

Pasti v diagnostiki in obravnavi celiakije

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Pregled

- **uvod**
- **smernice**
- **diagnostične metode**
 - **klinična slika**
 - **serologija**
 - **histologija**
 - **genetika**
- **skupine s tveganjem**
- **sledenje**
- **zaključek**



Uvod



Celiakija – definicija

- **sistemska** reverzibilna avtoimuna bolezen
- **genetska** predispozicija (HLA DQ₂/DQ₈)
- **gluten** (pšenica, rž, ječmen, oves?)
- tanko **črevo** (atrofija resic, hiperplazija resic, povečano število IEL – klasifikacija po Marshu)
- kompleksna **imunologija**
 - T-celični odgovor
 - **serologija** (EMA, t-TG, d-AG)



Smernice



Diagnostične smernice

Klasične smernice - ESPGHAN 1969

- zlati standard
 - biopsija tankega črevesa – *tkivna diagnoza celiakije*
- 3 biopsije

Revidirane smernice - ESPGHAN 1979

- 1 biopsija
- serološki označevalci (AGA, kasneje tudi EMA in t-TG)

Nove smernice - ESPGHAN 2012

- serološki označevalci (t-TG, d-GP, EMA)
- HLA tipizacija
- biopsija morda ni potrebna v vseh primerih



Diagnostične smernice

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease

*S. Husby, †S. Koletzko, ‡I.R. Korponay-Szabó, §M.L. Mearin, ||A. Phillips, ¶R. Shamir, #R. Troncone, **K. Giersiepen, ††D. Branski, ‡‡C. Catassi, §§M. Lelgeman, ||||M. Mäki, ¶¶C. Ribes-Koninckx, ###A. Ventura, and ****K.P. Zimmer, for the ESPGHAN Working Group on Coeliac Disease Diagnosis, on behalf of the ESPGHAN Gastroenterology Committee

ABSTRACT

Objective: Diagnostic criteria for coeliac disease (CD) from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) were published in 1990. Since then, the autoantigen in CD, tissue transglutaminase, has been identified; the perception of CD has changed from that of a rather uncommon enteropathy to a common multiorgan disease strongly dependent on the haplotypes human leukocyte antigen (HLA)-DQ2 and HLA-DQ8; and CD-specific antibody tests have improved. **Methods:** A panel of 17 experts defined CD and developed new diagnostic criteria based on the Delphi process. Two groups of patients were defined with different diagnostic approaches to diagnose CD: children with symptoms suggestive of CD (group 1) and asymptomatic children at increased risk for CD (group 2). The 2004 National Institutes of Health/Agency for Healthcare Research and Quality report and a systematic literature search on antibody tests for CD in paediatric patients covering the years 2004 to 2009 was the basis for the evidence-based recommendations on CD-specific antibody testing.

Results: In group 1, the diagnosis of CD is based on symptoms, positive serology, and histology that is consistent with CD. If immunoglobulin A anti-tissue transglutaminase type 2 antibody titers are high (>10 times the upper limit of normal), then the option is to diagnose CD without duodenal biopsies by applying a strict protocol with further laboratory tests. In group 2, the diagnosis of CD is based on positive serology and histology. HLA-DQ2 and HLA-DQ8 testing is valuable because CD is unlikely if both haplotypes are negative.

Conclusions: The aim of the new guidelines was to achieve a high diagnostic accuracy and to reduce the burden for patients and their families. The performance of these guidelines in clinical practice should be evaluated prospectively.

(*JPGN* 2012;54: 136–160)



Smernice ESPGHAN

Redefinicija bolezni

- **imunološko pogojena sistemska bolezen**
 - predominantni znaki avtoimunosti
- povzročena z **glutenom** (žita)
 - gluten in sorodni prolamini
- tipična **genetska** predispozicija
 - HLA DQ₂ ali DQ₈
- **dve skupini** bolnikov



