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olv Top in Zorg.

Coeliac disease: kinetics of antibody titers & clinical correlation after initiation of gluten-free diet

Critically Appraised Topic

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10 June 2021

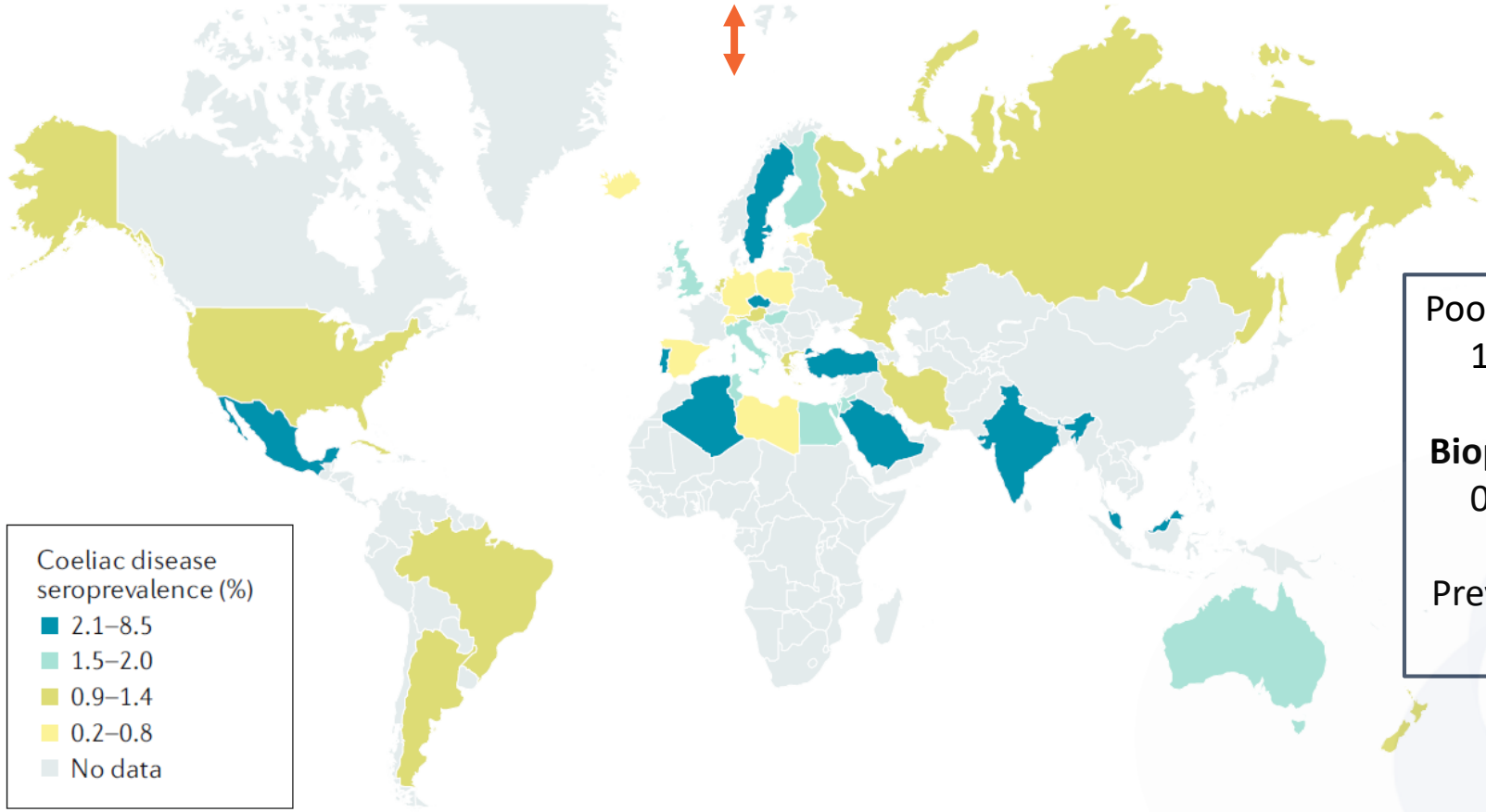
Fallacies and Facts

Prospective study results

Discussion

Fallacies and Facts

*"**coeliac disease** is an **uncommon disorder** that mainly affects **children** and is limited to **western Europe**"*



Pooled **global seroprevalence**
1.4% (95% C.I. 1.1-1.7%)

Biopsy confirmed prevalence
0.7% (95% C.I. 0.5-0.9%)

Prevalence **children > adults**
(0.9% vs 0.5%)

Fig. 1 | **The global seroprevalence of coeliac disease.** The map shows coeliac disease seroprevalence as determined by positive serum transglutaminase 2 and/or endomysial autoantibodies. More intensive colour indicates higher prevalence. Countries where no studies on the prevalence of coeliac disease have been conducted are presented without colour[3].

LINDFORS et al. Nature Reviews 2019;5:3
SINGH et al. Clinical Gastroenterology and Hepatology 2018;16:823-836

Fallacies and Facts

*"**symptoms** in coeliac disease are **limited to** abdominal symptoms"*

lack of awareness among health- care professionals

diagnostic delays can reach up to **10 years** in resource- rich countries

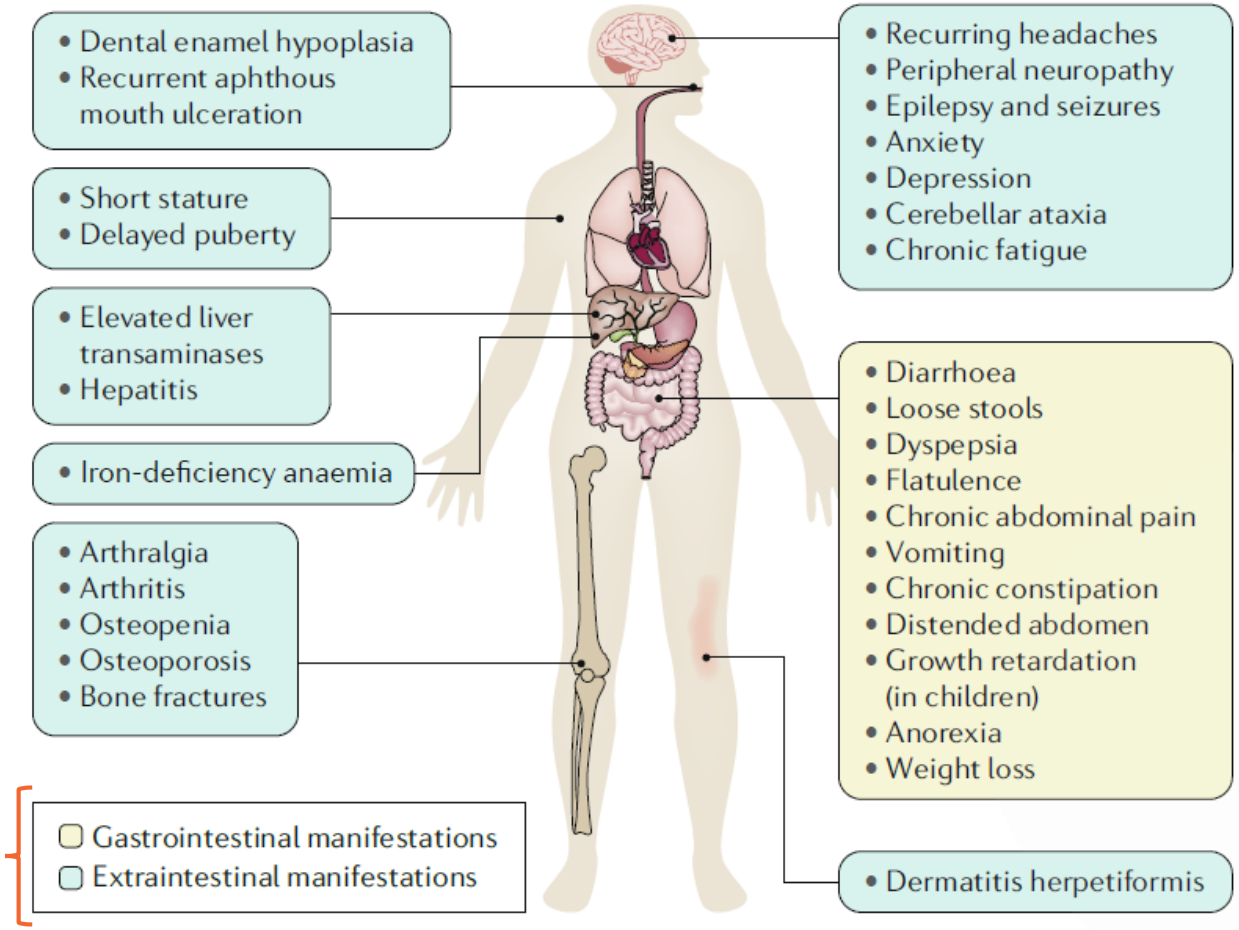


Fig. 6 | **The clinical manifestations of coeliac disease.** Coeliac disease can have diverse clinical presentations in addition to the classically anticipated gastrointestinal symptoms.

