor AK et al. Markers of Celiac Disease and Gluten Sensitivity in Children with Autism. PLoS One. 2013

PATOGENESI

All disease begins in the gut
- Hippocrates 460 BC

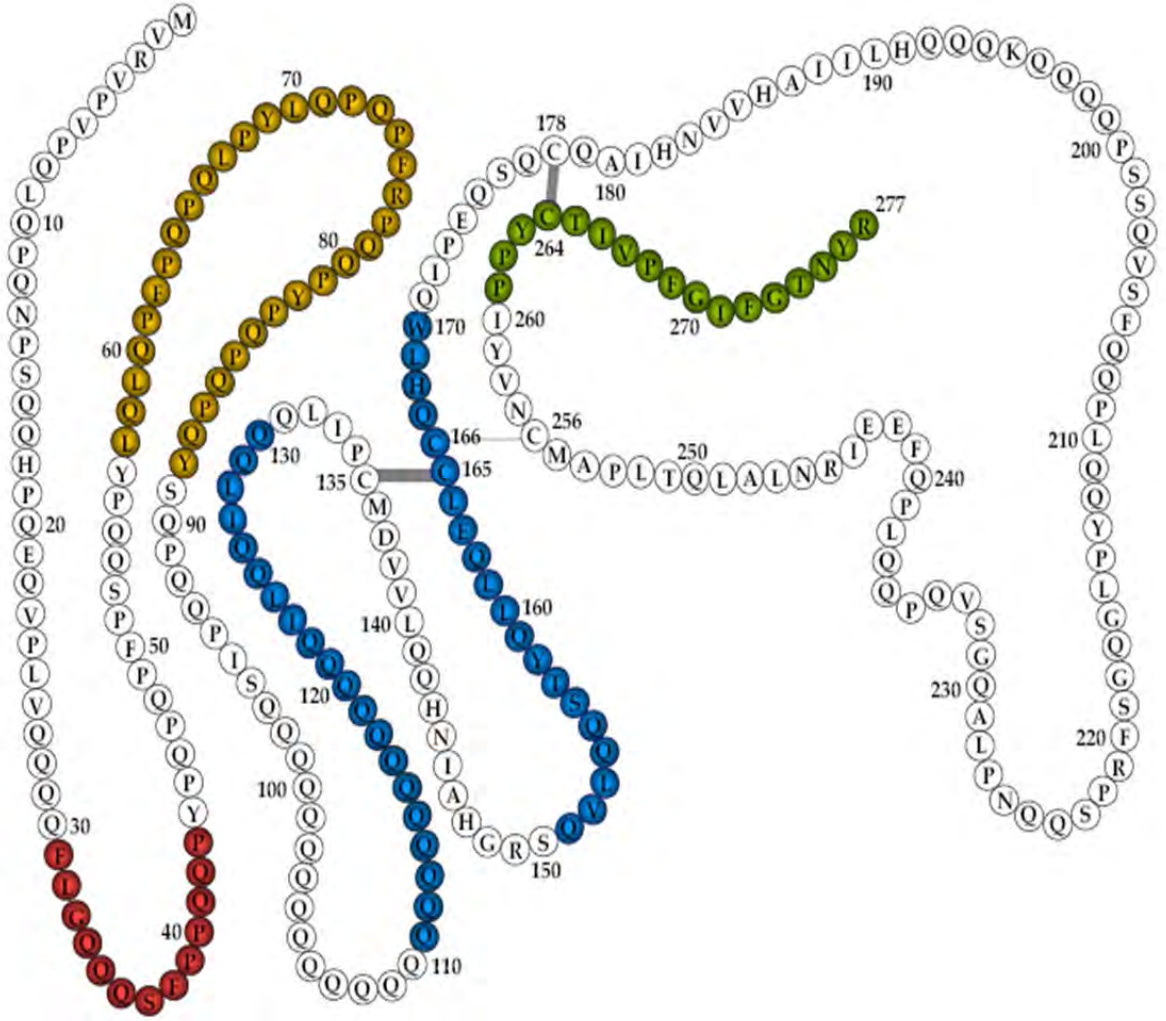
The intestinal mucosa is the battlefield on which friends and foes need to be recognized and properly managed to find the ideal balance between tolerance and immune response.