Smernice ESPGHAN

Dve skupini

1. otroci in adolescenti s simptomi
2. skupine s **povečanim tveganjem**

sorodniki v prvem kolenu

deficienca IgA

Druge avtoimune bolezni

DM tip 1

Tiroiditis

Avtoimuni hepatitis

Kromosomske nepravilnosti

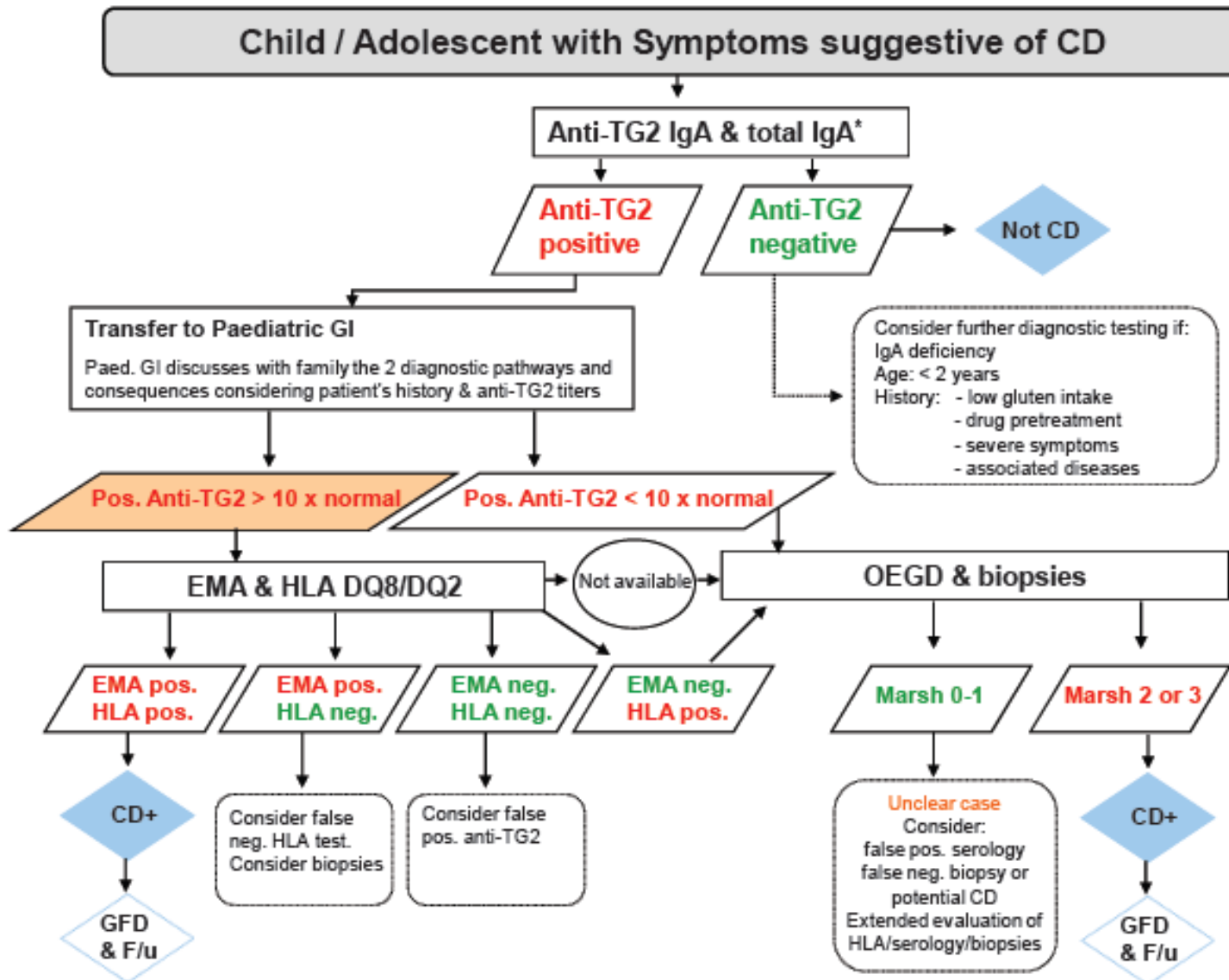
Downov sindrom

Turnerjev sindrom

Williamsov sindrom



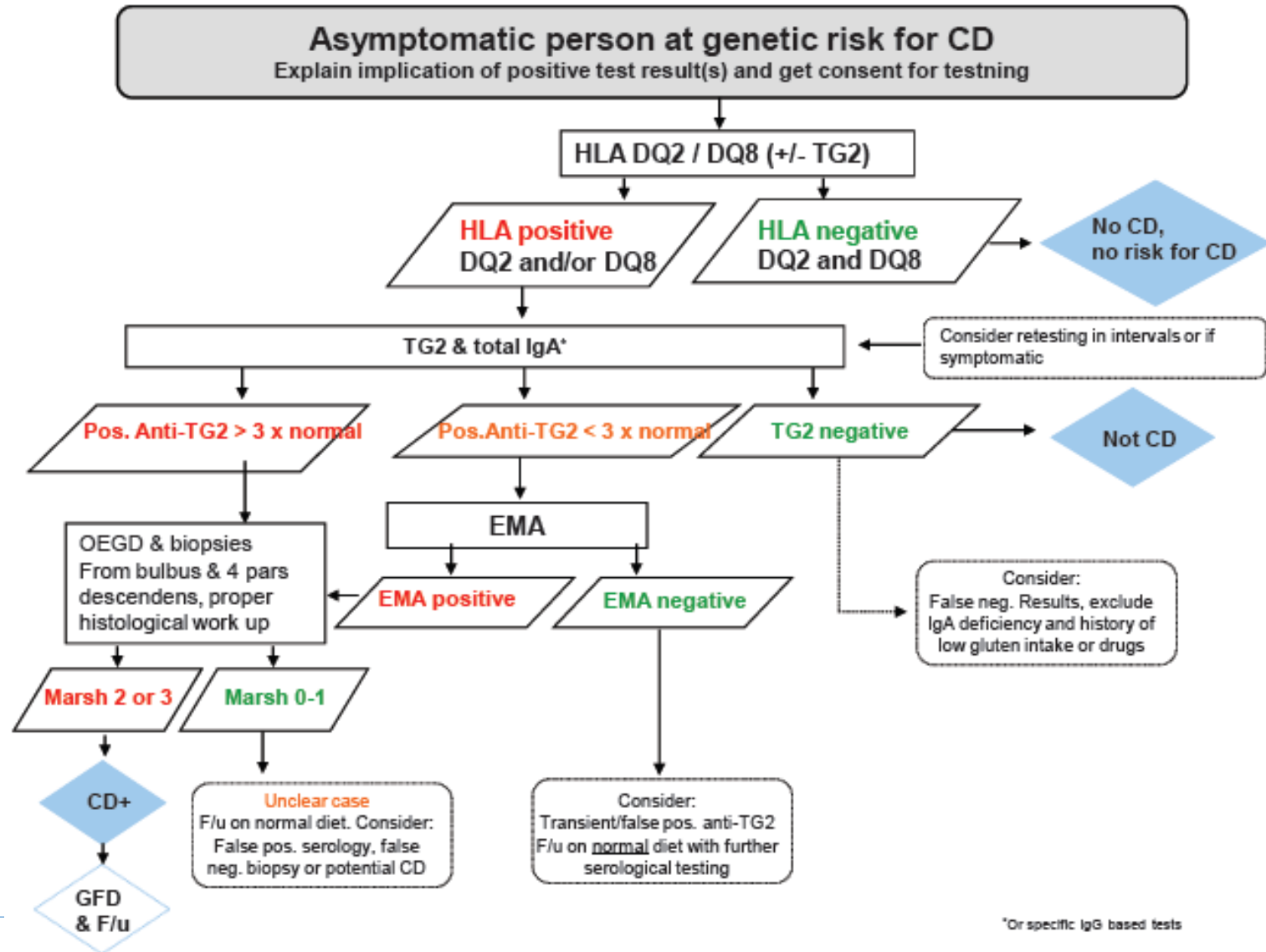
Smernice ESPGHAN



*Or specific IgG based tests



Smernice ESPGHAN



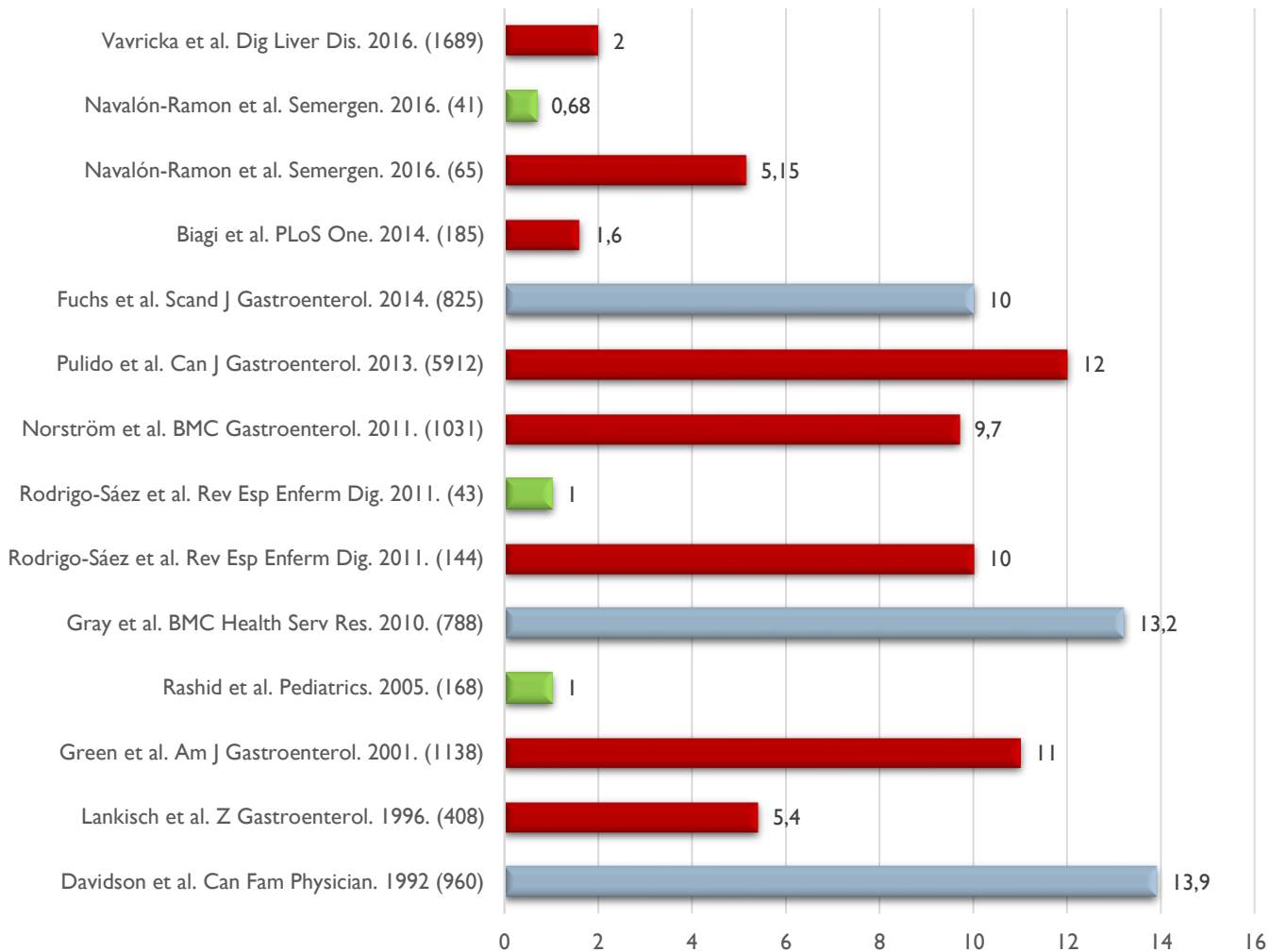
*Or specific IgG based tests



Pasti



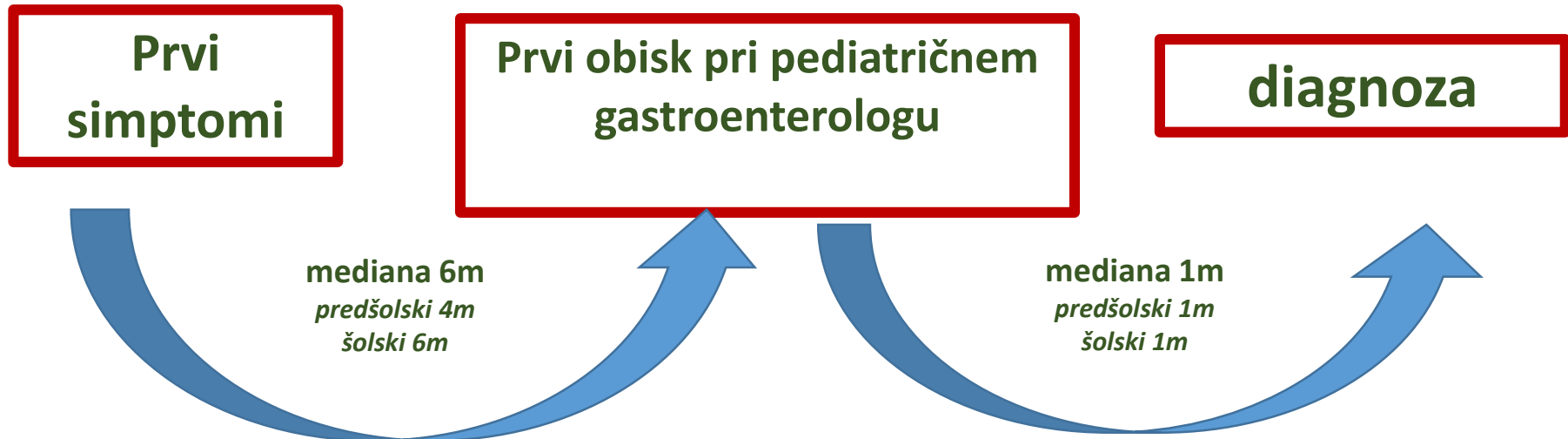
Celiakija – diagnostične zamude



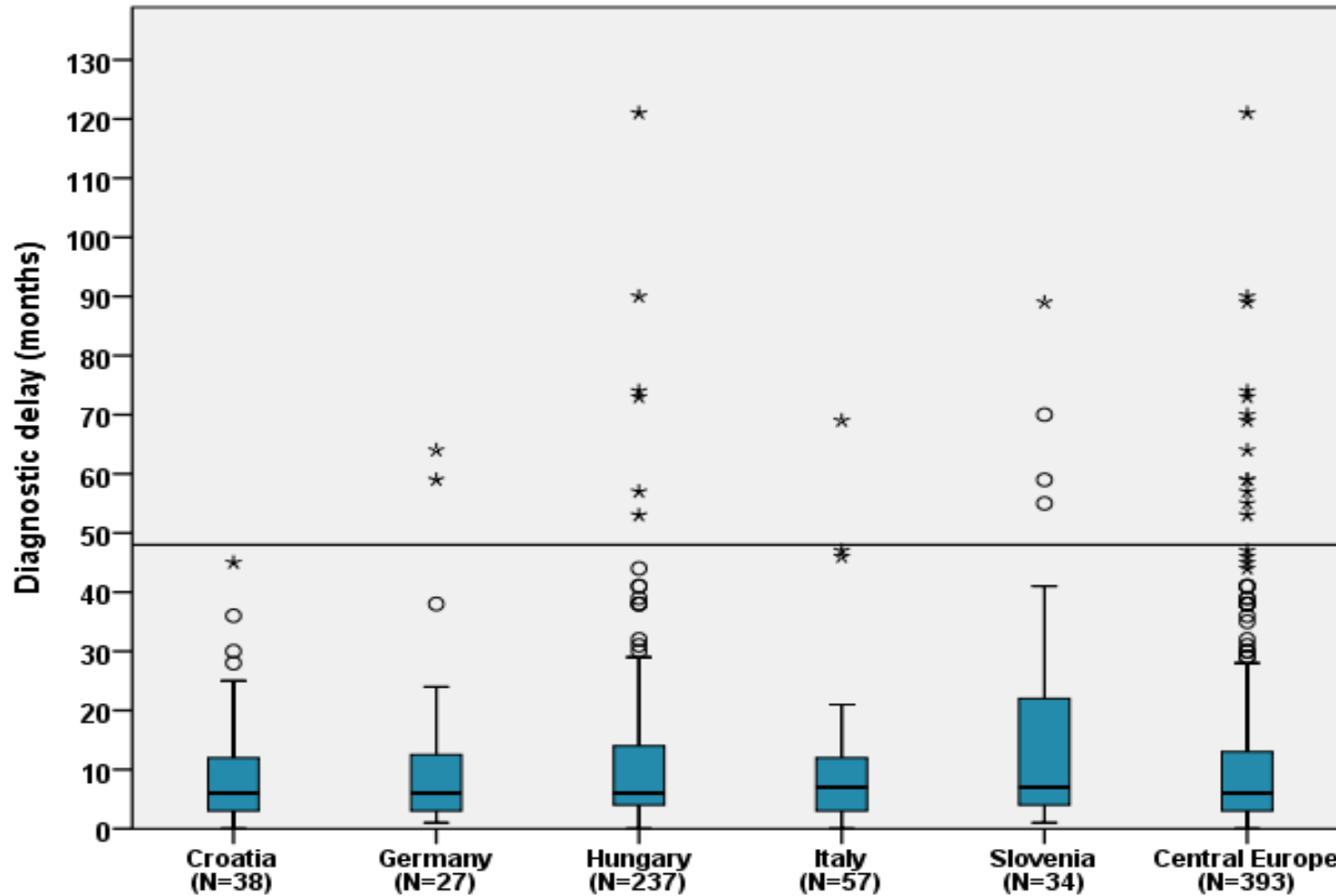
Celiakija – diagnostične zamude - CE

diagnostične zamude

mediana 8m
predšolski 6m
šolski 9m



Celiakija – diagnostične metode - CE



3.3%
delay > 4y!!!
(84.6% girls,
age 12y)



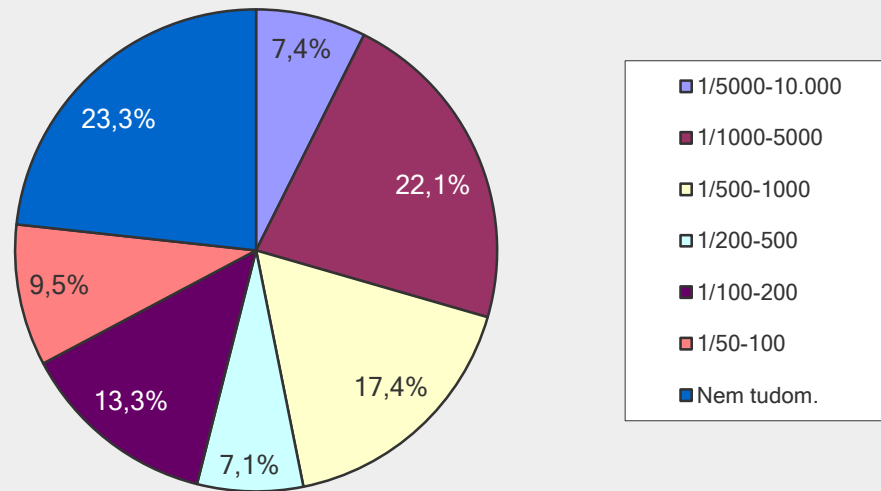


Kje/kaj je problem?