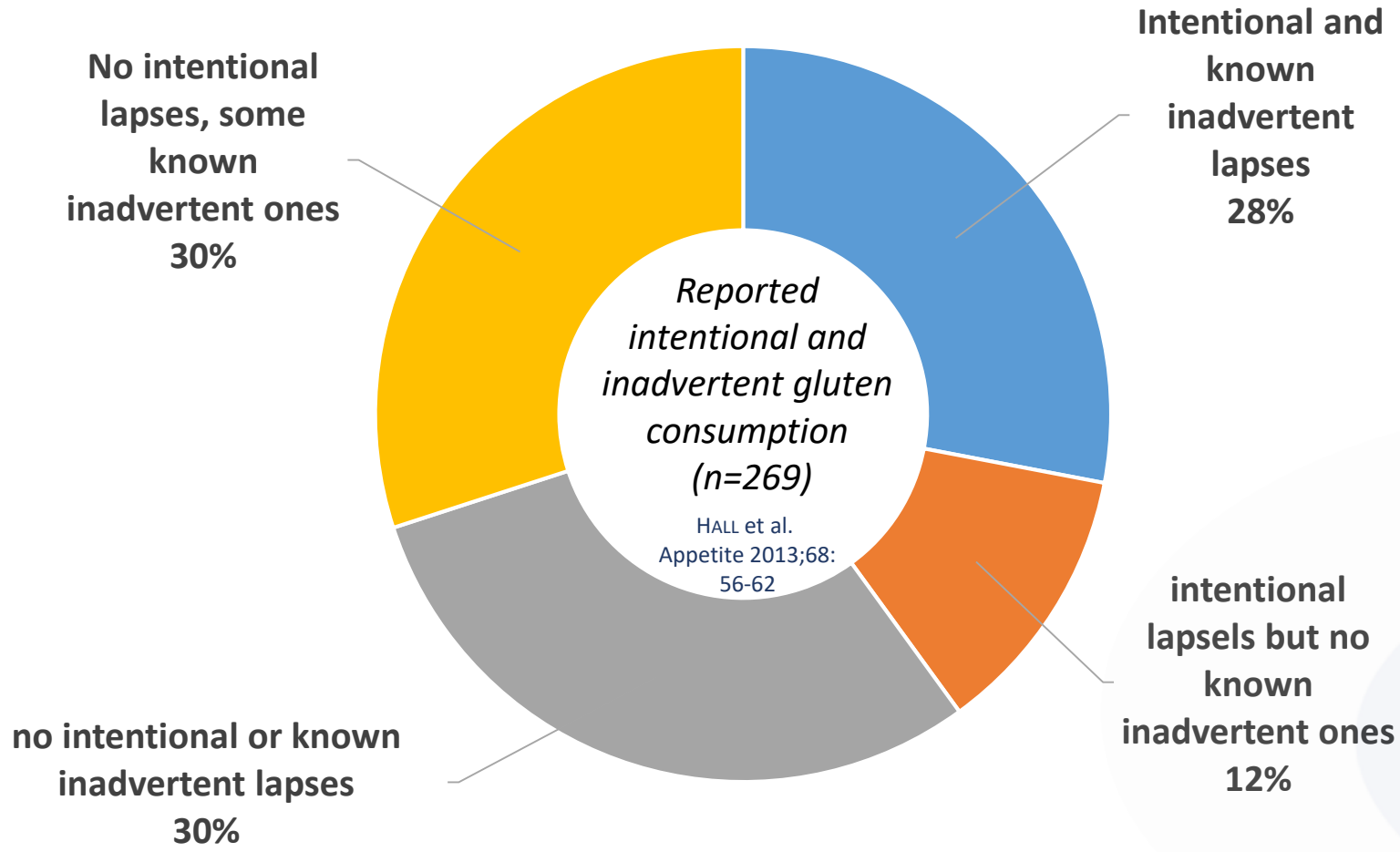
LINDFORS et al. Nature Reviews 2019;5:3

Fallacies and Facts

*"**a gluten-free diet (GFD)** has **solved the problem** of coeliac disease"*

7-30%
"nonresponsive celiac disease"
(NRCD)

0.04-1.5%
"refractory celiac disease"

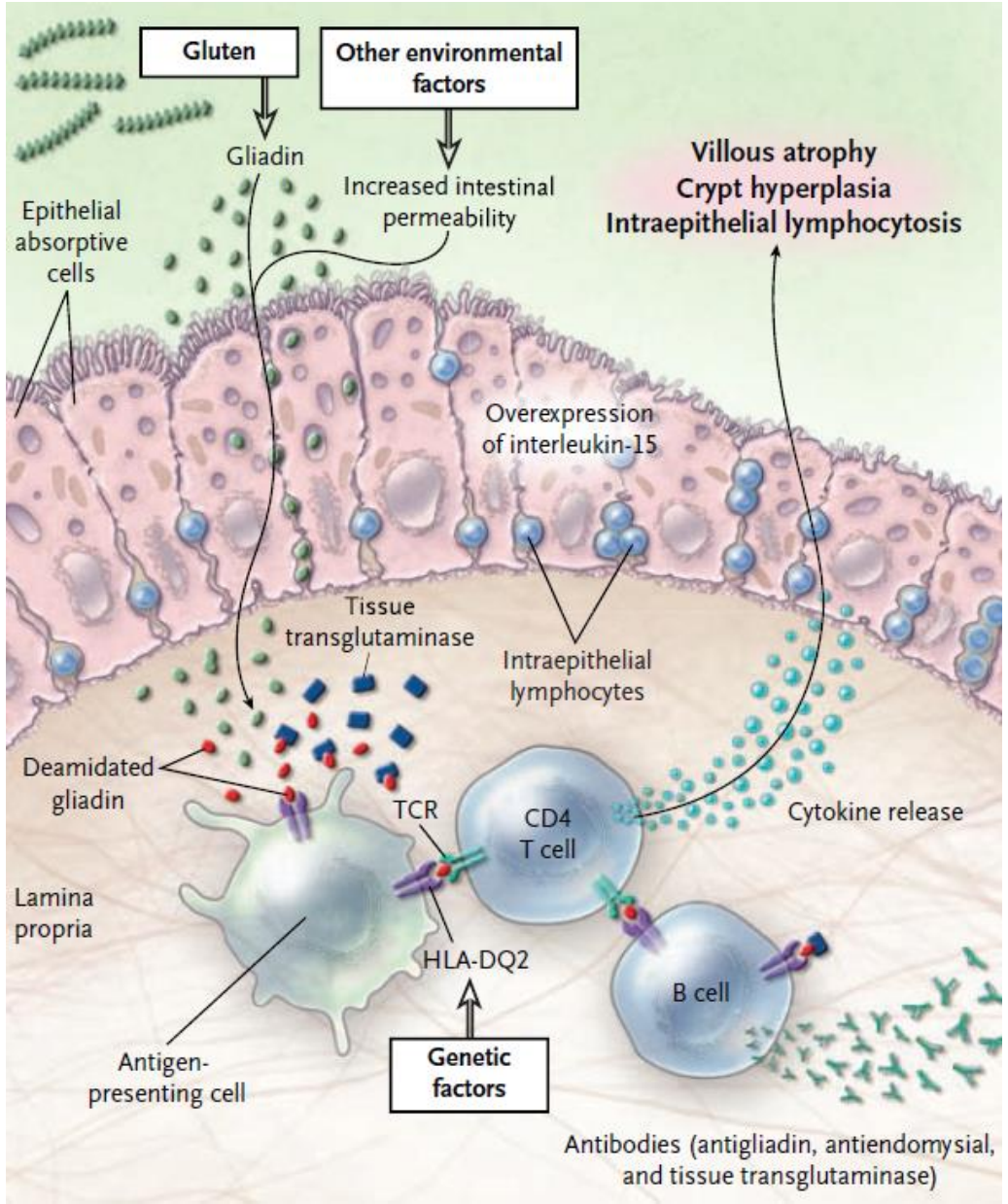


All guidelines:
lifelong afherence to strict GFD

Multidisciplinary monitoring

Leffler et al. Clin Gastroenterol Heparol. 2007;5(4):445-50
Silvester et al. Am J Gastroenterol 2021;00:1-8

Fallacies and Facts

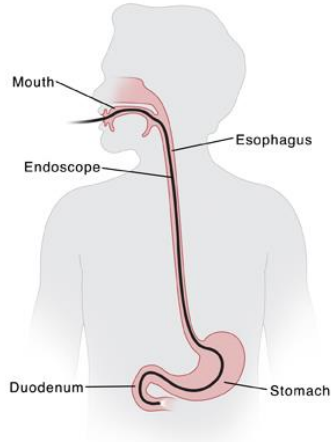


<u>Diagnosis</u>:

small intestinal mucosal morphology

+

serology testing



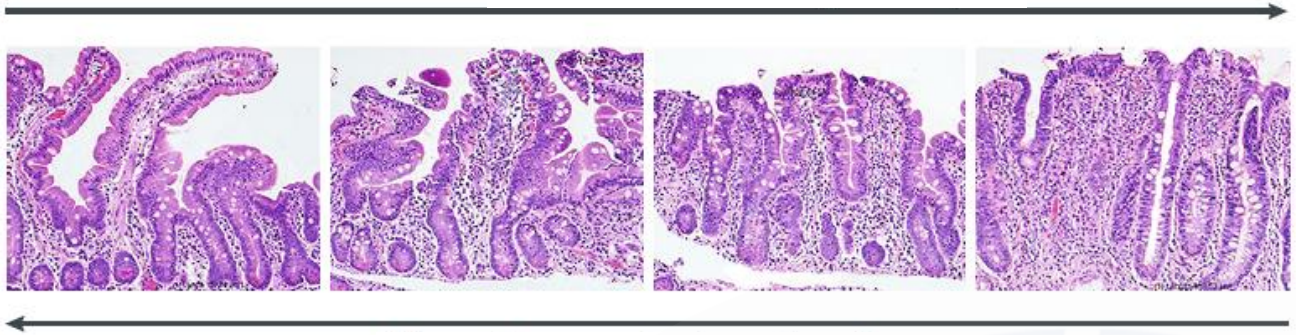


Fig. 7 | **The continuum of small intestinal mucosal damage in coeliac disease.** In coeliac disease, gluten-induced small intestinal mucosal lesions develop over time, from normal villous architecture (far-left panel) to mucosal inflammation with crypt hyperplasia (middle-left panel) and finally progressing to villous atrophy with crypt hyperplasia (middle-right and far-right panels). Images are mucosal sections cut perpendicular to the luminal surface from biopsy samples from patients with coeliac disease. Damage to the mucosa reverses upon the initiation of a strict gluten-free diet. Figure adapted from REF.[221], Springer Nature Limited.