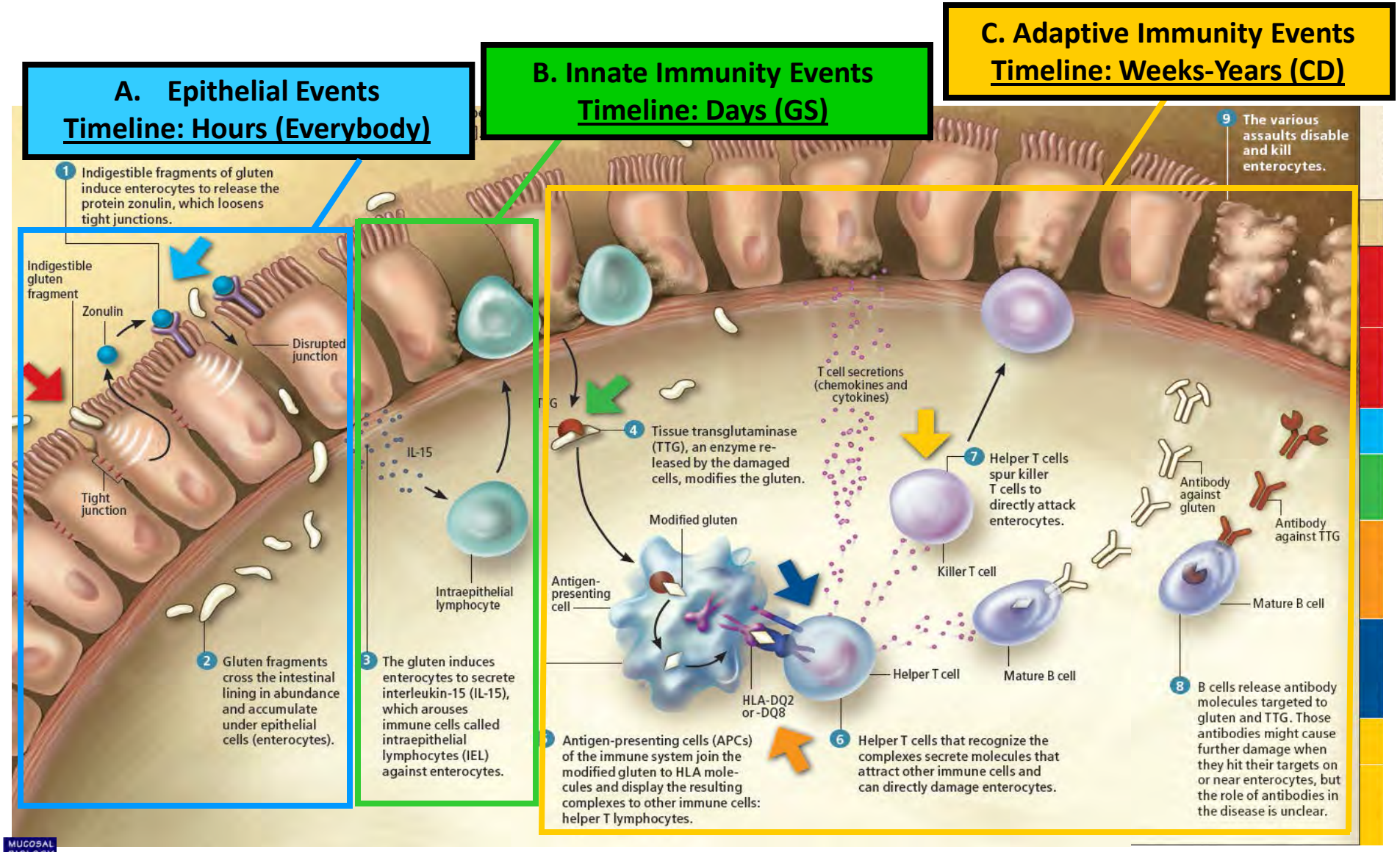
PATOGENESI

Celiac disease as the ideal paradigm to study how friends can become foes.

Gliadina, una molecola "urticante" per il sistema immunitario umano



Innate and Adaptive Immune Responses are Activated in Genetically Susceptible Individuals



Clemente MG et al *Gut* 2003; Drago et al *Scand J Gastroenterol 2006;* Sapone A. et al. *JADD* 2010

Gluten Sensitivity (NCGS): Facts
Pathogenesis

Immune-mediated (likely innate immune)

Sapone A, Lammers KM, Mazzarella G, Mikhailenko I, Cartenì M, Casolaro V, Fasano A. Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. Int Arch Allergy Immunol. 2010;152(1):75-80.