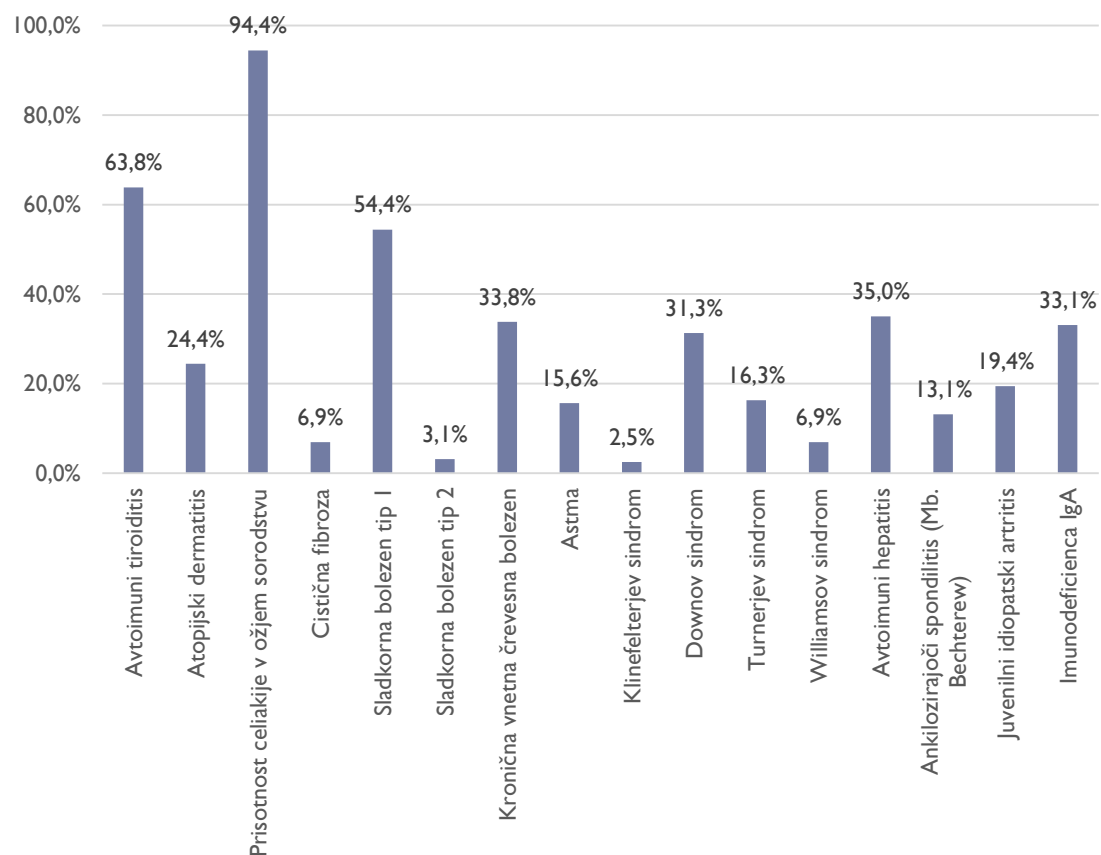
Znanje/osveščenosť

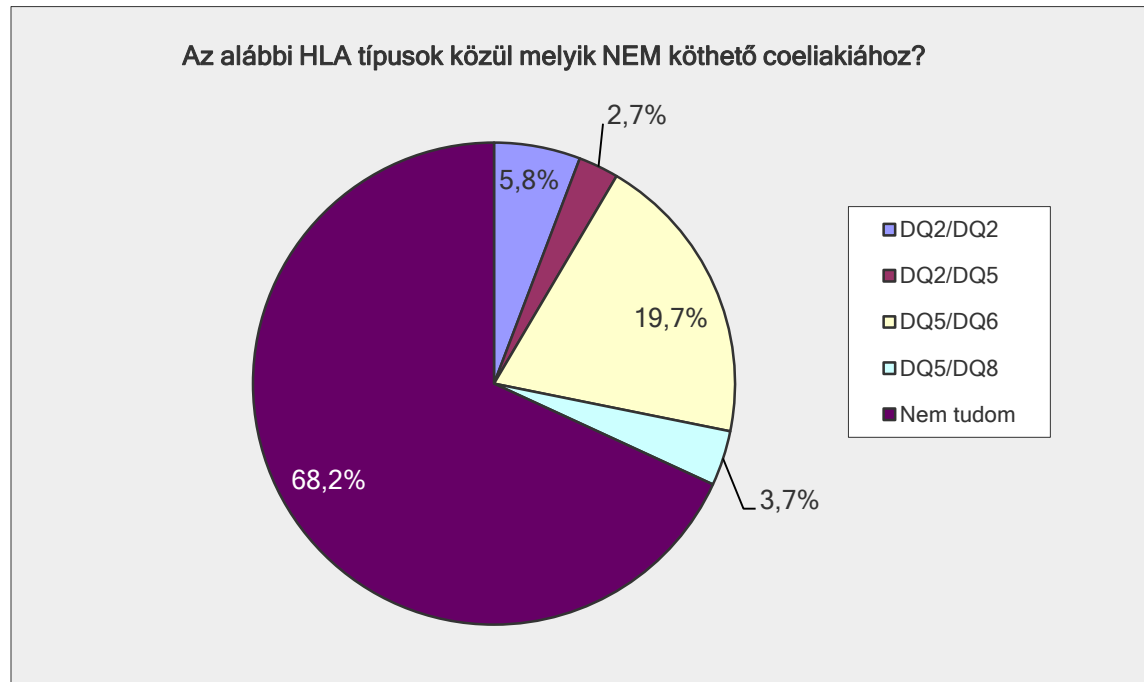
Milyen gyakori a coeliakia Európában?



Znanje/osveščenosť

Katero od naštetih stanj/bolezni predstavlja večjo verjetnost za razvoj celiakije?





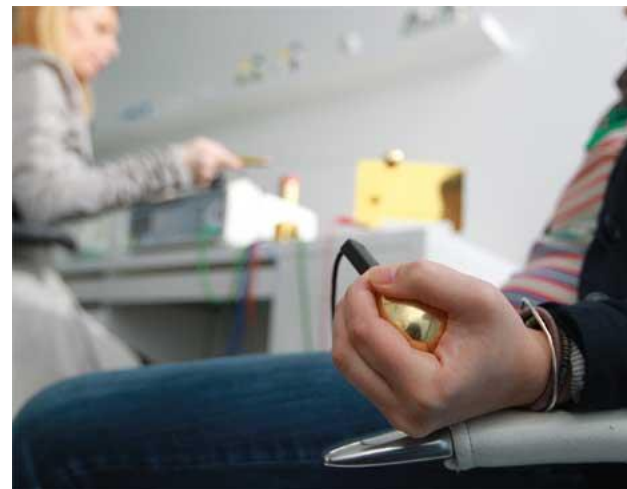
Celiakija – diagnostične metode



Celiakija – diagnostika



The secrets of
PULSE DIAGNOSIS



Diagnostične smernice

- **ESPGHAN 2012** (možno „no-biopsy“)
- **NASPGHAN 2005/20016** (obvezna biopsija)
- **AGA 2013** (obvezna biopsija)
- **BSPGHAN 2013** (možno „no-biopsy“)
- **Oslo definicija** (biopsija)

Ni mednarodne harmonizacije!!!



Diagnosticiranje celiakije



Diagnostični postopek

- klinična slika
- serologija
- genetika
- biopsija tankega črevesa



Diagnostični postopek

- družina z manj glutena
- uvedba diete pred testiranjem
- imunosupresivi
- ...

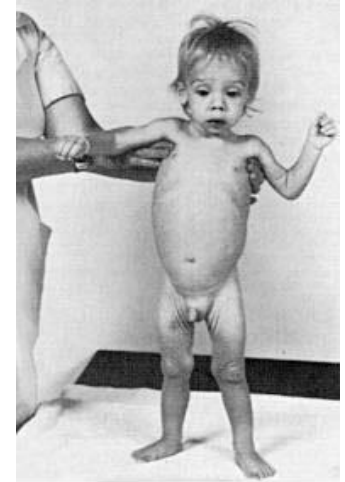


Klinična prezentacija

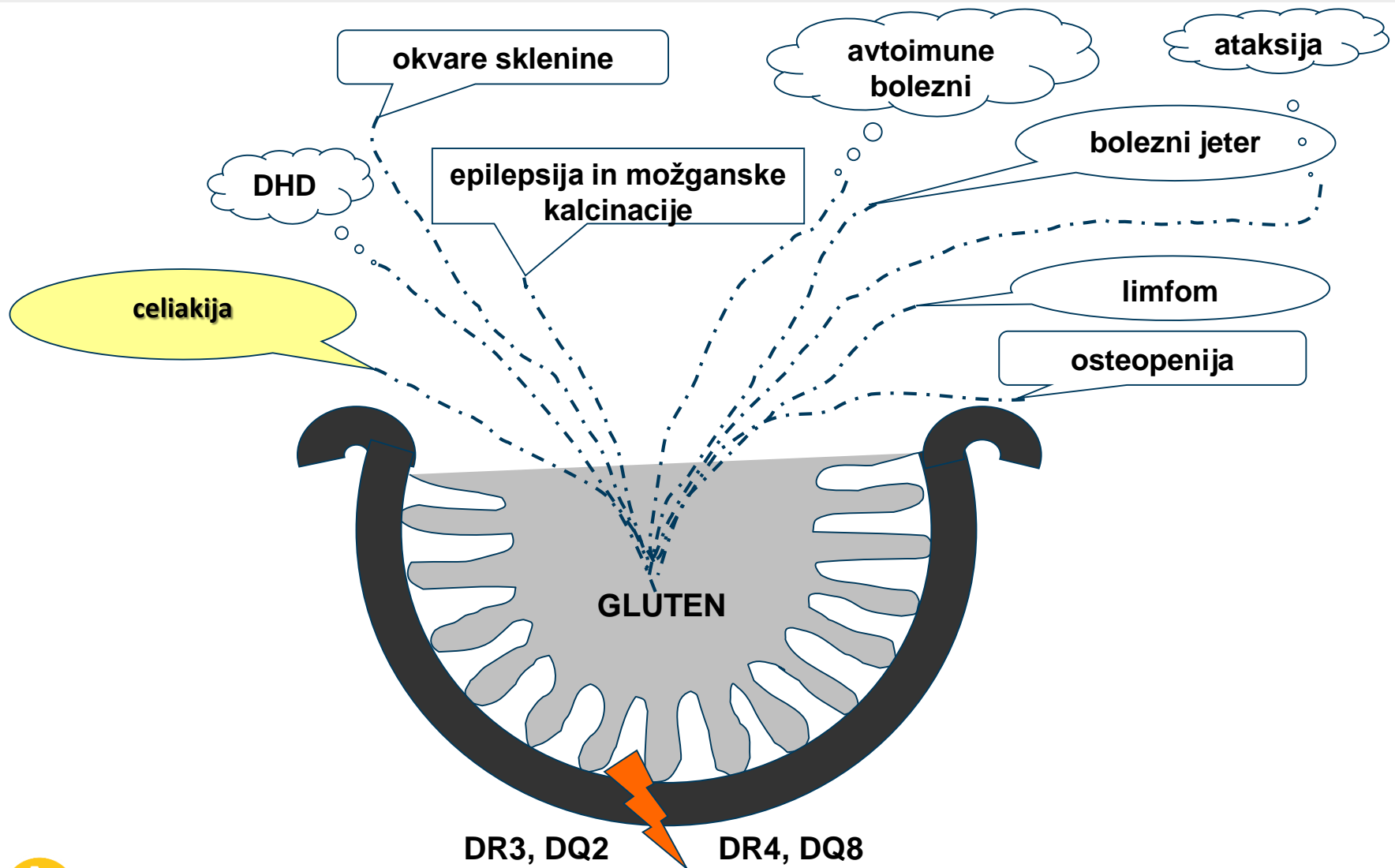


Clinical presentation

- **simptomatska celiakija**
 - “klasična” celiakija
 - simptomi/znaki s strani GIT z malabsorpcijo
 - “ne-klasična” celiakija
 - drugi (vključno z ne – GIT) simptomi/znaki
- **asimptomatska celiakija**