LINDFORS et al. Nature Reviews 2019;5:3

GREEN P., CELLIER C. N Engl J Med 2007;357:1731-43

Fallacies and Facts

Diagnosis:

small intestinal mucosal morphology

+

serology testing

Table 2. Sensitivity and specificity of different serological tests.

Antigen	Antibody type	Sensitivity, % (range)	Specificity, % (range)
Gliadin (obsolete)	IgA	85 (57–100)	90 (47–94)
	IgG	80 (42–100)	80 (50–94)
Endomysium	IgA	95 (86–100)	99 (97–100)
Indirect immunofluorescence (IIF)	IgG	80 (70–90)	97 (95–100)
Tissue transglutaminase	IgA	98 (78–100)	98 (90–100)
ELISA-based (CLIA, FEIA)	IgG	70 (45–95)	95 (94–100)
Deamidated gliadin peptide	IgA	88 (74–100)	90 (80–95)
ELISA-based (CLIA, FEIA)	IgG	80 (70–95)	98 (95–100)

AL-TOMA et al. United European Gastroenterol J. 2019;7(5):583-613

Fallacies and Facts

Diagnosis:
small intestinal mucosal morphology
+
serology testing

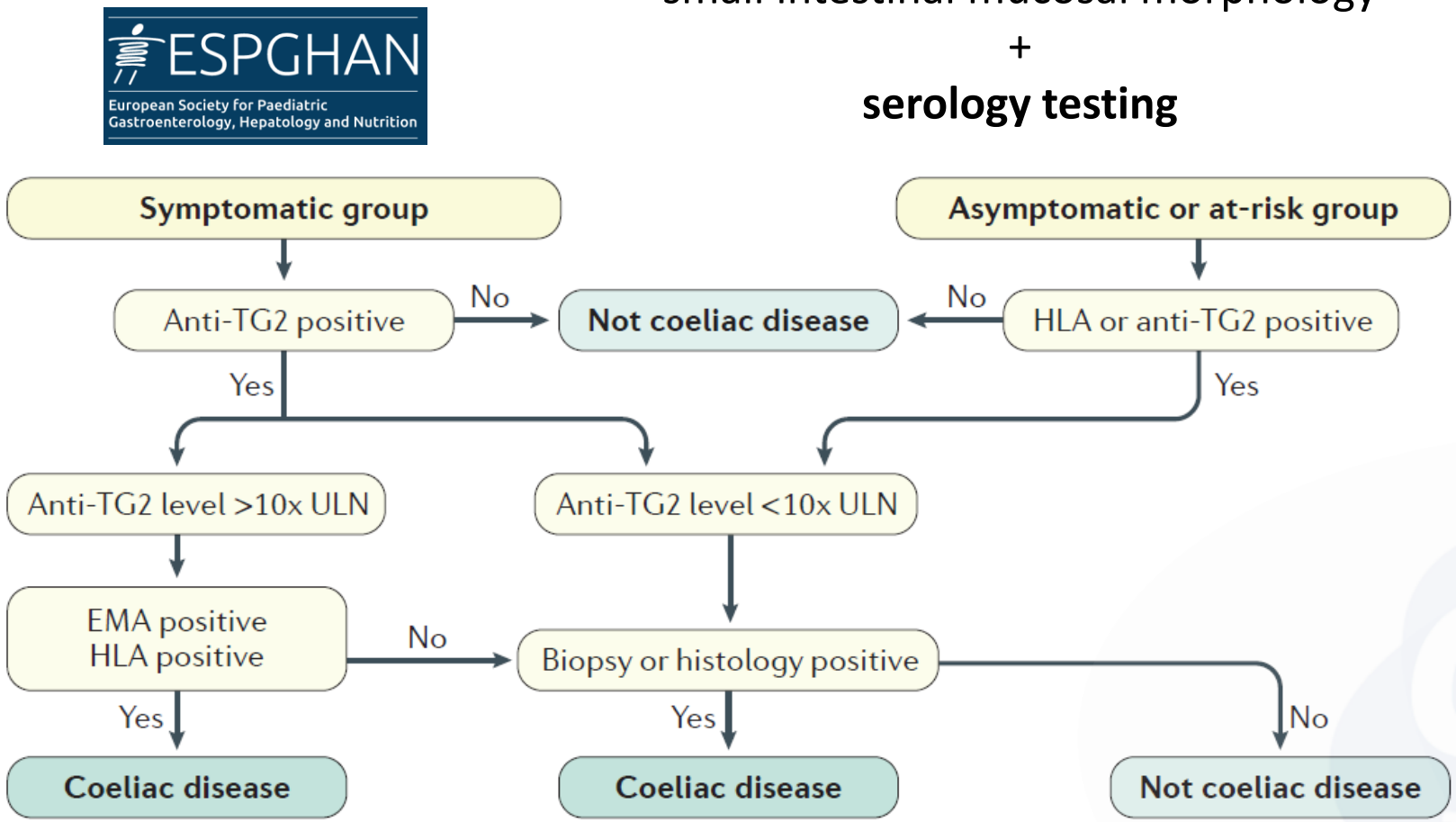


Figure 1 | **Suggested biopsy-avoiding diagnostic pathway for coeliac disease.** Non-biopsy diagnosis of coeliac disease based on the European Society for the Study of Paediatric Gastroenterology, Hepatology and Nutrition criteria in a symptomatic child with strongly positive tissue transglutaminase 2 antibody (anti-TG2) values, >10 times the upper limit of normal (ULN), a positive endomysial IgA antibody (EMA) on another blood sample and the presence of the appropriate HLA type. On the right is the process for an asymptomatic or at-risk child. A positive anti-TG2 result should lead to biopsies and histological analysis for diagnosis.

REILLY et al. Nature Reviews Gastroenterology & Hepatology 2018;15:60-66

Fallacies and Facts

Diagnosis:
small intestinal mucosal morphology
+
serology testing

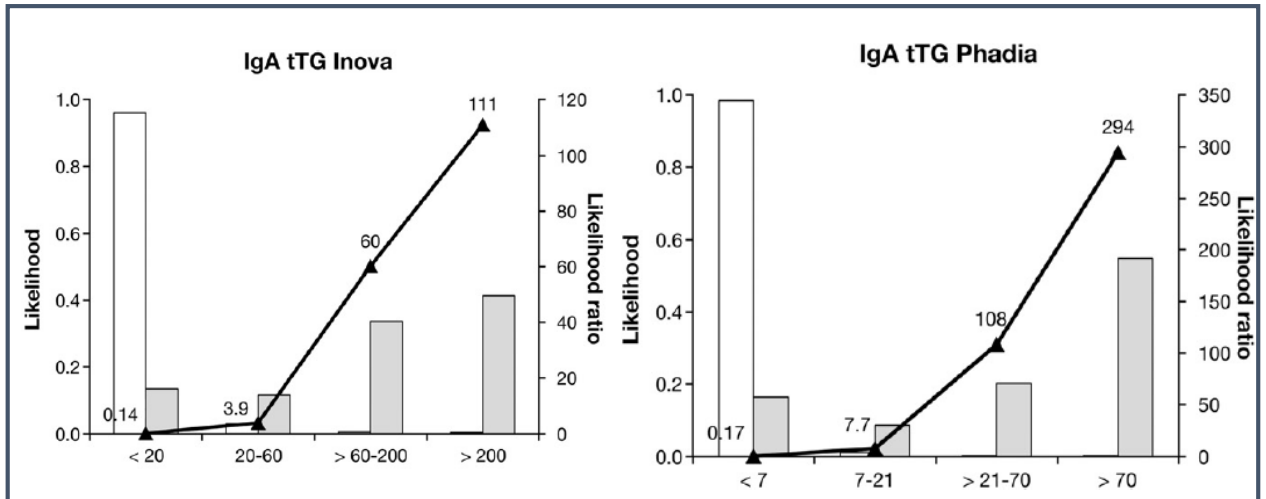


Figure 1. Likelihoods (or probabilities) (*left*, y-axis) for various IgA anti-tTG test result intervals given the disease status (celiac disease, *gray filled bars*; controls, *white bars*). The *triangles* represent the likelihood ratios (*right*, y-axis).