Sapone A, Lammers KM, Casolaro V, Cammarota M, Giuliano MT, De Rosa M, Stefanile R, Mazzarella G, Tolone C, Russo MI, Esposito P, Ferraraccio F, Cartenì M, Riegler G, de Magistris L, Fasano A. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Med. 2011 Mar 9;9:23

Junker Y, Zeissig S, Kim SJ, Barisani D, Wieser H, Leffler DA, Zevallos V, Libermann TA, Dillon S, Freitag TL, Kelly CP, Schuppan D.
Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med. 2012 Dec 17;209(13):2395-408.

PATOGENESI

Le informazioni sui meccanismi patogenetici della NCGS provengono in larghissima parte da studi condotti su soggetti non sottoposti ad appropriate procedure di challenge.

26 pazienti con NCGS,

42 pazienti con CD attiva

39 controlli

- Pazienti con **NCGS**, a differenza di pazienti con CD attiva, **non mostravano aumento della permeabilità intestinale**.
- Permeabilità intestinale significativamente ridotta rispetto ai controlli sani.
- Su campioni bioptici duodenali si osservava un aumento della claudina 4, una proteina coinvolta nelle giunzioni cellulari.

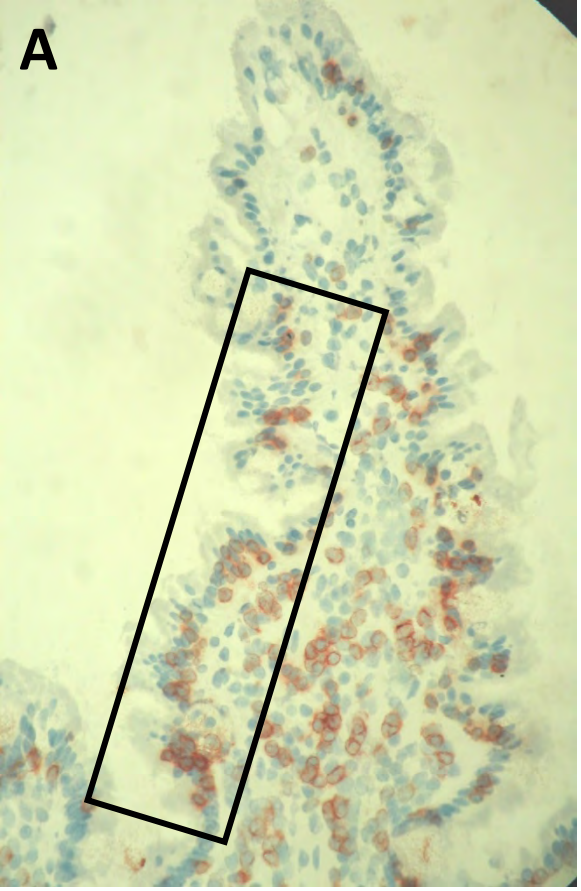
Sapone A, Lammers KM, Casolaro V et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Med. 2011