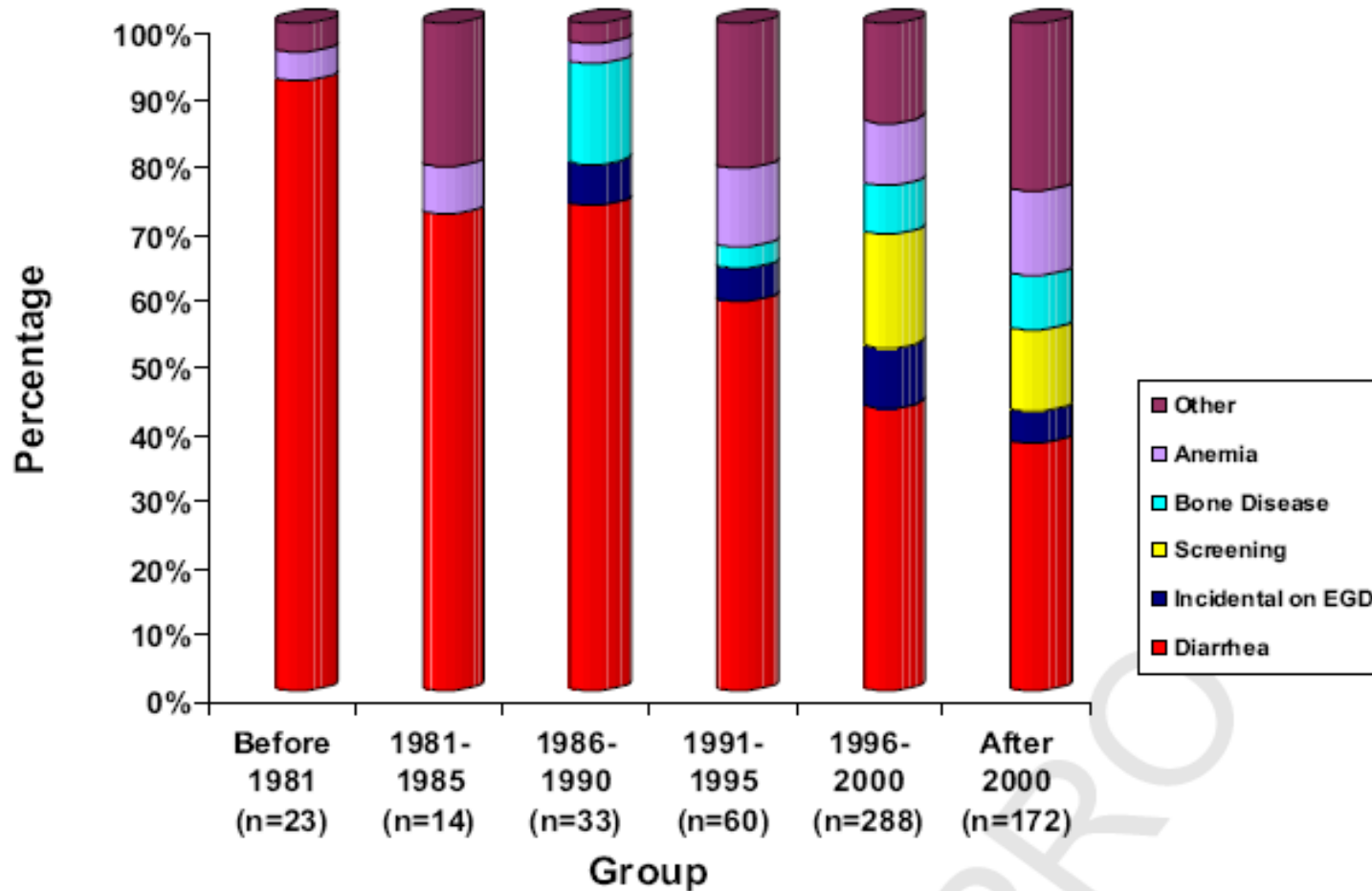


Celiakija – sistemska bolezen



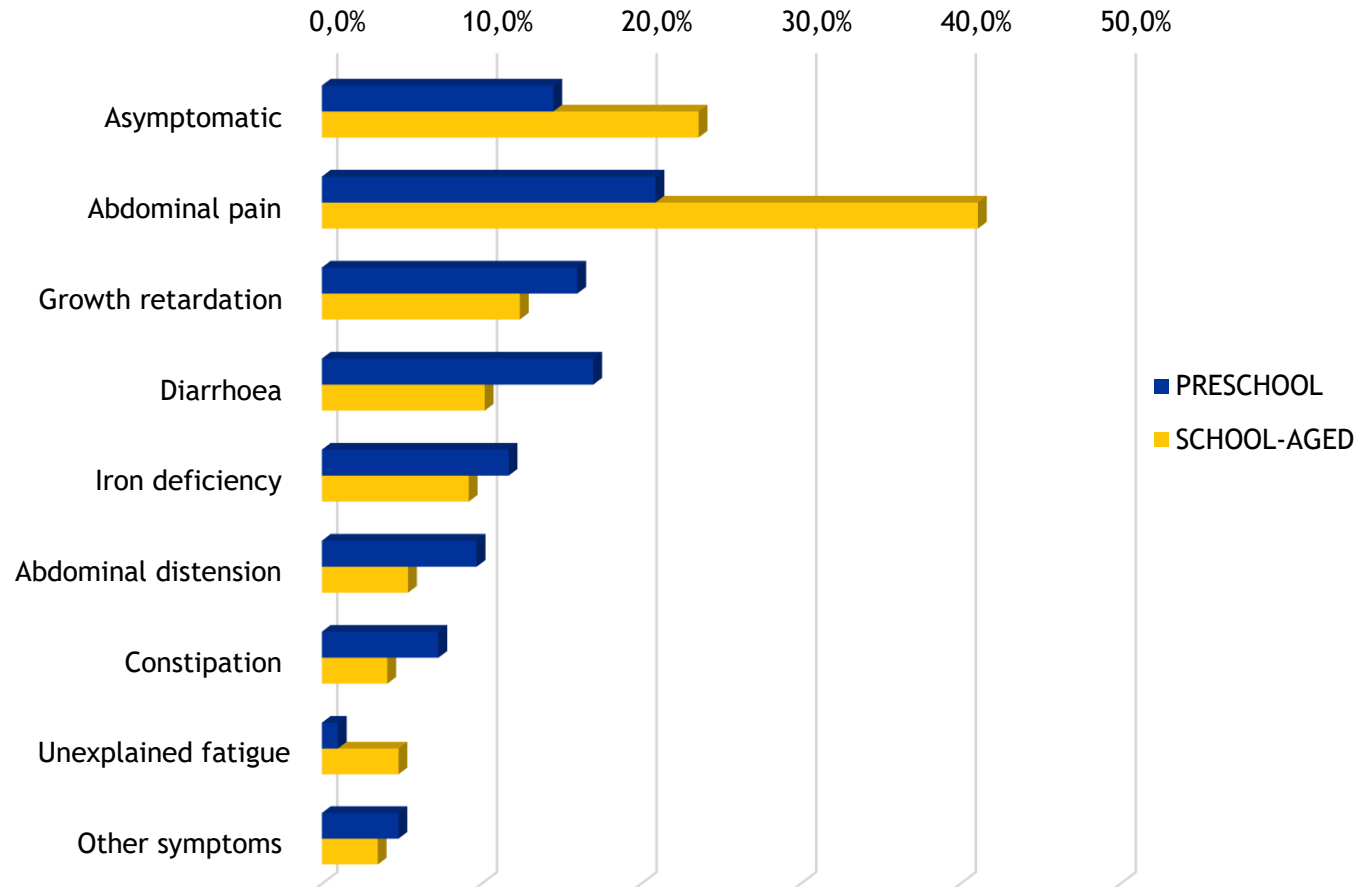
Klinična slika - spremembe

- Rampertab SD, et al. Am J Medicine 2006

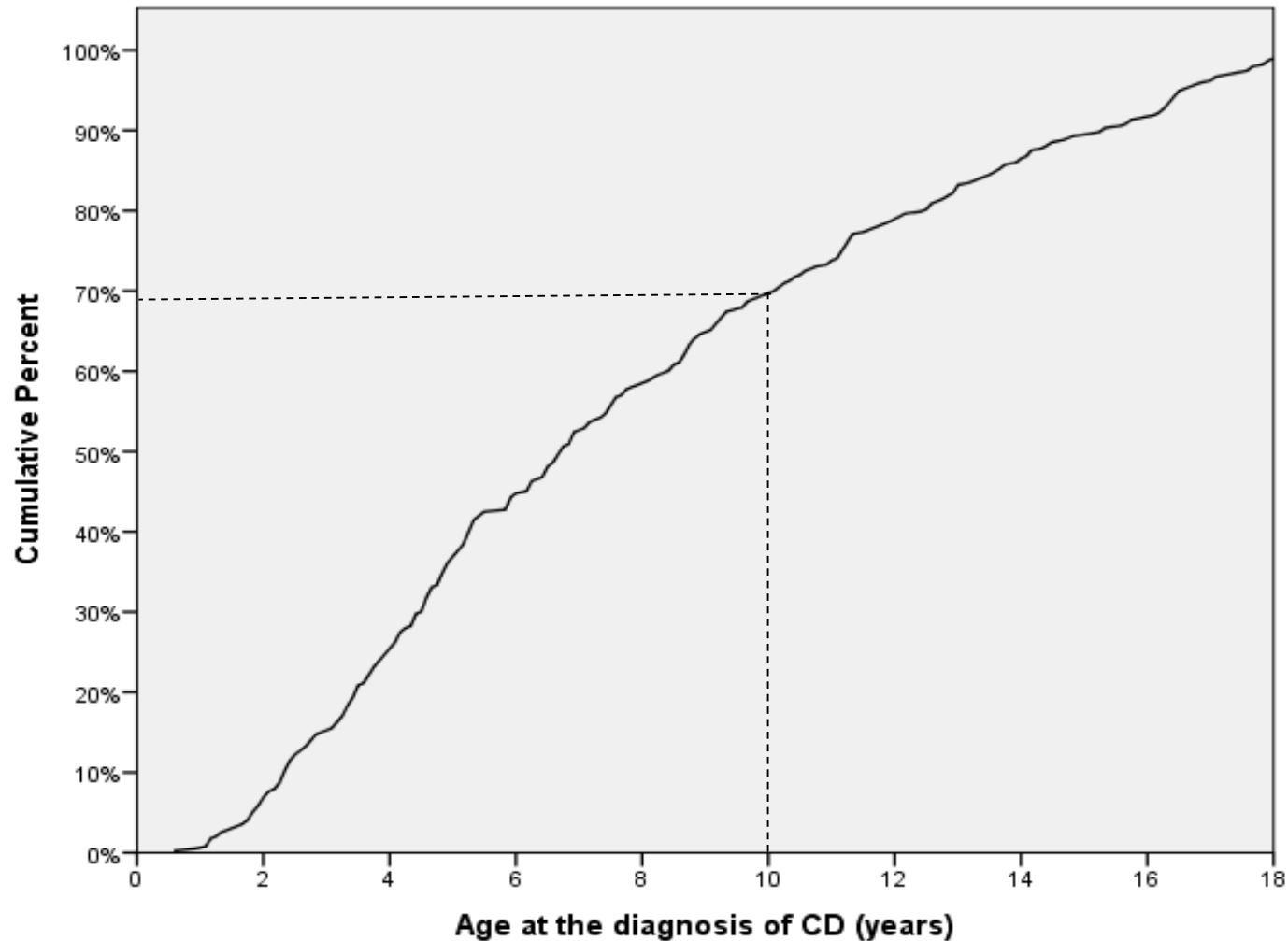


Klinična slika - CE

Spremembe v klinični sliki pri predšolskih in šolskih otrocih



Starost ob diagnozi - CE



Diagnostične metode



Diagnostične metode

- **bolezensko specifične metode**

- serološki testi
- genetski testi
- biopsija/histologija

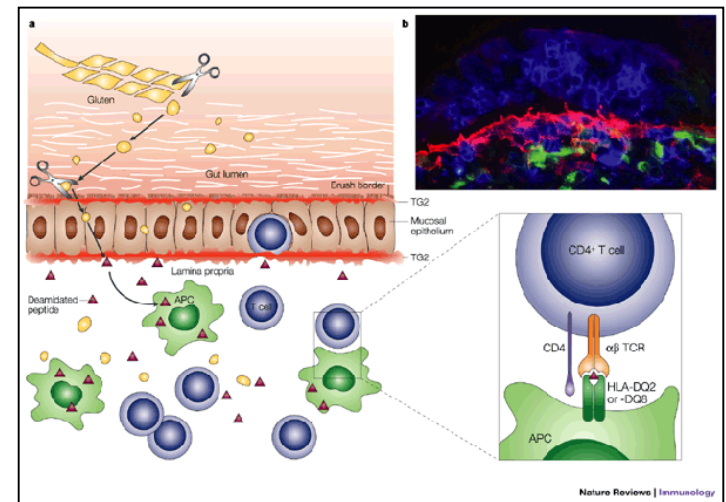
- **ne-specifične metode**

- klinična slika
- testi malabsorpcije
- ...