N = 104 CD patient (adults + children)
N = 537 controls

↑ tTG IgA → ↑ LR for CD
Thresholds tTG IgA:
better based on **predefined LR's** or on **pre-defined specificities**

N = 91 CD patient (children)
N = 605 controls

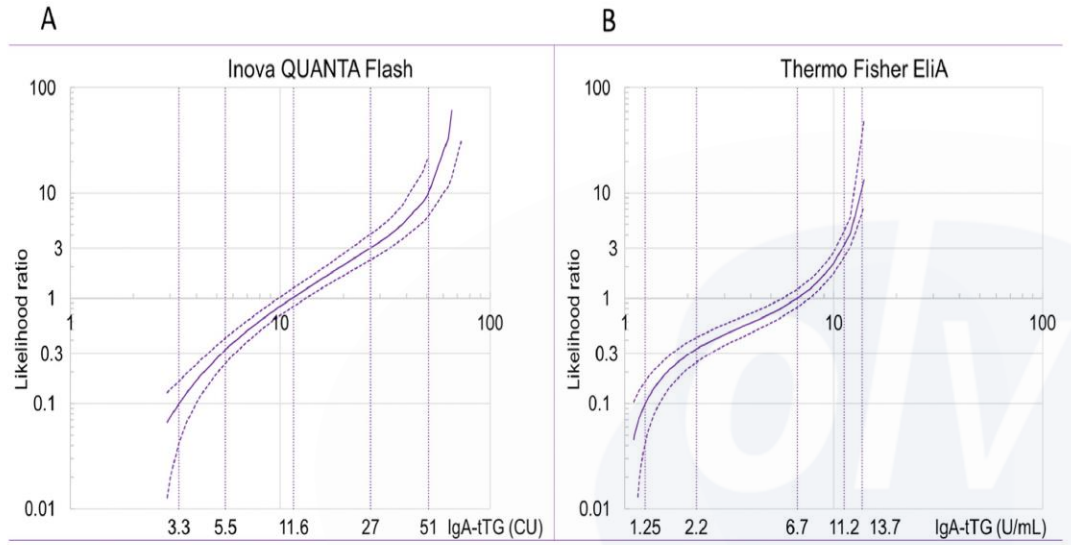


Fig. 4. IgA-tTG test result-specific likelihood ratios (LR) for celiac disease.
The figure shows the IgA-tTG test result specific LRs (full line) and 95% confidence intervals (dashed lines) for celiac disease. The left hand panel (A) shows the results for Inova QUANTA Flash and the right hand panel (B) for Thermo Fisher EliA. In both panels, the test results that are associated with a LR of 0.1, 0.33, 1, 3 and 10 are indicated.

VERMEERSCH et al. Clin Gastroenterol Hepatol. 2013;11:398-403
BOGAERT et al. Autoimmunity Reviews 2020;19(5):102513

Fallacies and Facts

<u>Diagnosis</u>:
small intestinal mucosal morphology
+
serology testing

↕

<u>Monitoring</u>:
serological usefulness less evidence-based

Questions Critically Appraised Topic

1) *How does the **kinetic profile** differ between the **different serological assays** (tTG IgA/IgG vs. DGP IgA/IgG)?*
2) *Is the **clinical interpretation dependent** on the **assay** that is used (Thermo Fisher vs. INOVA)?*
3) *How does **serological status**, **complaints** and **routine laboratory test** differ between **strictly, partially and non-compliant CD patients**?*

Fallacies and Facts

Prospective study results

Discussion

Study protocol

PART 1 — *Pre- and post-test probabilities of coeliac disease*

Review
Autoimmunity Reviews 19 (2020) 102513

Optimization of serologic diagnosis of celiac disease in the pediatric setting

Laura Bogaert[a,b,1], Mathieu Cauchie[c,1], Lieve Van Hoovels[a,g], Pieter Vermeersch[b], Walter Fierz[d], Gert De Hertogh[e], Ilse Hoffman[f], Xavier Bossuyt[b,g,*]

PART 2 → **Prospective** sample collection

start November 2016

Patients **(>2 years old)**
with GI and/or non-specific symptoms
Confirmation CD by **serology + biopsy**

start of **GFD**

- **T = 0** months
- **T = 3** months
- **T = 6** months
- **T = 12** months
- **T = 24** months

- **Clinical** assessment by treating **physician**
- **Complaints diary** completed by **patient**
- **Blood sample**: tTG-IgA, Hb, AST, ALT, Iron, Ferritin, 25-OH-D

Additional analyses April 2021

anti-tissue transglutaminase (**tTG**) **IgA** and **IgG**
deamidated gliadin peptide (**DGP**) **IgA** and **IgG**
→ **INOVA** (CLIA) / **Thermo Fisher** (FEIA)

Complaints diary
score sytem:
- no complaints: "0"
- maximum complaints "10"

We vragen u om in het kader v … net glutenallergie te
quoteren van 0 tot 10. U kan nc … t om de klachten die
u ervaart. Het gaat voornamelijl … neer u geen klachten
hebt, geeft u dit aan met een 0. … en cijfer tussen de 1
en de 4. Bij veel klachten kunt u …

Omcirkel voor de volgende symptomen een cijfer van 0 tot 10.

Anorexie/niet willen eten: *anorexia / refusal to eat*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Aanslepende diarree: *persistent diarrhoea*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Obstipatie: *constipation*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Gewichtsverlies: *loss-of-weight*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Braken: *vomiting*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Irritabiliteit: *irratibility*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Huidproblemen: *skin problems*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

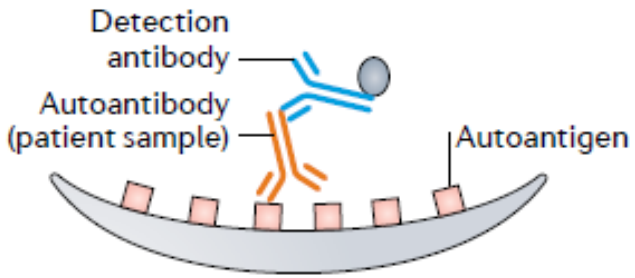
Aften in de mond: *Aphthous stomatitis*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Hoofdpijn: *headache*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

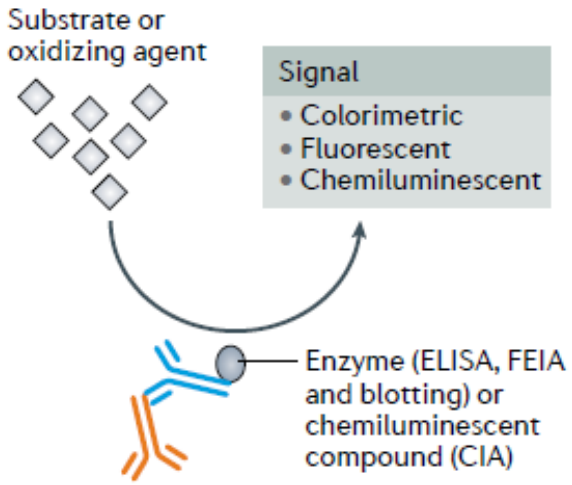
Vermoeidheid: *tiredness*
0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Study protocol

Antibody **labelling**



Antibody **detection**



ThermoFisher SCIENTIFIC

Celikey® IgA – Celikey® IgG
Gliadin^{DP} IgA – Gliadin^{DP} IgG

Negative <7 EliA U/mL
Dubious 7-10 EliA U/mL
Positive >10 EliA U/mL

FEIA = fluorescence enzyme immunoassay

Inova Diagnostics
A Werfen Company

QUANTA Flash® h-tTG IgA – QUANTA Flash® h-tTG IgG
QUANTA Flash® DGP IgA – QUANTA Flash® DGP IgG

Negative <20 CU
Weak positive 20-30 CU
Positive >30 CU

CLIA = chemiluminescent immunoassay

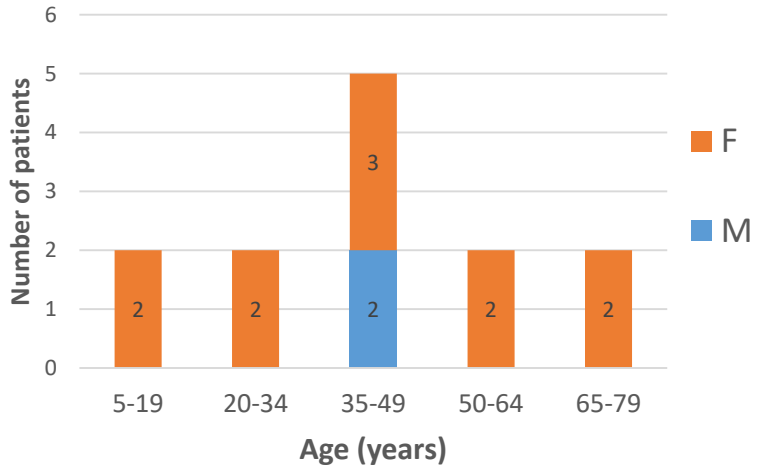
anti-tissue transglutaminase (**tTG**) **IgA** and **IgG**
deamidated gliadin peptide (**DGP**) **IgA** and **IgG**

INOVA (CLIA)
Thermo Fisher (FEIA)