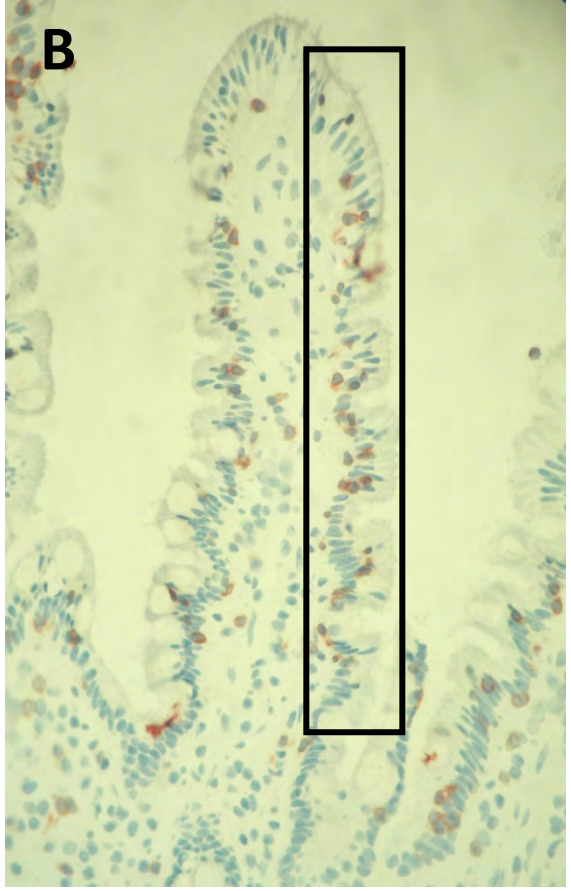
Markers immunitari

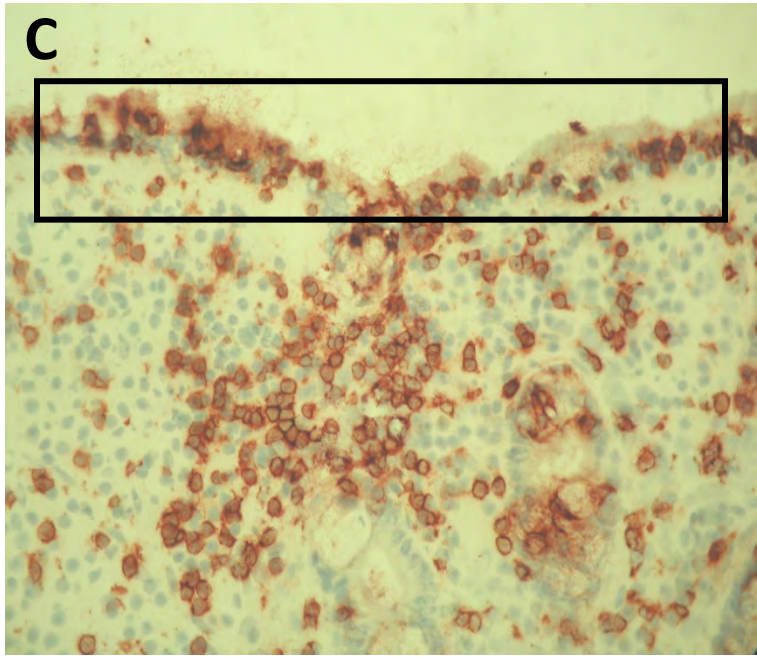
NCGS presentavano:

- **aumento dei linfociti intraepiteliali CD3** rispetto ai controlli
- livello dei **linfociti γδ paragonabile ai controlli**, (meccanismo immunitario diverso rispetto a quello coinvolto nella CD)
- Valutando l'espressione dei Toll Like Receptors (TLRs) 1, 2 e 4, coinvolti nell'immunità innata (aumentati nella CD) si è visto che **il TLR2 era aumentato nelle biopsie dei NCGS** rispetto ai controlli, così come era presente una riduzione nell'espressione di FOXP3 e TGFB1, due molecole marker delle cellule T regolatorie.

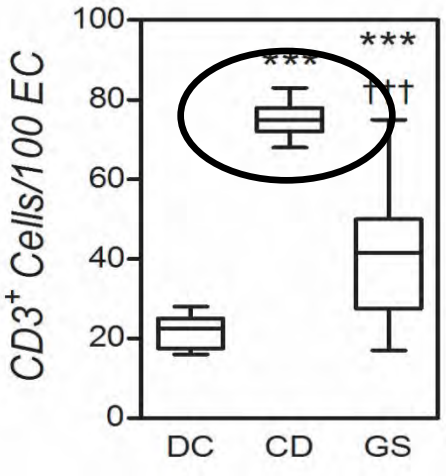
Duodenal IHC CD3+ IELs







40 X

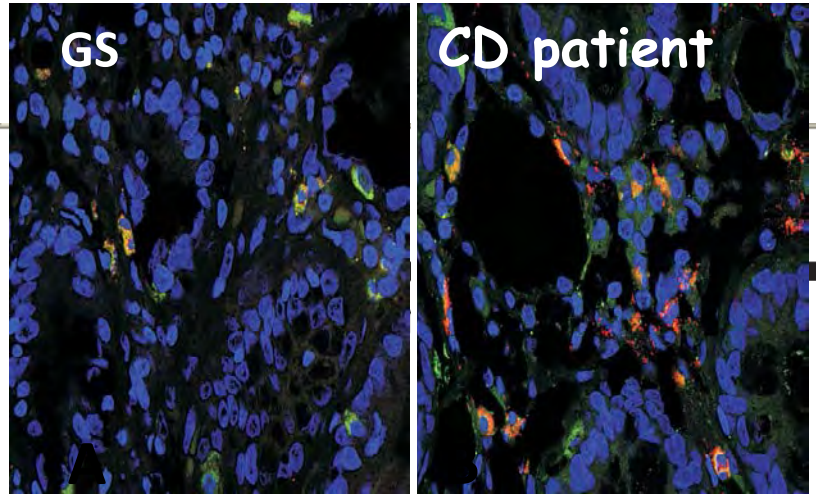


A= Gluten Sensitive

B= Controls

C= CD Active

Sapone A. et alt, Int. Arch. of Allergy and Immunology 2009



International Archives of Allergy and Immunology

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 Mazzarella[d] Irina Mikhailenko[c]
Maria Cartenì[a] Vincenzo Casolaro[b, e] Alessio Fasano[b]