Celiakija – serologija

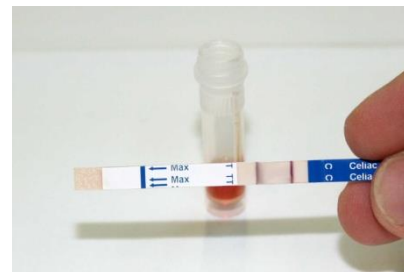
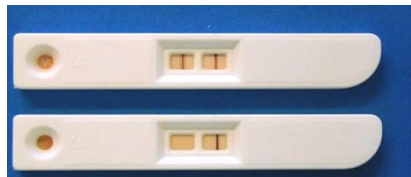
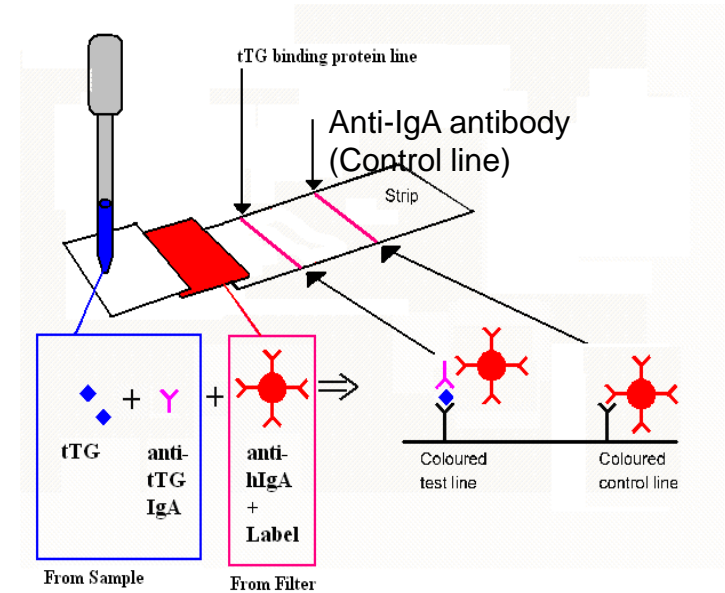
- **Serološki označevalci**
 - ~~AGA IgA in IgG~~
 - nezanesljiva
 - **označevalci avtoimunosti**
 - EMA IgA (IgG) - IIF
 - t-TG IgA (IgG) - ELISA
 - dGP IgA (IgG) - ELISA
- **pomen določanja celokupnih IgA**
 - deficienca IgA (določanje IgG protiteles)



Celiakija – serologija

- **PoC testi**

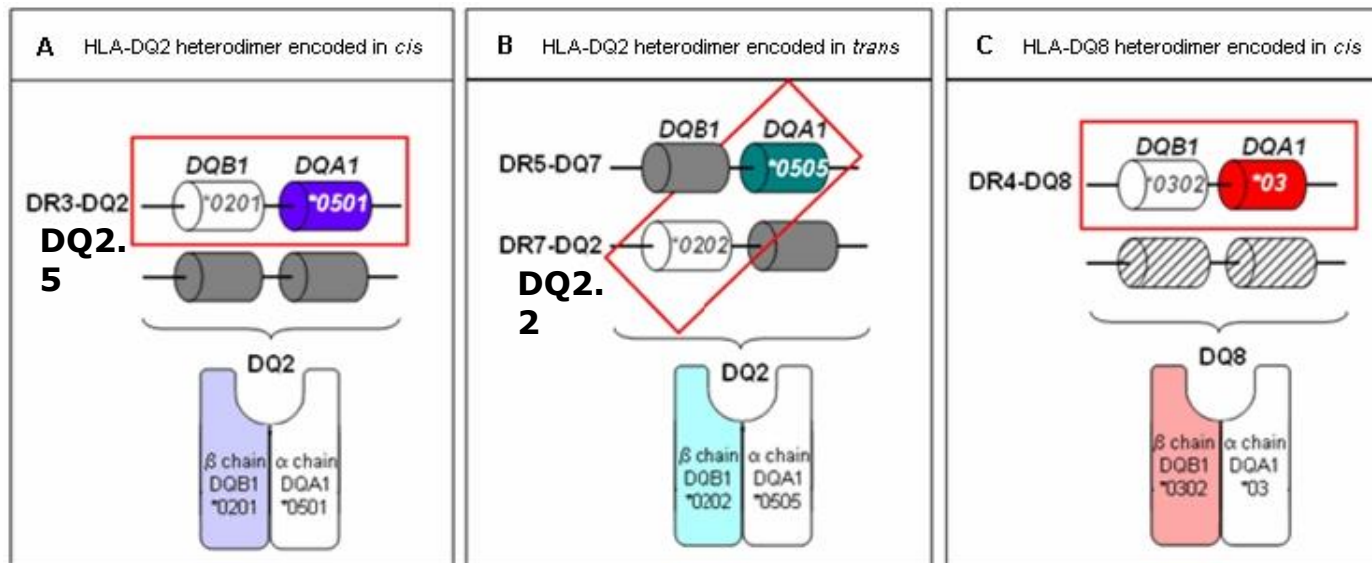
- **hitri testi (kapljica krvi)**
- **imunokromatografija**
 - antigen: lastna t-TG (d-GP)
- **mного komercialnih testov**
 - poceni
- **srednja občutljivost in specifičnost**
 - izkušeno osebje



Celiakija – genetika

Genetska predispozicija za CD

- HLA lokus (kromosom 6p21.3)
- HLA-DQ2 ali HLA-DQ8



Celiakija – genetika

Genetska predispozicija za CD

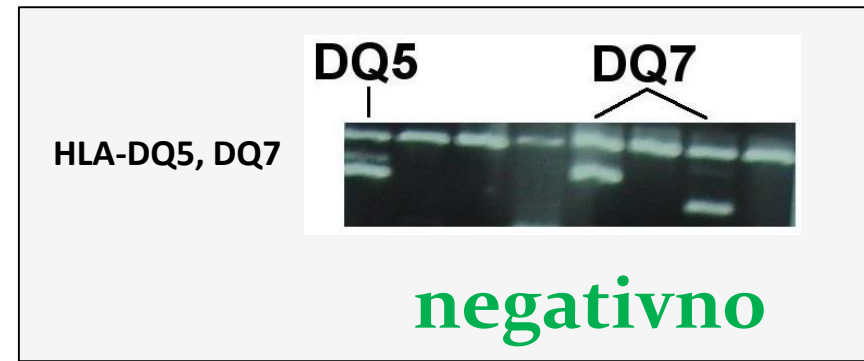
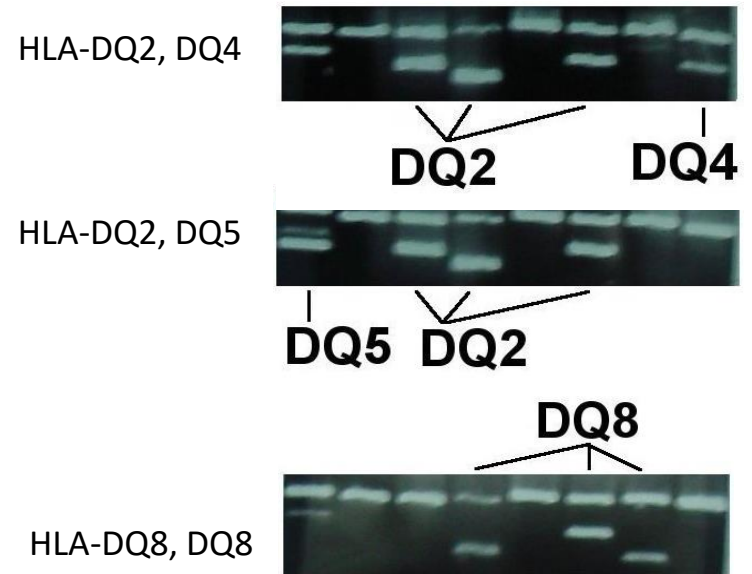
- HLA DQ2/DQ8 negativni bolniki (4/1008) (61 je imelo polovico verige)



Celiakija – genetika

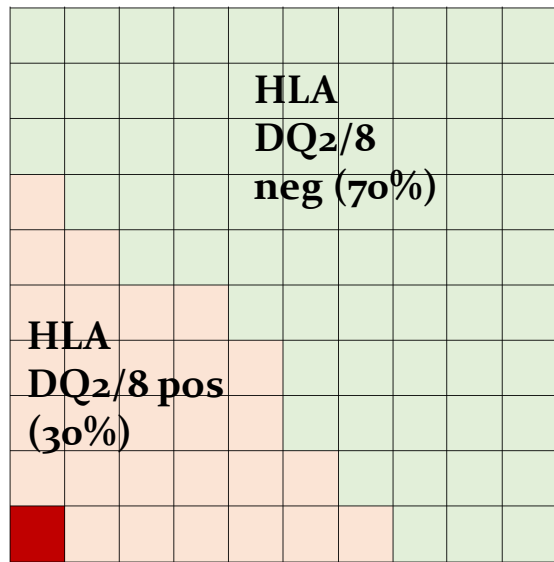
• HLA DQB1 tipizacija

- DQ SSP Low Resolution kit
- metoda PCR
- aleli HLA DQB1
 - DQB1*02 (DQ2)
 - DQB1*0302 (DQ8)
- 30% splošne populacije
- **nizka PPV, visoka NPV**



Celiakija – genetika

Celotna populacija



↑
Celiakija
(1%)

HLA-DQ₂/8 pozitivni



↑
Celiakija
(3%)



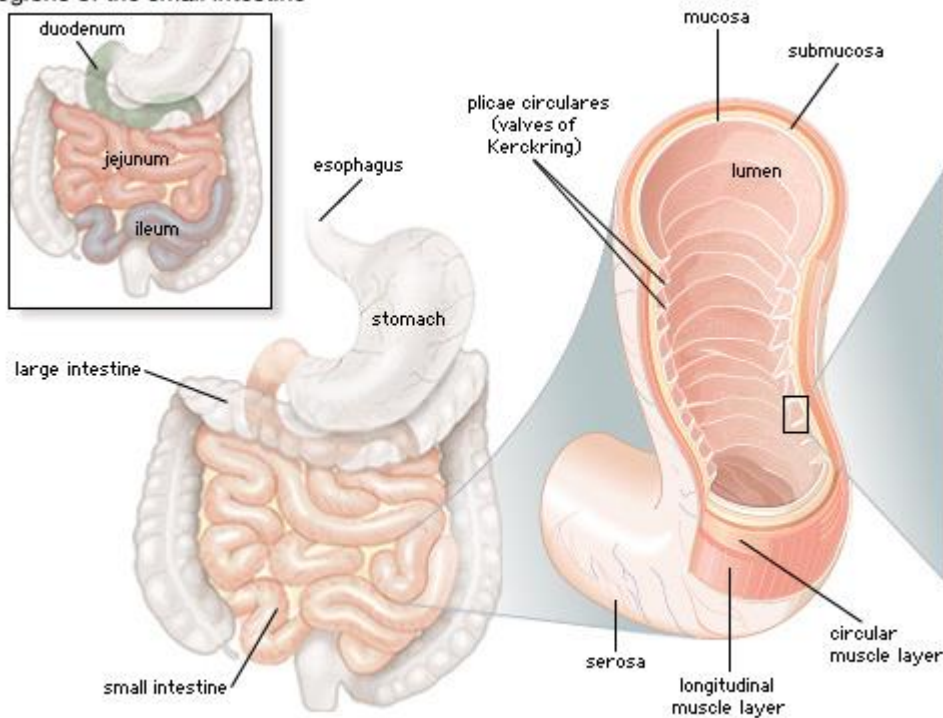
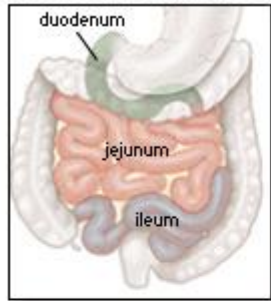
Celiakija – histologija

- **Histološke spremembe – biopsija tankega črevesa**
 - aspiracijska kapsula
 - endoskopska biopsija