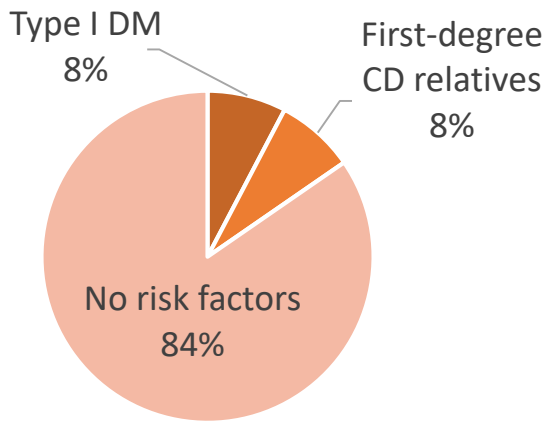
Bossuyt et al. Nat Rev Rheumatol. 2020;16(12):715-726

Sample collection (n = 13) – data at diagnosis

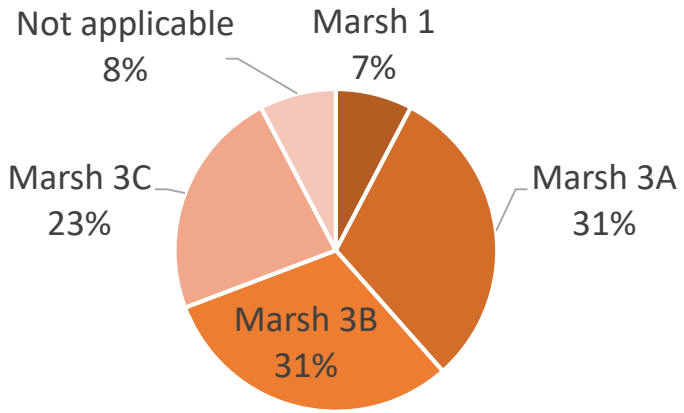
Demographic features



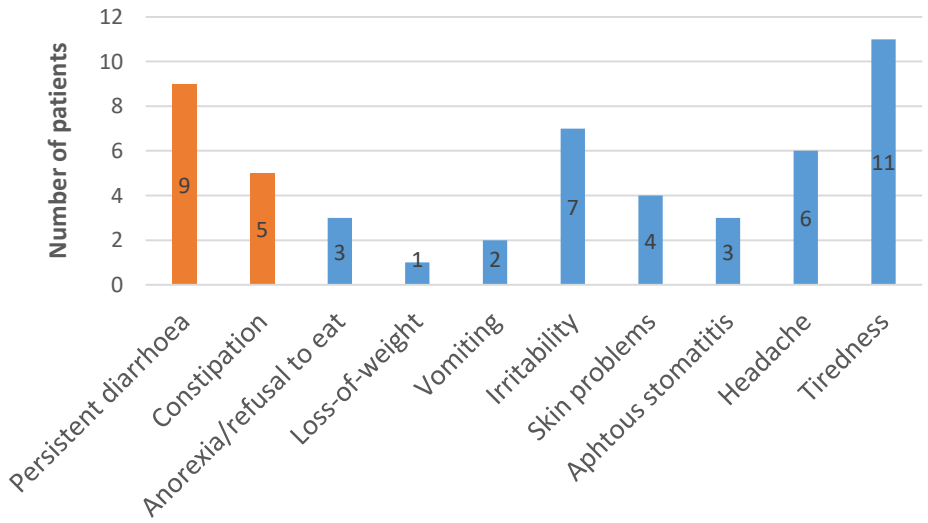
Risk factors



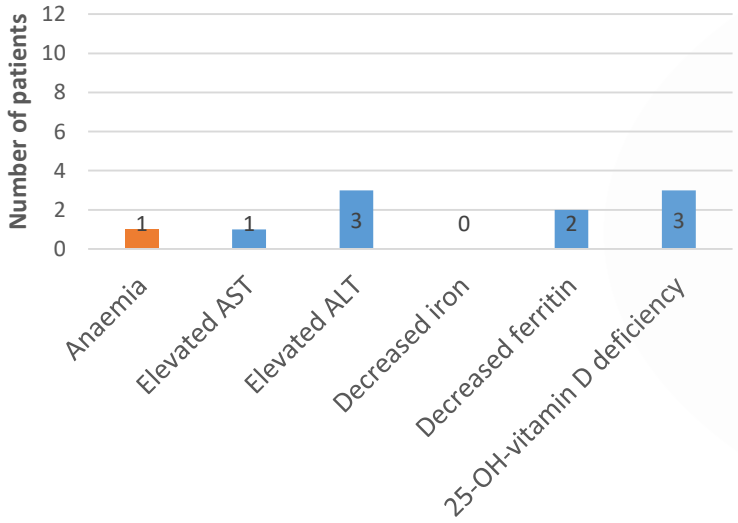
Histological findings



Patient complaints



Laboratory data



Conclusions

♀ >> ♂

↑ **prevalence** of **extra-intestinal** symptoms

↓ **prevalence** of **biochemistry/hematological abnormalities** at t=0

Results

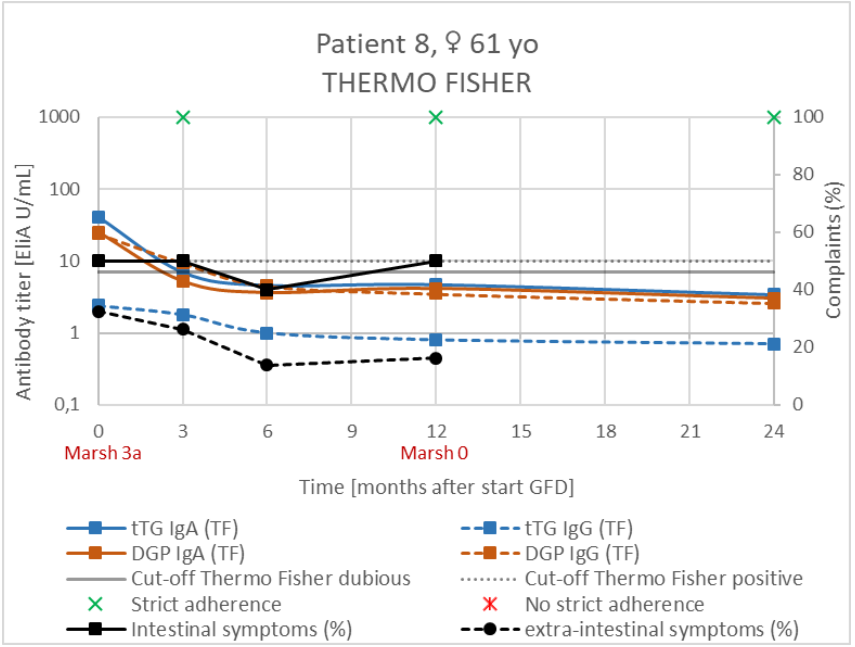
GFD adherence :

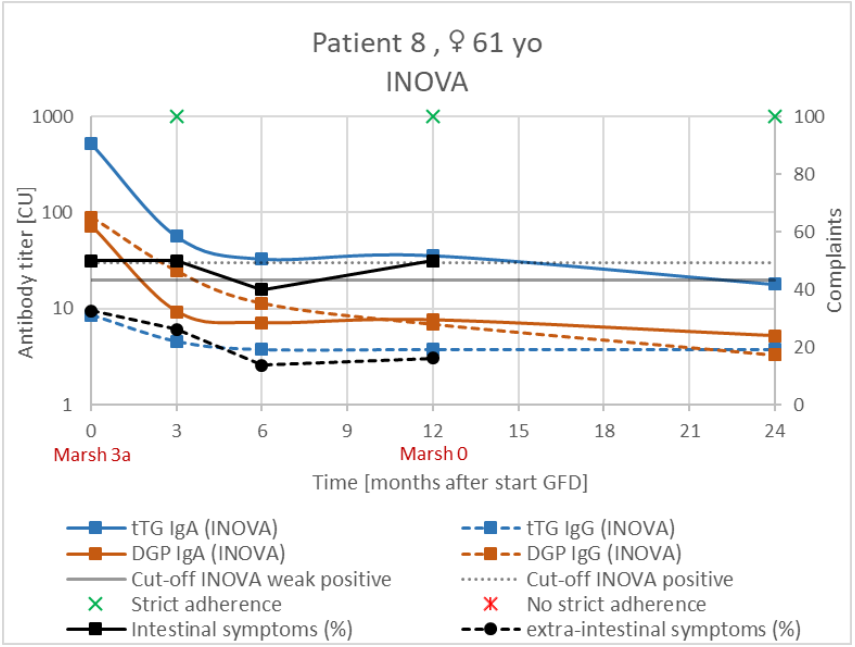
100% compliant (n=7)