[a]Sezione Biotecnologia e Biologia Molecolare, Dipartimento di Medicina Sperimentale, Seconda Università degli Studi di Napoli, Naples, Italy; [b]Mucosal Biology Research Center and [c]Center for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, Md., USA; [d]Istituto Scienze Alimentari, CNR, Avellino, Italy; [e]Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, Md., USA

Anche in questo studio, circa il 50% dei pazienti con NCGS presentava una positività per gli AGA.

Questi dati suggerirebbero che CD e NCGS siano due entità distinte con diverse risposte mucosali al glutine.

We can speculate that gluten ingestion may determine innate epithelial stress independently of adaptive intestinal immunity (even in gluten sensitivity…)

In biopsie di 30 pazienti con NCGS HLA-DQ2 positivi e 15 pazienti con CD, tutti a DSG, ottenute prima e dopo un challenge in aperto al glutine, è stato esplorato il ruolo dell'immunità nella NCGS

(espressione di IFN-γ, IL-8, TNF-α, MCP-1, Hsp-27 e Hsp-70, molecole coinvolte nell'immunità innata e adattativa, di MxA, proteina effettrice del pathway dell'IFN-α, e delle cellule CD3)

Brottveit M, Beitnes AC, Tollefsen S et al. Mucosal cytokine response after short-term gluten challenge in celiac disease and non-celiac gluten sensitivity. Am J Gastroenterol. 2013

Aumento dei linfociti CD3 nella mucosa dei pazienti con NCGS indipendentemente dal challenge.

L'IFN-γ, che nello studio di Sapone risultava più basso nei NCGS rispetto ai CD, aumentava nelle biopsie dei pazienti con NCGS in risposta al challenge con glutine, mentre era costitutivamente aumentato nelle biopsie dei pazienti con CD.

Alcuni autori hanno infine riportato una risposta immunitaria innata scatenata da componenti del grano diversi dal glutine, come gli amylase/trypsin inhibitors (ATIs), ed è stato ipotizzato un loro ruolo nella genesi della NCGS.