Celiakija – histologija

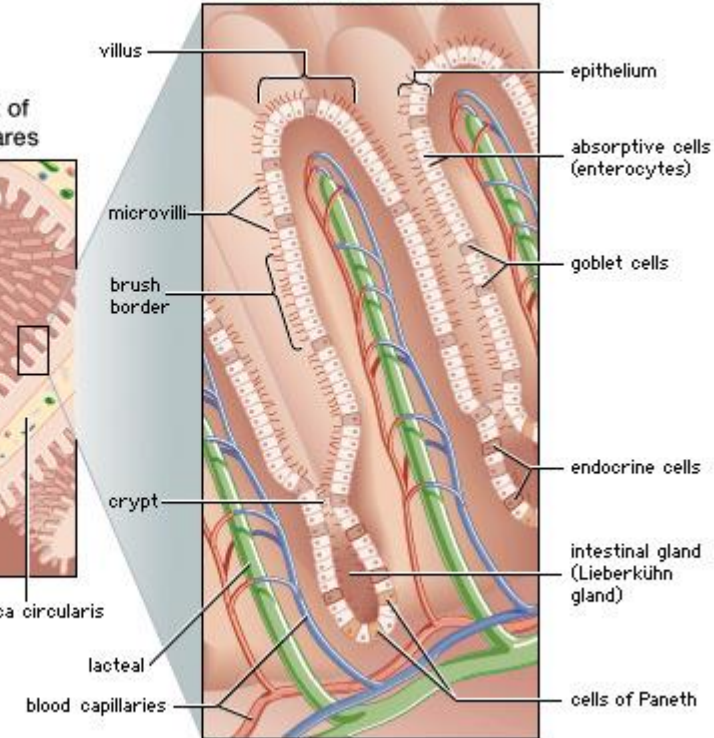
Regions of the small intestine



Enlargement of plicae circulares



Structure of a villus

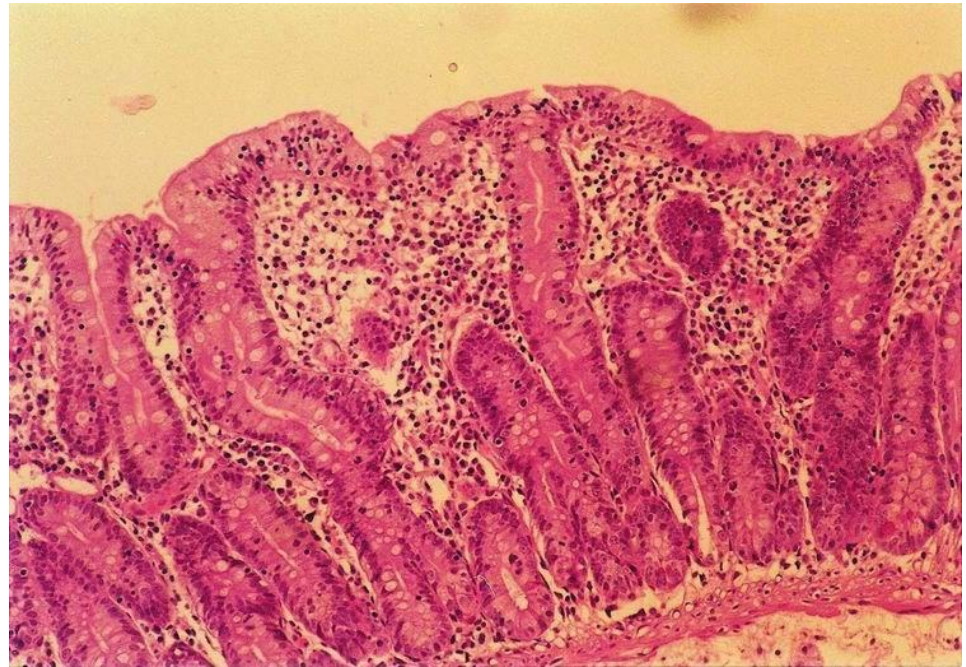
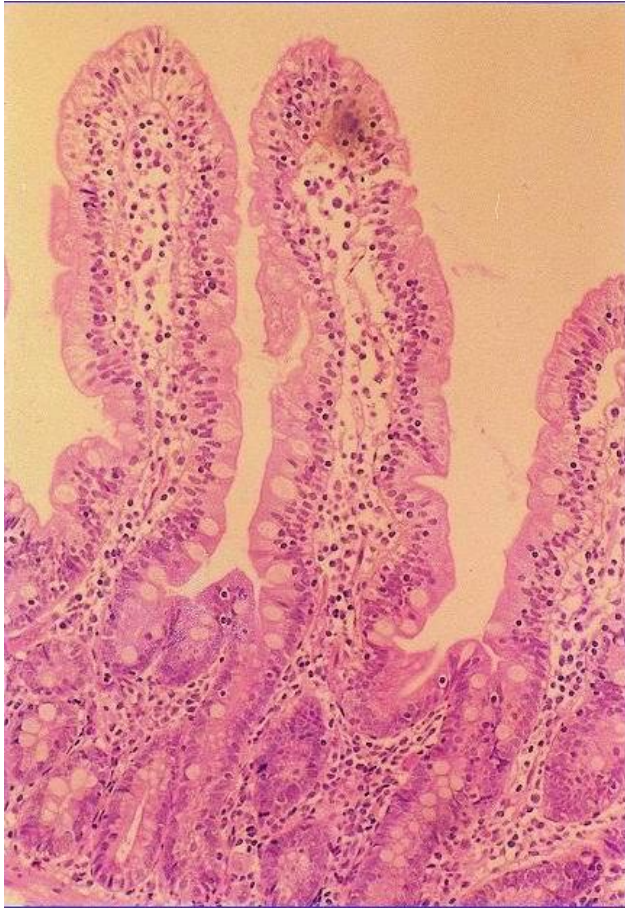


Površina sluznice tankega črevesa

- 30 m² vs 300 m²



Celiakija – histologija



Celiakija – histologija

Histološke spremembe

- **atrofija sluznice**
 - **klasifikacija** Marsh/Oberhuber
 - tip 0: preinfiltrativna faza (normalno)
 - tip 1: infiltrativna faza
 - tip 2: infiltrativno-hiperplastična faza
 - tip 3 (a, b, c): destruktivna faza
 - tip 4: atrofično-hipoplastična faza
 - **atrofija resic, hiperplazija kript, število IEL**



Celiakija – histologija

Histološke spremembe

- atrofija sluznice
 - klasifikacija /Marsh/Oberhuber vs. Corazza/Villanacci

Marsh-Oberhuber	Corazza	IEL	Crypts	Villi
Type 0		< 40	Normal	Normal
Type 1	Grade A	>40	Normal	Normal
Type 2		>40	Hypertrophic	Normal
Type 3a	Grade B1	>40	Hypertrophic	Mild atrophy
Type 3b				Marked atrophy
Type 3c	Grade B2			Total atrophy
Type 4		<40	Normal	Total atrophy



Standardizacija – Reproductibilnost ocene po Marshu

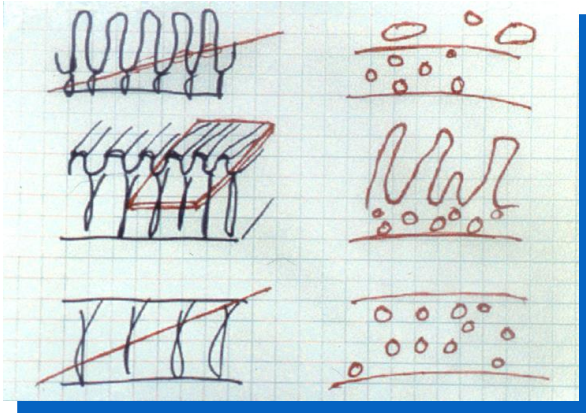
- Mubarak et al. Reproducibility of the histological diagnosis of coeliac disease. Scand J Gastroenterol 2011 (The Netherlands)
 - Interobserver variability for the different Marsh classifications as moderate, **Kappa value 0.486**
- Corazza et al. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. Clin Gastroenterol Hepatol 2007 (Italy)
 - Interobserver variability for the Marsh-Oberhuber classification was fair, **Kappa value 0.35**
- Arguelles-Grande et al. Variability in small bowel histopathology reporting between different pathology practice settings: impact on the diagnosis of coeliac disease. J Clin Pathol 2012 (USA)
 - Within different Marsh score categories, agreement was poor (Kappa <0.0316) for score 1 and 2 and **fair or moderate** for scores 3a and 3b.
- Picarelli et al. Weaknesses of histological analysis in celiac disease diagnosis: new possible scenarios. Scand J Gastroenterol 2014 (Italy)
 - Our study stresses the limits of histological interpretation due to the lack of uniformity in the use of Marsh-Oberhuber classification



Validation of Morphometric Analyses of Small-Intestinal Biopsy Readouts in Celiac Disease

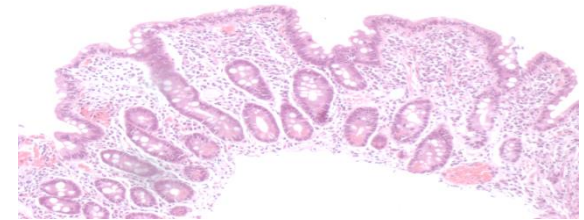
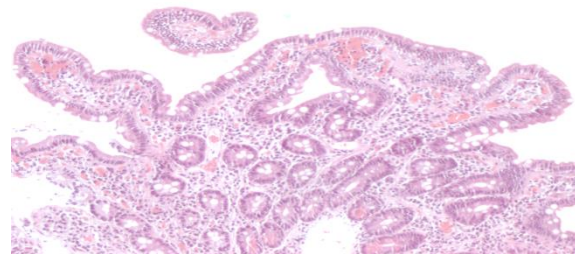
Juha Taavela¹, Outi Koskinen¹, Heini Huhtala², Marja-Leena Lähdeaho¹, Alina Popp^{1,3}, Kaija Laurila¹, Pekka Collin⁴, Katri Kaukinen^{4,5,6}, Kalle Kurppa¹, Markku Mäki^{1*}

PLoS ONE 8(10): e76163. (2013)



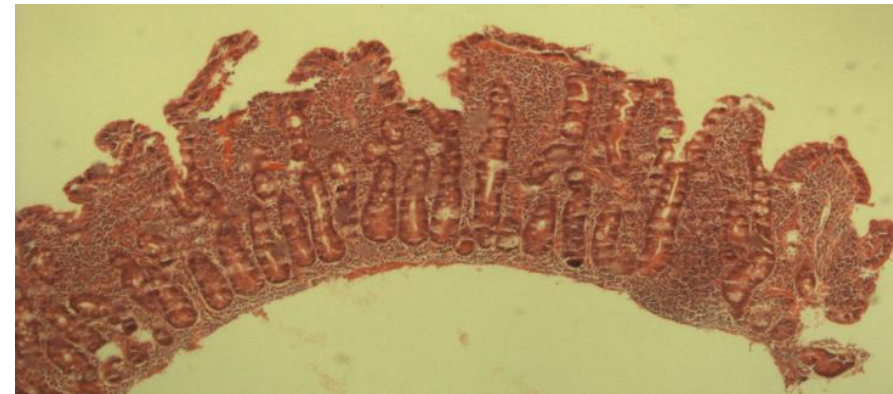
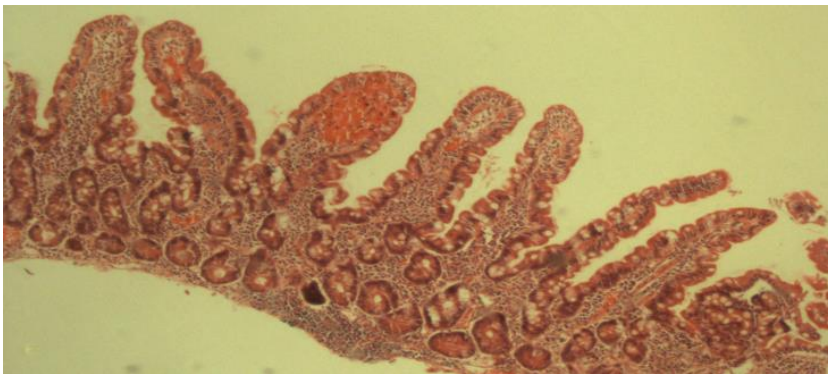
No readout allowed