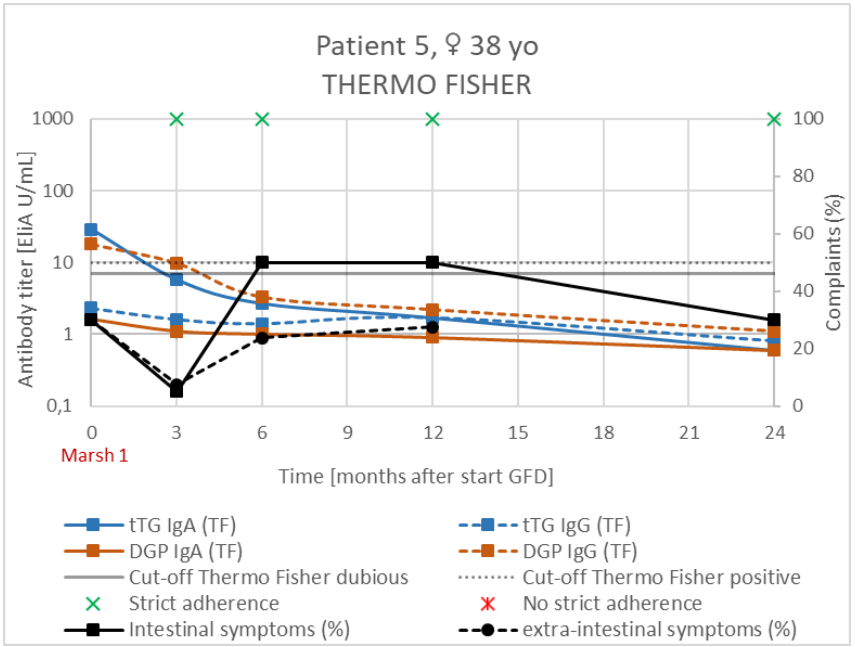
CONCLUSIONS

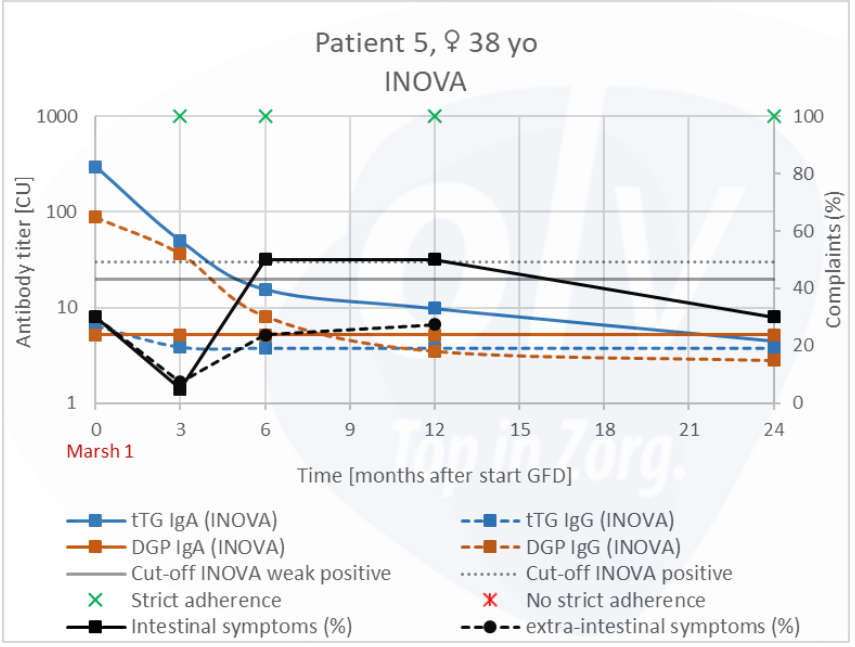
Same kinetic profile of all CD serology tests between **TF and Inova**

Kinetic profile different from **patient's (extra-)intestinal symptoms** profile









Results

GFD adherence :

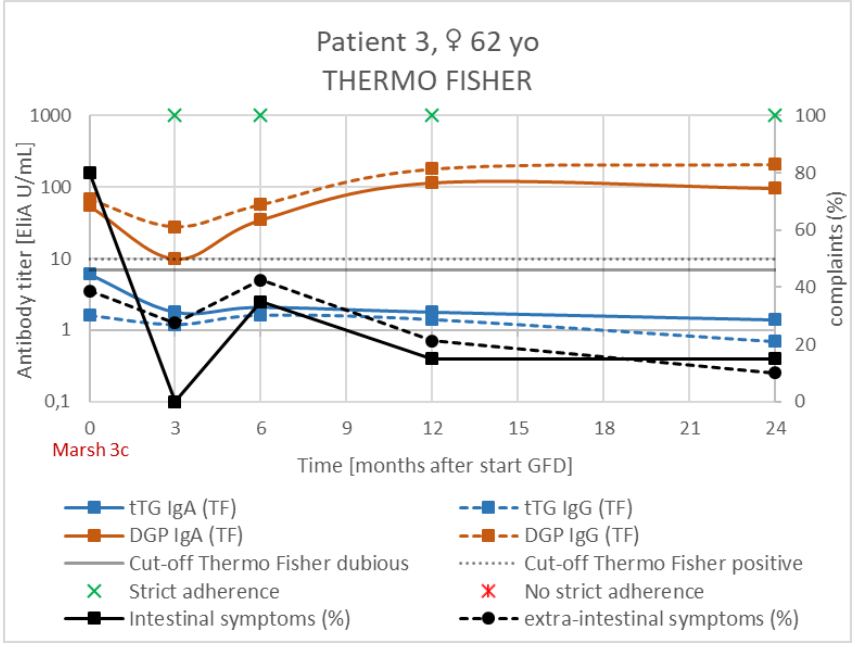
100% compliant (n=7)

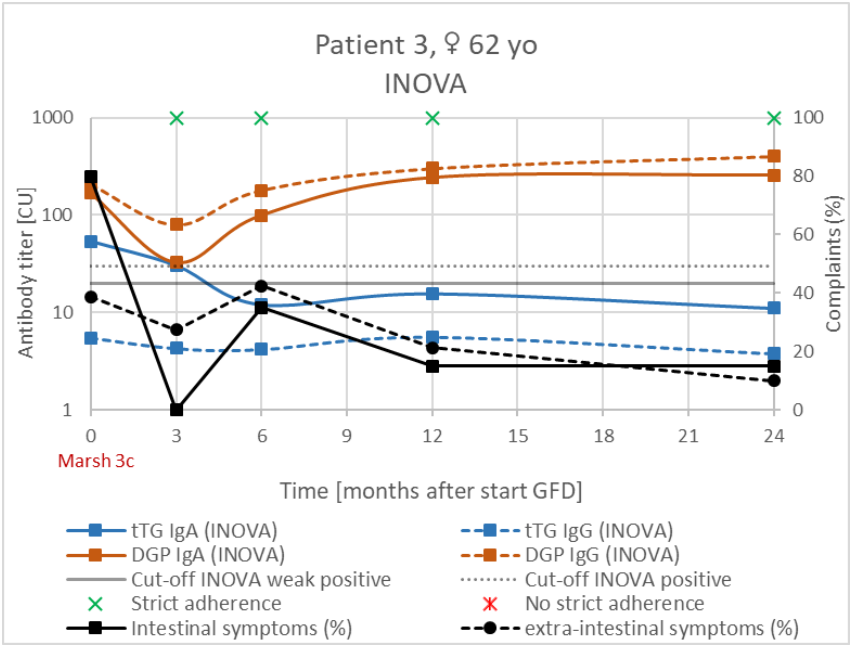
CONCLUSIONS

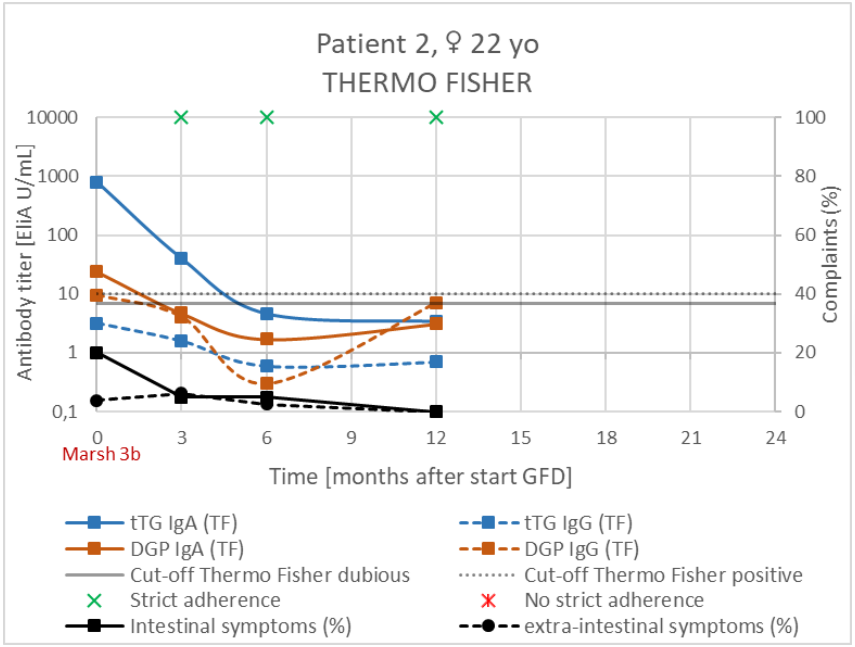
Same kinetic profile of all CD serology tests between **TF and Inova**

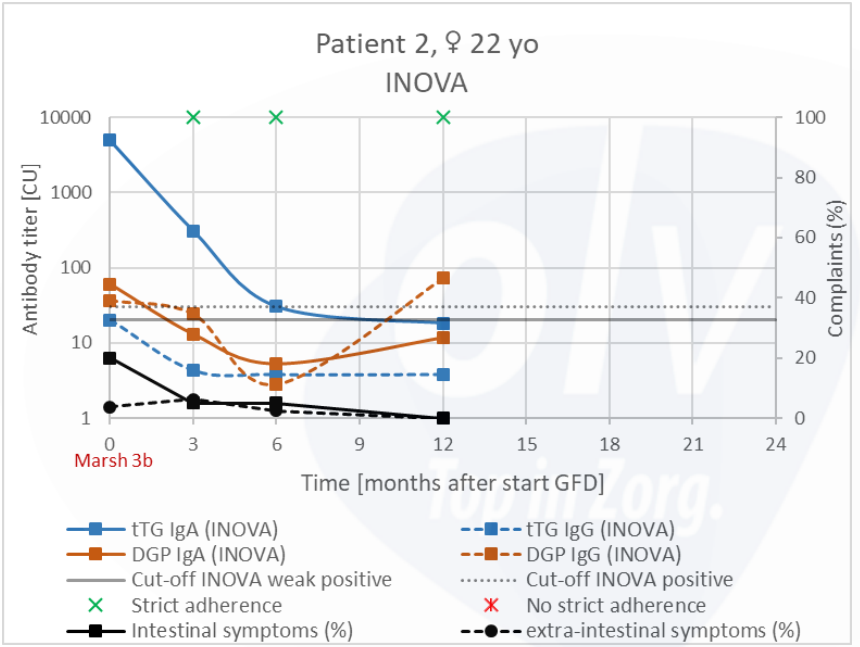
Kinetic profile different from **patient's (extra-)intestinal symptoms** profile