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

The amylase tryptase inhibitors (ATIs) and FODMAPs in wheat involved in NCGS

```
CM3    MACKSSCSLLLLAAVLLSVLAAASASGSCVPGVAFRTNLLPHCRDYVLQQTCGTFTPGSK 60
0.19   ----------------------SGPWMCYPGQAFQVPALPACRPLLRLQCNGSQVPEAV 37
                             *..  * ** **:.  ** **  :  *  *: .* :

CM3    LPEWMTSASIYSPGKPYLAKLYCCQELAEISQQCRCEALRYFIALPVPSQPVDPRSGNVG 120
0.19   LRD-------------------CCQQLAHISEWCRCGALYSMLDSMYKEHGAQE-----G 73
       * :                  ***:**.**: *** **  ::     .: .:      *

CM3    ESGLIDLPGCPREMQWDFVRLLVAPGQCNLATIHN---VRYCPAVEQPLWI 168
0.19   QAGTGAFPRCRREVVKLTAASITAVCRLPIVVDASGDGAYVCKDVAAYPDA 124
       ::*   :* * **:    .  :.*  :  :..  .   .  *  *
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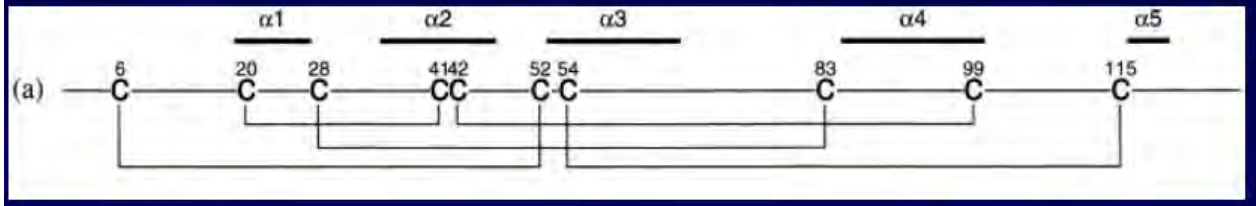
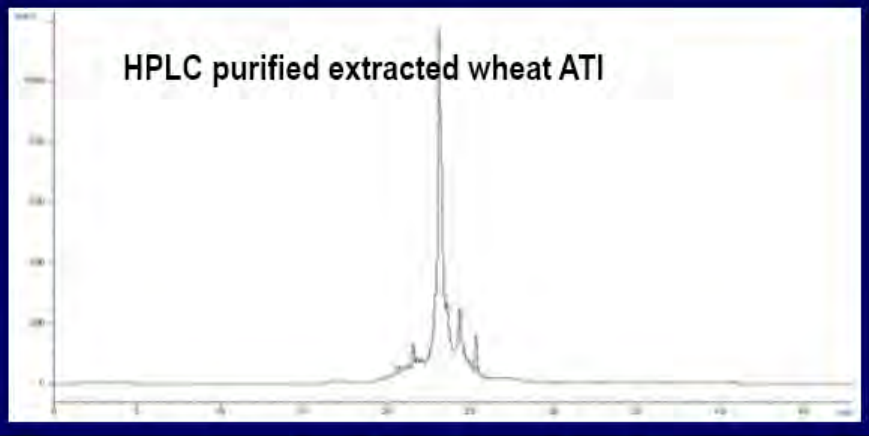
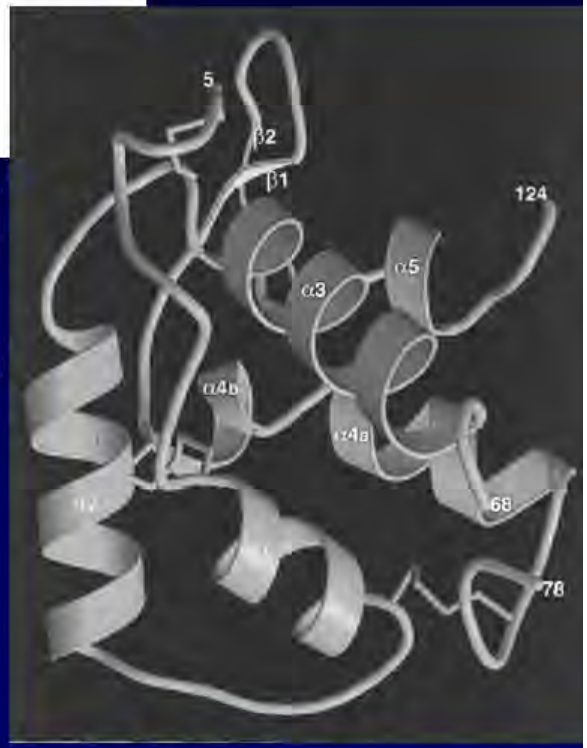






Oda Y et al, Biochemistry 1997

Junker Y et al. J Exp Med. 2012;209:2395-408

ClinicalTrials.gov : 8 studies

Gluten Sensitivity in Non-Celiac Patients (GS)

This study is currently recruiting participants.
Verified April 2013 by Second University of Naples
Sponsor: Second University of Naples
Information provided by (Responsible Party):
Laura de Magistris, Second University of Naples