Reoriented, recut



No readout allowed

Reoriented, recut

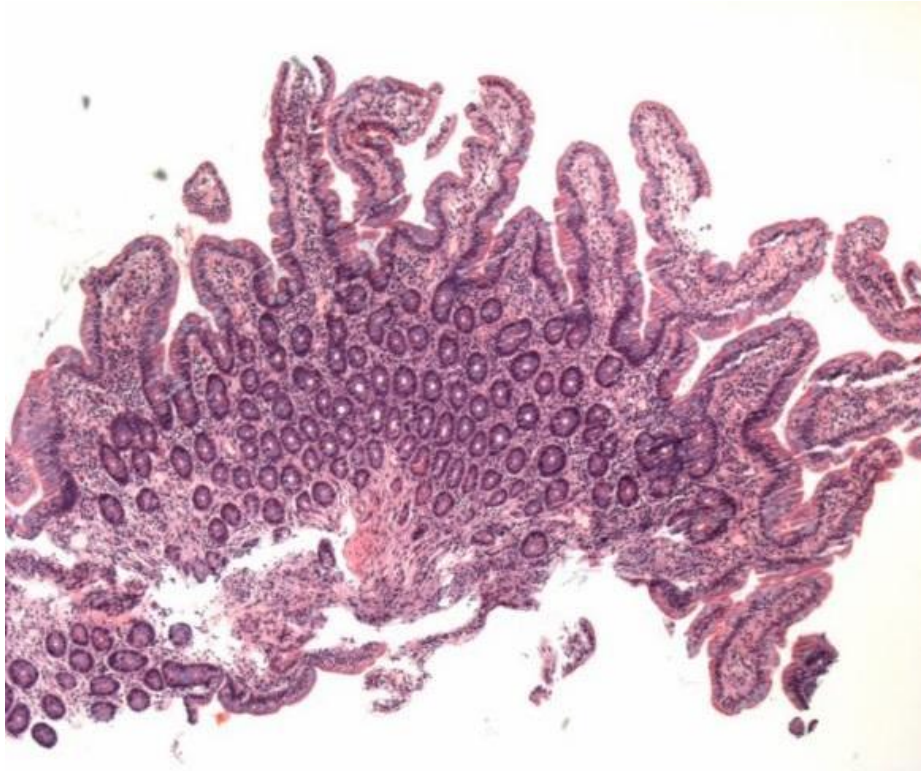


- Marsh 0-I
- Marsh I
- Marsh 0-I
- Marsh 0-I
- Marsh I

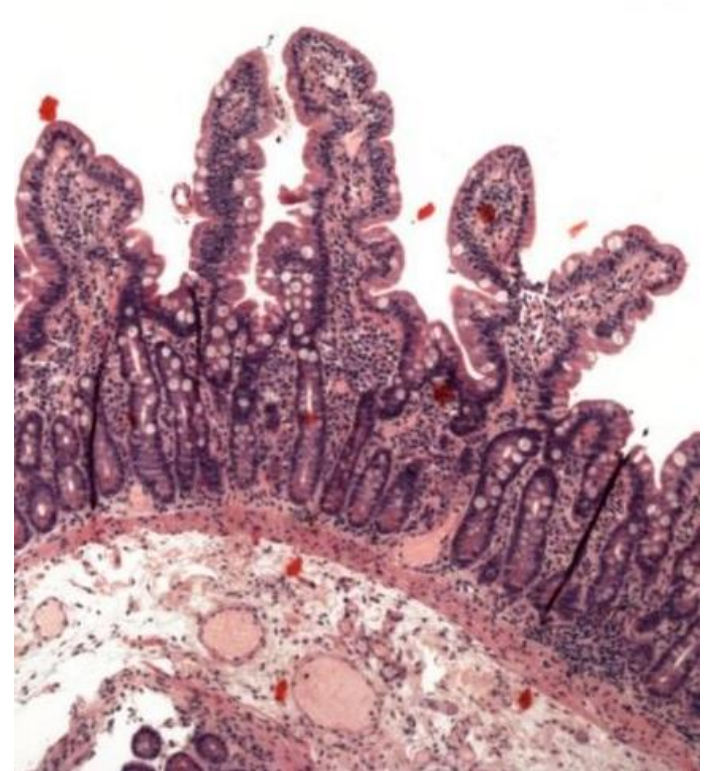
- Marsh IIIc
- Marsh IIIb
- Marsh IIIc
- Marsh IIIb
- Marsh IIIb



Celiakija – histologija



Marsh 1???



Marsh 2!!!



Celiakija – histologija



Fig 1 *Tangentially cut biopsy. The crypts of Lieberkuhn are cut in cross section. HE × 15.*

Risdon et al. Gut 1974: Only those biopsies were considered in which the plane of sectioning was perpendicular to the luminal surface, as judges by the fact that the crypts of Lieberkuhn were cut longitudinally and **not in cross section.**



CLINICAL—ALIMENTARY TRACT

Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice



Katharina Julia Werkstetter,¹ Ilma Rita Korponay-Szabó,^{2,3} Alina Popp,^{3,4} Vincenzo Villanacci,⁵ Marianna Salemme,⁵ Gabriele Heilig,¹ Søren Thue Lillevang,⁶ Maria Luisa Mearin,⁷ Carmen Ribes-Koninckx,⁸ Adrian Thomas,⁹ Riccardo Troncone,¹⁰ Birgit Filipiak,¹ Markku Mäki,³ Judit Gyimesi,² Mehri Najafi,¹¹ Jernej Dolinsek,¹² Stine Dydensborg Sander,¹³ Renata Auricchio,¹⁰ Alexandra Papadopoulou,¹⁴ Andreas Vécsei,¹⁵ Peter Sztanyai,¹⁶ Ester Donat,⁸ Rafaella Nenna,¹⁷ Philippe Alliet,¹⁸ Francesca Penagini,¹⁹ Hélène Garnier-Lengliné,²⁰ Gemma Castillejo,²¹ Kalle Kurppa,³ Raanan Shamir,²² Almuthe Christine Hauer,²³ Françoise Smets,²⁴ Susana Corujeira,²⁵ Myriam van Winckel,²⁶ Stefan Buderus,²⁷ Sonny Chong,²⁸ Steffen Husby,¹³ and Sibylle Koletzko,¹ on behalf of the ProCeDE study group

Table S20: Agreement between local and central Marsh-Oberhuber staging

Table S20: Agreement between local and central Marsh-Oberhuber staging

Local histopathology Marsh-Oberhuber	Reference histopathology Marsh-Oberhuber staging						
	0	1	2	3A	3B	3C	Total
0	25	15	5	7	0	1	53
1	6	9	4	5	2	2	28
2	0	3	1	7	5	2	18
3A	5	3	5	37	22	25	97
3B	0	6	4	65	61	80	216
3C	3	2	4	25	81	149	264
Total	39	38	23	146	171	259	676*

* in 31 patient the local pathologist did not indicate Marsh staging



Celiakija – histologija

Marsh MN, Rostami K. What is normal intestinal mucosa?

Gastroenterology 2016, <http://dx.doi.org/10.1053/j.gastro.2016.09.030>

- The Marsh classification needs no counting nor morphometric measurements, its 4 stages being easily recognizable by **experienced histopathologists**. Marsh stages IIIa, b and c subdivisions are entirely unsatisfactory, get rid of Oberhuber's meddling.
- The usefulness on VH:CrD ratios or villus-crypt units as measuring devices vanishes with Marsh stage II/III lesions, because there are no villi to measure, and because the true crypt-villus interphase cannot be objectively defined.
- Surfaces of flat mucosae do not lie at the level of crypt openings, but are raised above it by 150-200 μm .

Future

- Reconstructing biopsies in virtual space, rotating them through 360 degrees.



Celjenje sluznice tankega črevesa



Celiakija – celjenje sluznice t.č.

Učinek BGD

- popolna normalizacija sluznice??
- 7648 odraslih na Švedskem
 - 5 let po uvedbi diete
 - 3317 (43%) perzistentna atrofija
- 40 otrok
 - 6 (15%) perzistentna atrofija



Zdravljenje



Gluten/gliadin/glutamin/glu.....



Celiakija – zdravljenje

Koliko glutena je dovoljeno

- **kaj pomeni 20 ppm???**
- **varen vnos glutena???**
- **10 mg/dan**
 - **brez sprememb črevesne sluznice**
- **50 mg/dan**
 - **več kot 20% znižanje resic po 6 tednih**
- **rezina kruha (cca 25 g) = 2-2,5-5 g glutena**



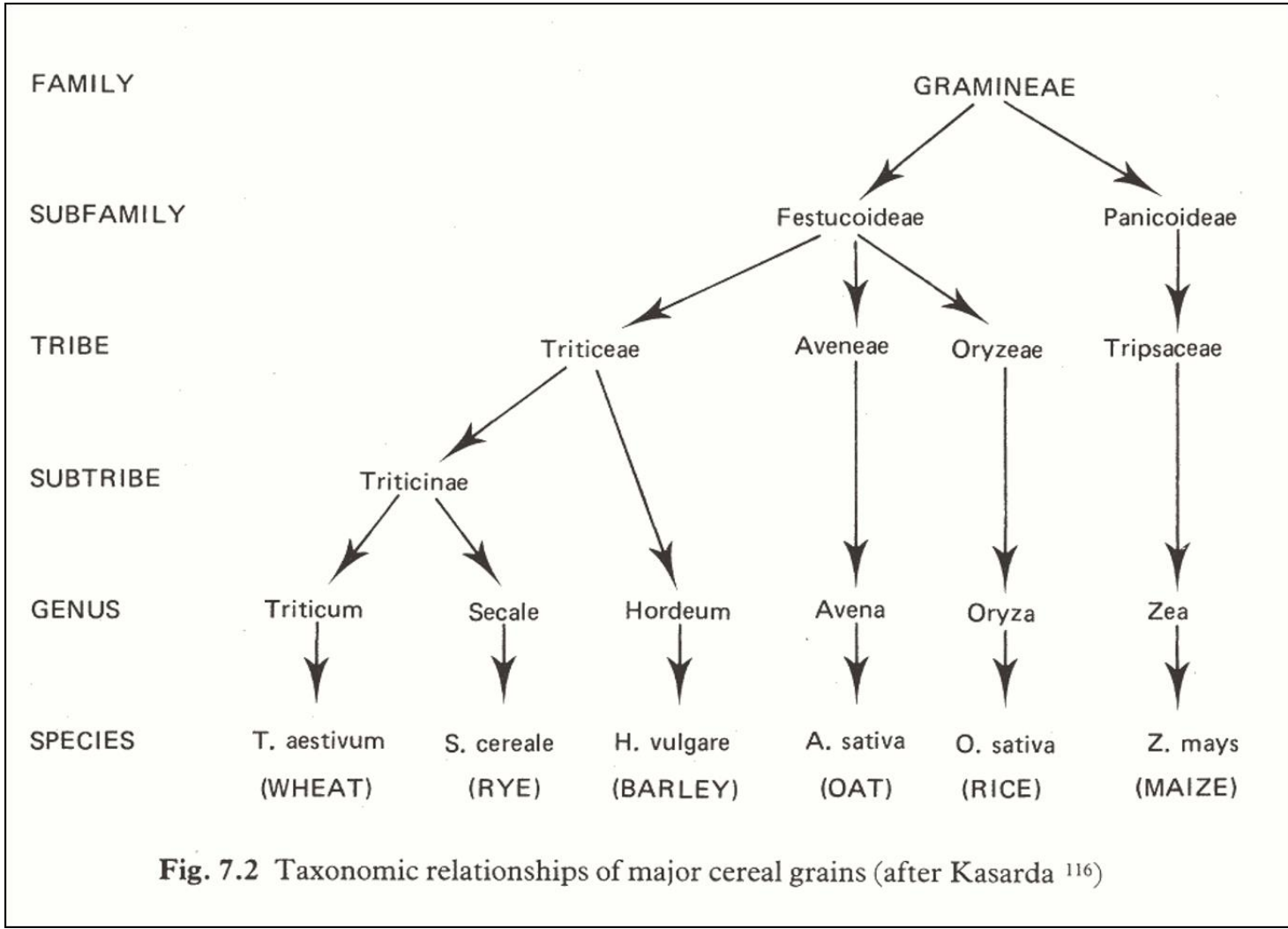
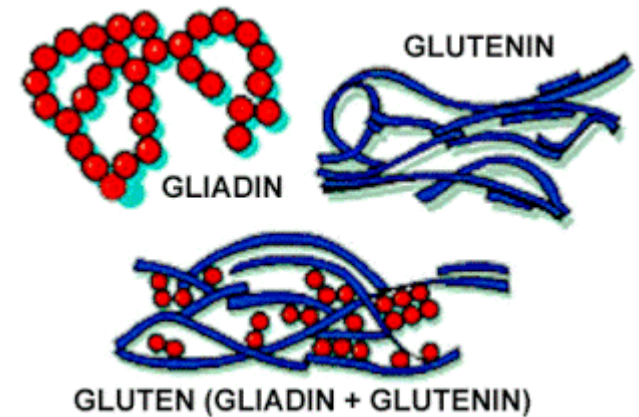
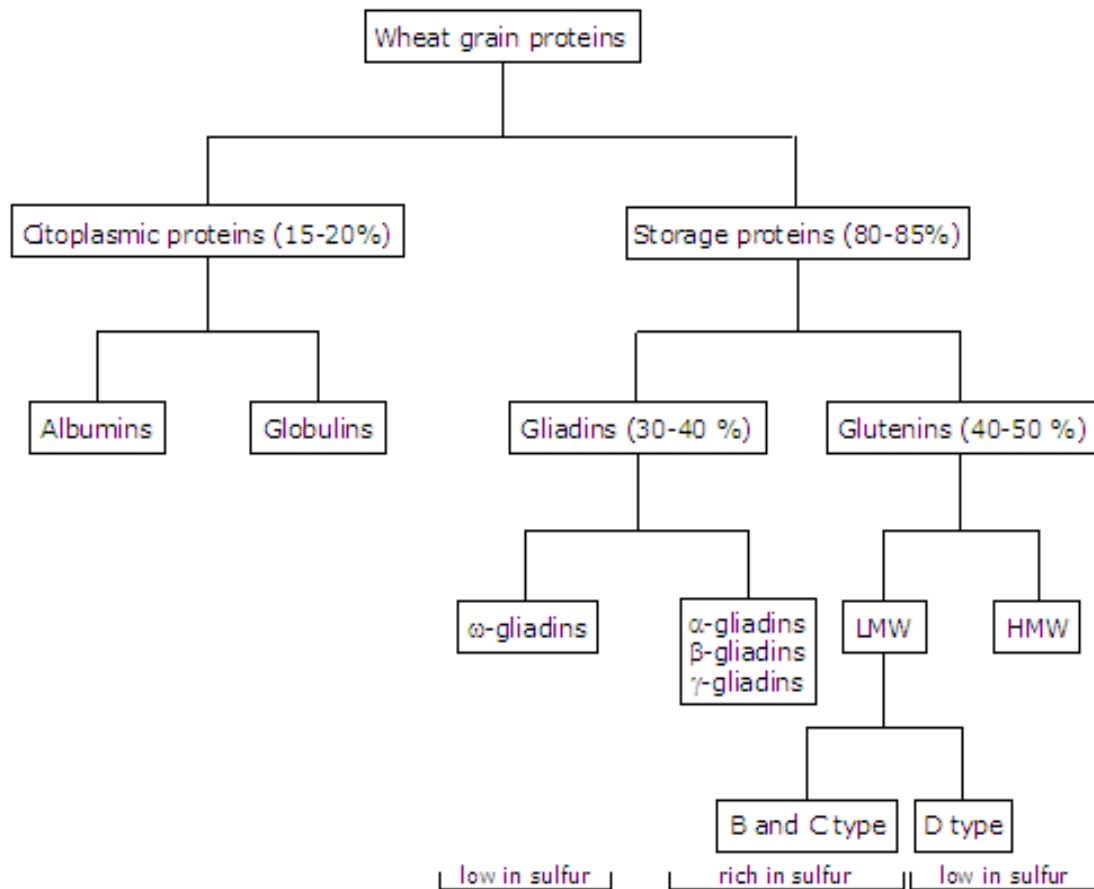