Kinetic profile of **tTG and DGP** significantly **different** for **patient 2 and 3**









Results

GFD adherence :

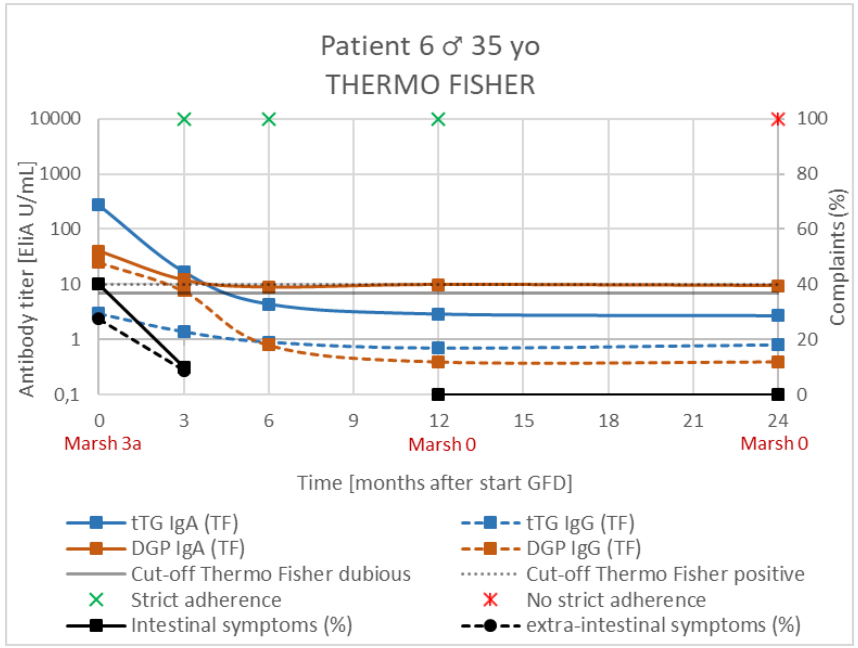
Partially compliant (n=2)

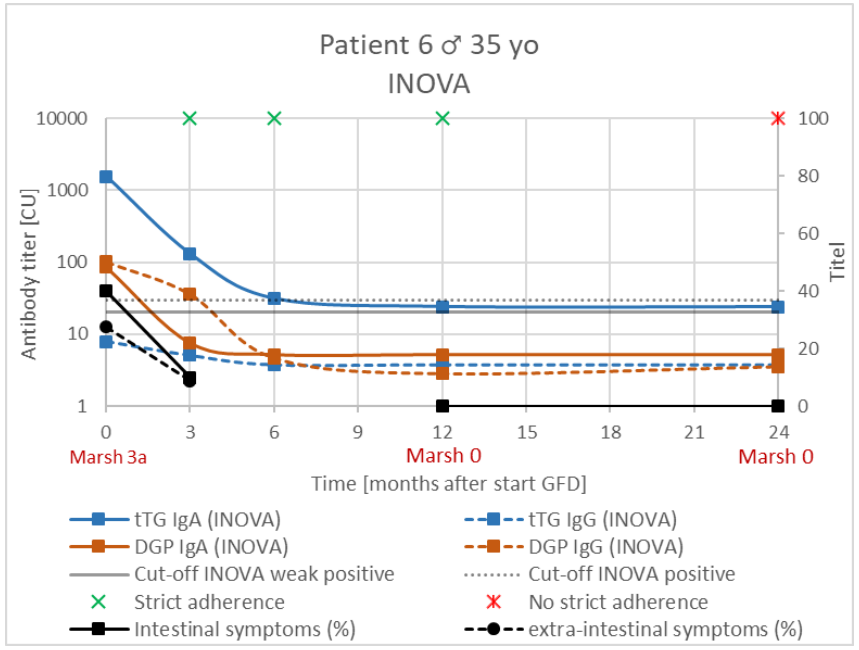
CONCLUSIONS

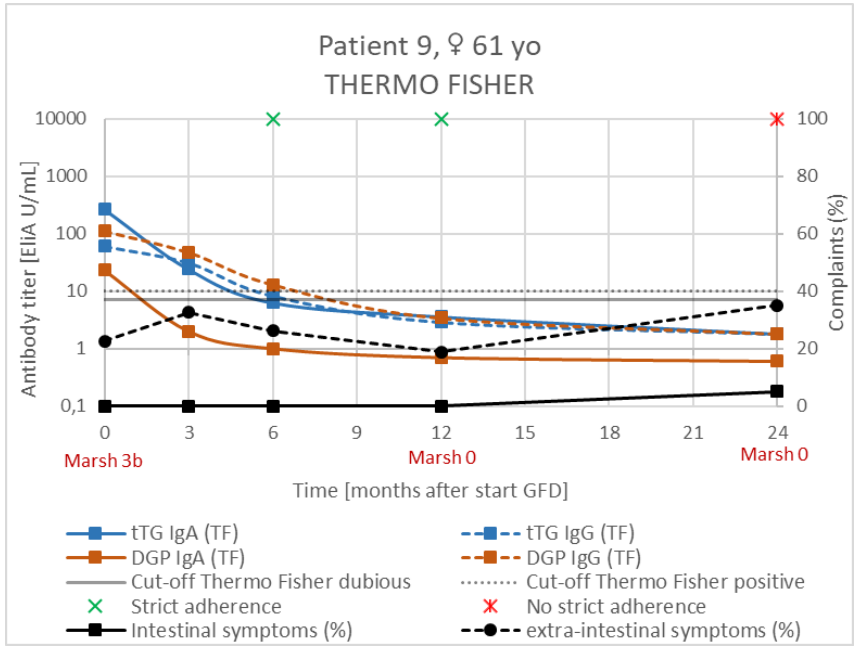
Same kinetic profile of all CD serology tests between **TF and Inova**

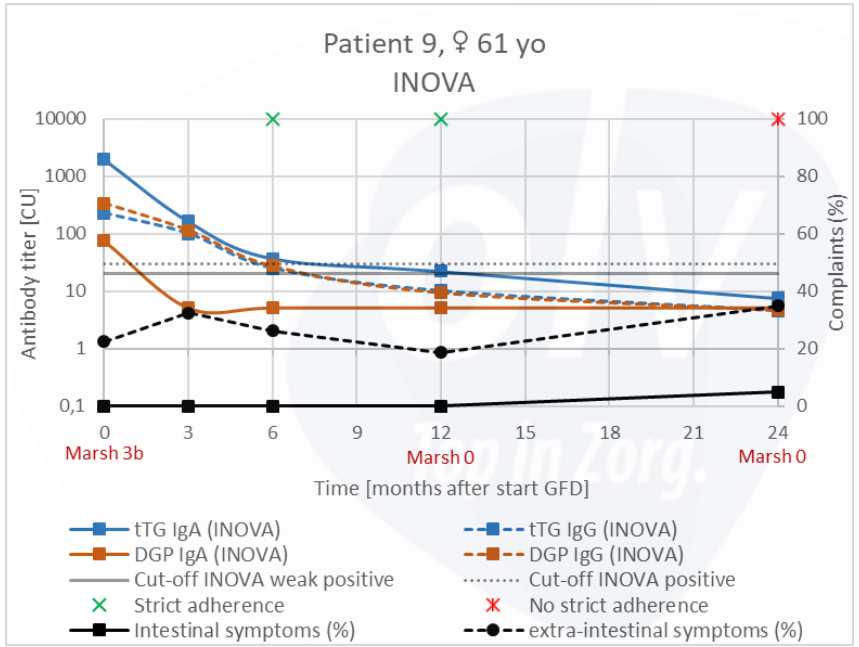
Kinetic profile different from **patient's (extra-)intestinal symptoms** profile

Kinetic profile of **tTG and DGP** significantly **different** for **patient 2 and 3**









Results

GFD adherence :

Non-compliant (n=2)