ClinicalTrials.gov Identifier: NCT01485341
First received: November 17, 2011

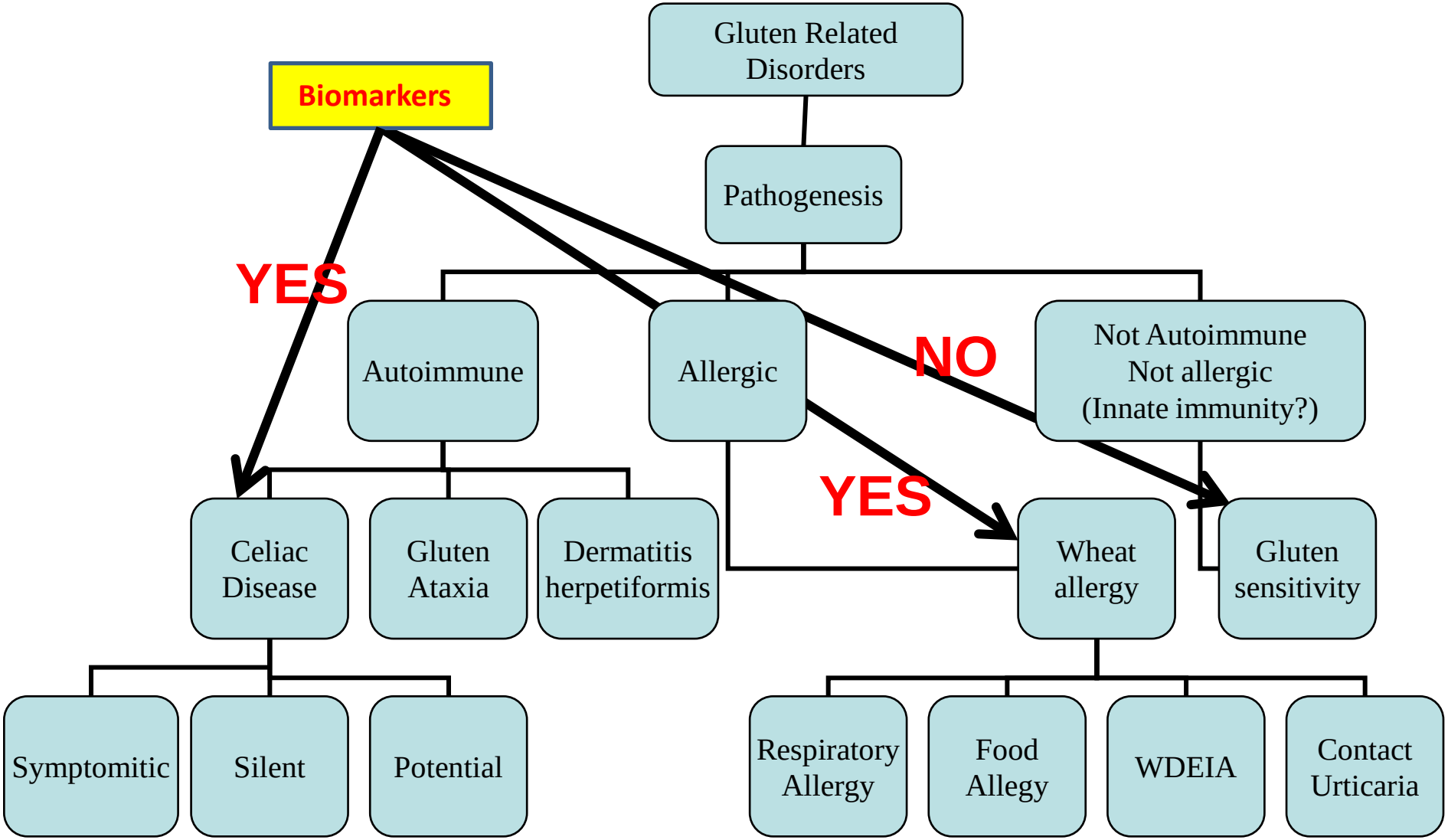
Bio-markers of Not-celiac Wheat Sensitivity

This study is currently recruiting participants.
Verified January 2013 by University of Palermo
Sponsor: University of Palermo
Information provided by (Responsible Party):
Pasquale Mansueto, University of Palermo
ClinicalTrials.gov Identifier: NCT01762579
First received: January 4, 2013

Bioelectrical Impedance Analysis of Not-celiac Wheat Sensitivity Patients

This study is currently recruiting participants.
Verified January 2013 by University of Palermo
Sponsor: University of Palermo
Information provided by (Responsible Party):
Pasquale Mansueto, University of Palermo
ClinicalTrials.gov Identifier: NCT01762566
First received: January 4, 2013

Proposed New Classification of Gluten Related Disorders



CONCLUSIONI

- L’assenza di biomarkers e in molti casi la inadeguatezza delle procedure diagnostiche rendono difficilmente stimabile la prevalenza e le caratteristiche della NCGS.
- Il ruolo del glutine è ancora da definirsi, così come i meccanismi immunitari eventualmente coinvolti.
- Va infine sottolineato il pericolo, soprattutto nella popolazione adulta, che l’autodiagnosi di NCGS e l’autoprescrizione della DSG impedisca la corretta diagnosi di CD.