Fig. 7.2 Taxonomic relationships of major cereal grains (after Kasarda ¹¹⁶)



Celiakija – kaj je gluten



Celiakija – kaj je gluten

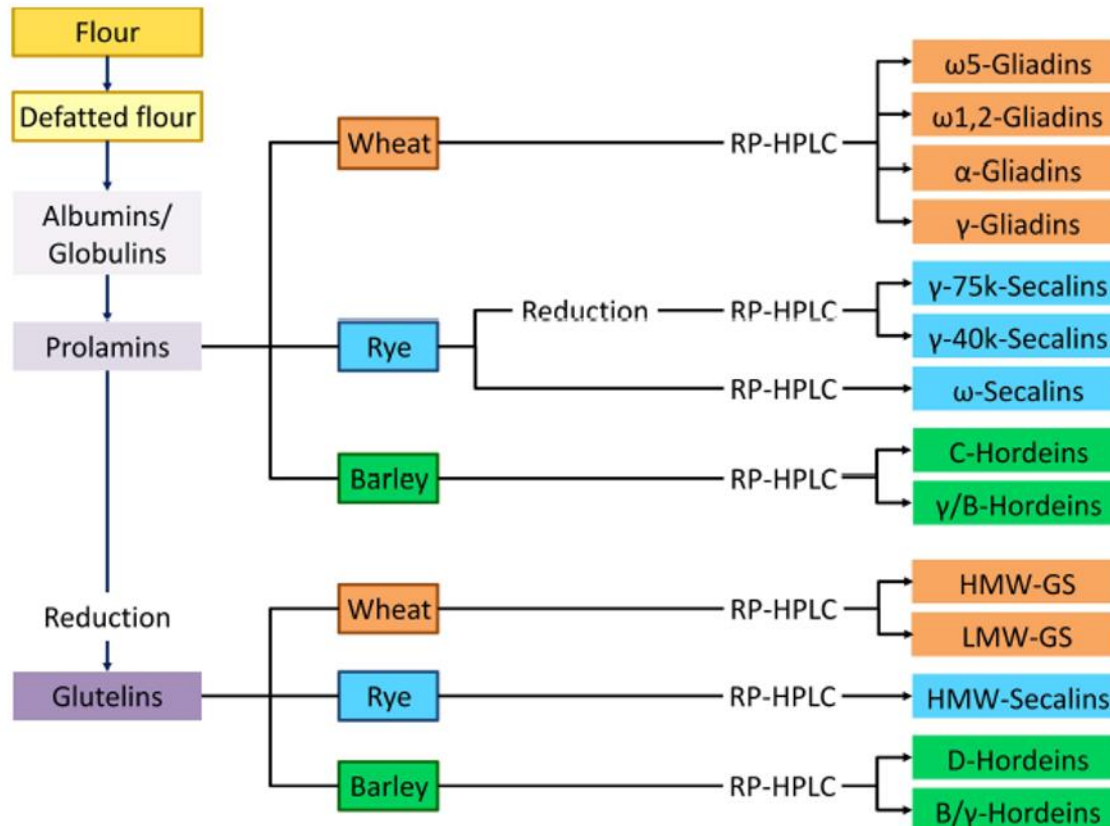


Fig 3. Overview of the preparative strategy. This strategy allows the isolation of well-defined gluten protein fractions and types from wheat, rye, barley and oat flours. HMW-GS, high-molecular-weight glutenin subunits, LMW-GS, low-molecular-weight glutenin subunits.

doi:10.1371/journal.pone.0172819.g003



Celiakija – kje je gluten

Gluten percentage:

- **Wheat flour Type 630** 9,4g / 100g
- **Wheat flour Type 405** 8,7g / 100g
- **Spelt flour Type 630** 10,3g / 100g

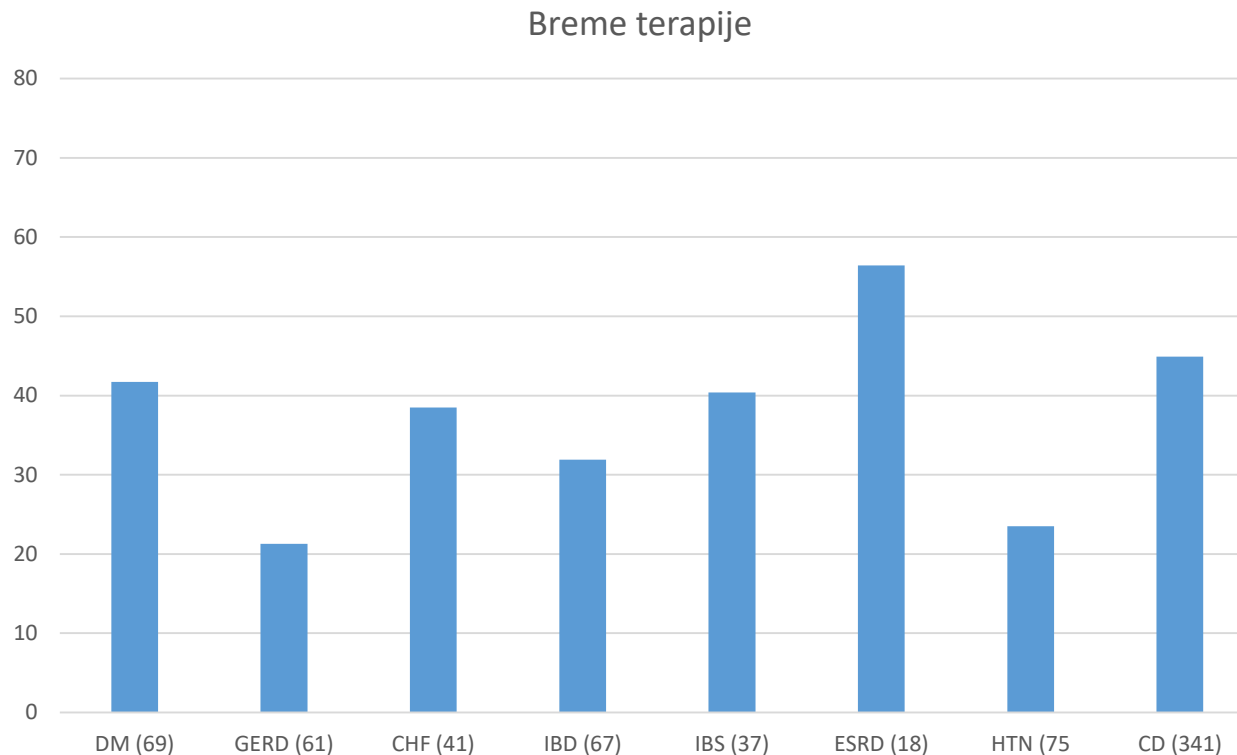


Kvaliteta življenja bolnikov s celiakijo



Celiakija – QoL

Breme zdravljenja z BGD



Zaključki



Zaključki

- pogosta/pogosto spregledana/nediagnosticirana bolezen
- prevalenca narašča
- prizadene otroke in odrasle
- klinična slika se spreminja in je nespecifična
- obstajajo skupine z večjim tveganjem
- resni zapleti, če se ne odkrije/zdravi



Zaključki

- diagnostične metode so dobro opisane in dostopne
 - **TODA!**
 - pomembno je boljše poznavanje
 - seroloških testov
 - vloge, pomena in pomanjkljivosti genetike
 - vloge, pomena in pomanjkljivosti histologije
- pomen rednega sledenja
- potreba po ustreznem dietetskem svetovanju



Two groups – probably not any more

- all children and adolescents with symptoms and/or risk groups

- intestinal biopsy – not in all patients

- dominant role of serology (t-TG)

Nove smernice ESPGHAN – 2019 cases

- histology remains important

- for many of patients

- no changes in the treatment

- STRICT LIFELONG GLUTEN FREE DIET



Zaključek

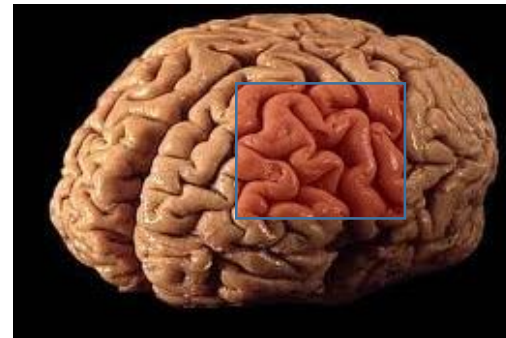
The true gold standard is not histology but the real gold standard in the diagnosis of CD is the

gastroenterologist,

the only one who knows the patient, establishes the tests and their timing, and the only one who can reasonably interpret all the panels of available data (clinical, serological, histological and genetic).

Gold standard in coeliac disease diagnosis. V Villanacci , Dig Liver Dis 2010





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