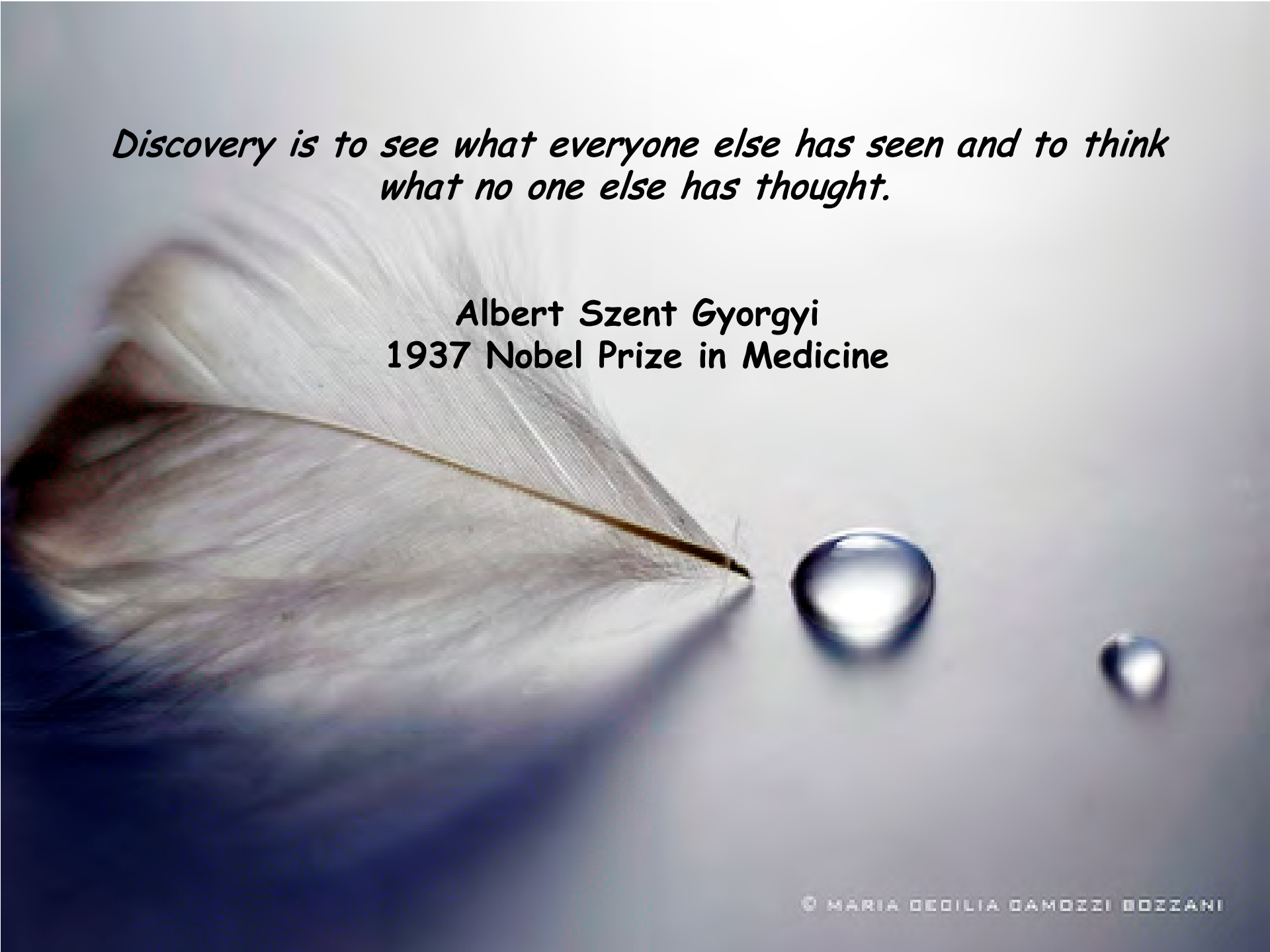
Controversial questions about NCGS

Take Home Messages:

- Gluten Sensitivity is not rare;
- Gluten Sensitivity cannot be distinguished from Celiac Disease purely on the clinical basis;
- Gluten Sensitivity can present with vague, non-specific symptoms;
- A gluten free diet can be considered only when other forms of gluten reactions and other causes of pt's symptoms have been ruled out;
- A DBPC study is needed to clarify to find biomarker(s) for the correct diagnosis.
- Listen to your patient!!!

Key Points

- **La "Non Celiac Disease Gluten Sensitivity" (NCGS) è una sindrome complessa, i cui aspetti epidemiologici,** clinici e patogenetici restano da definire.
- **La clinica dei pazienti che si ritiene siano affetti da NCGS è varia.**
- **Oltre al glutine, è possibile la responsabilità di altri componenti della dieta, come i FODMAPs.**
- **Alcuni studi suggeriscono il possibile ruolo di un meccanismo immunitario, seppur diverso da quello** attivo nella celiachia, ma non è possibile escludere al momento alterazioni della motilità intestinale e/o della sensibilità viscerale


Discovery is to see what everyone else has seen and to think what no one else has thought.
Albert Szent Gyorgyi
1937 Nobel Prize in Medicine
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