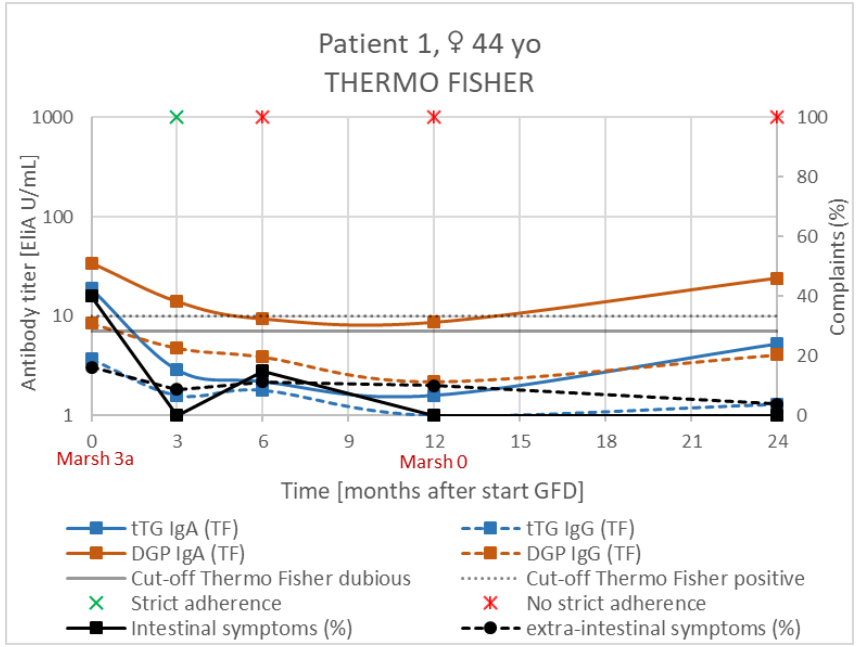
CONCLUSIONS

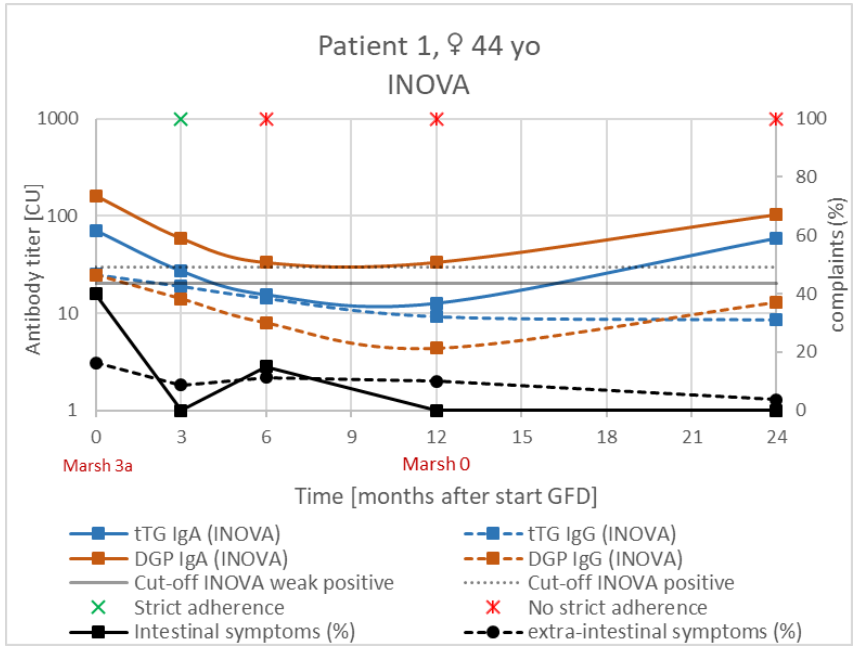
Same kinetic profile of all CD serology tests between **TF and Inova**

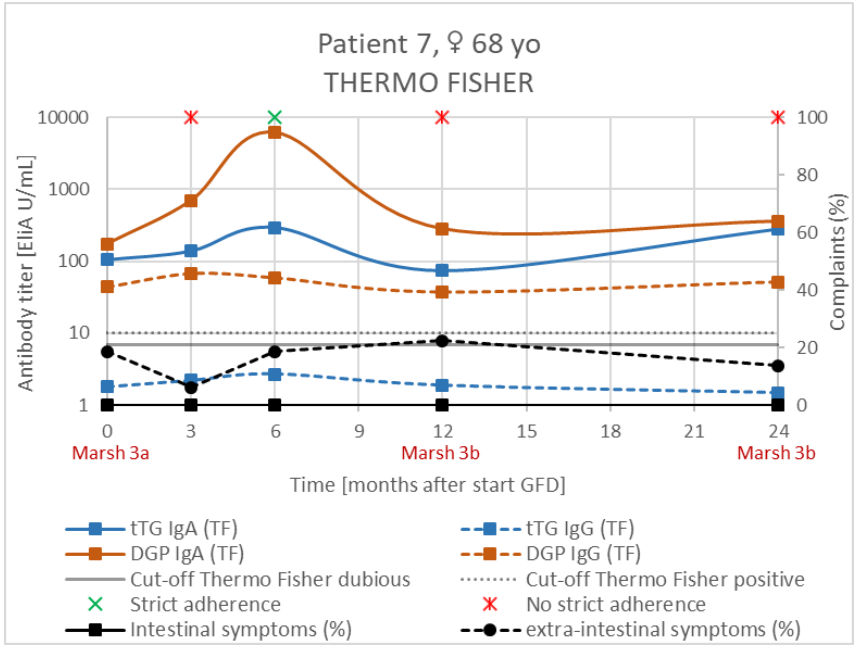
Kinetic profile different from **patient's (extra-)intestinal symptoms** profile

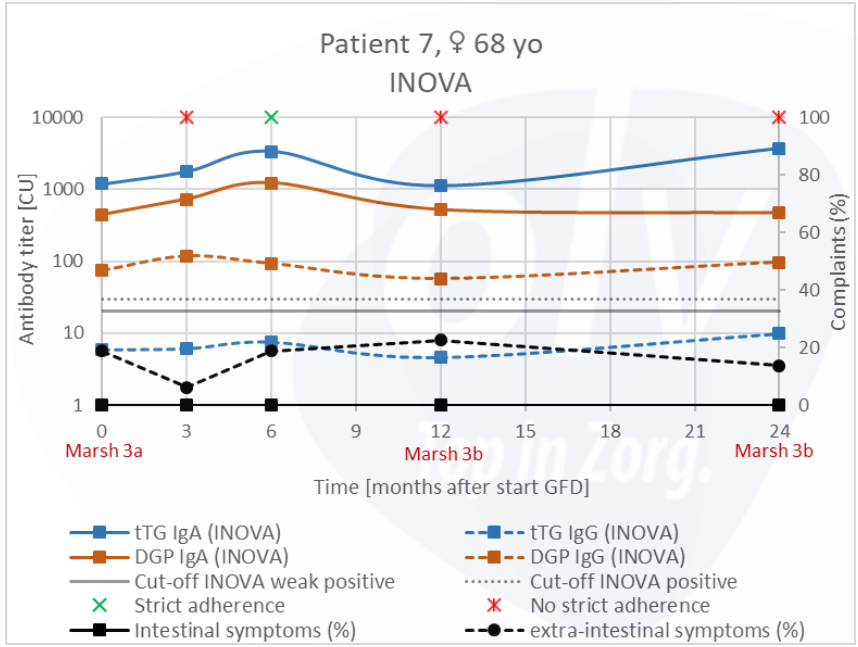
Kinetic profile of **tTG and DGP** significantly **different** for **patient 2 and 3**

Kinetic profile different in **compliant** (100% - and partially) patient **vs. non-compliant** patients



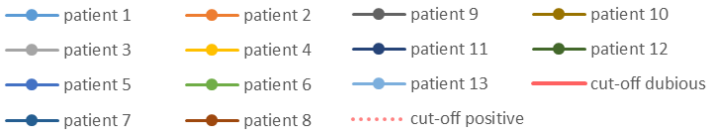






Results

Total kinetics (n=13)



CONCLUSIONS

Same kinetic profile of all CD serology tests between **TF and Inova**

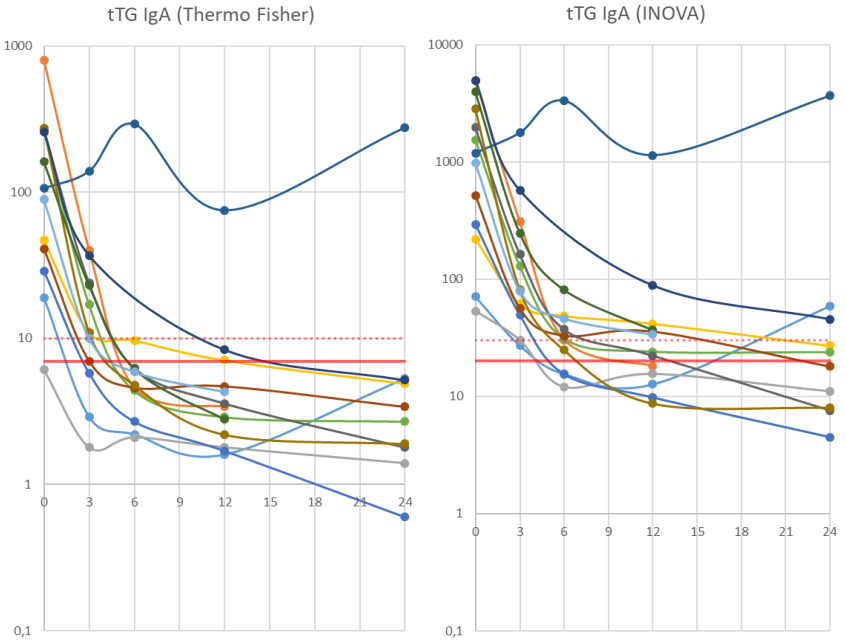
Kinetic profile different from **patient's (extra-)intestinal symptoms** profile

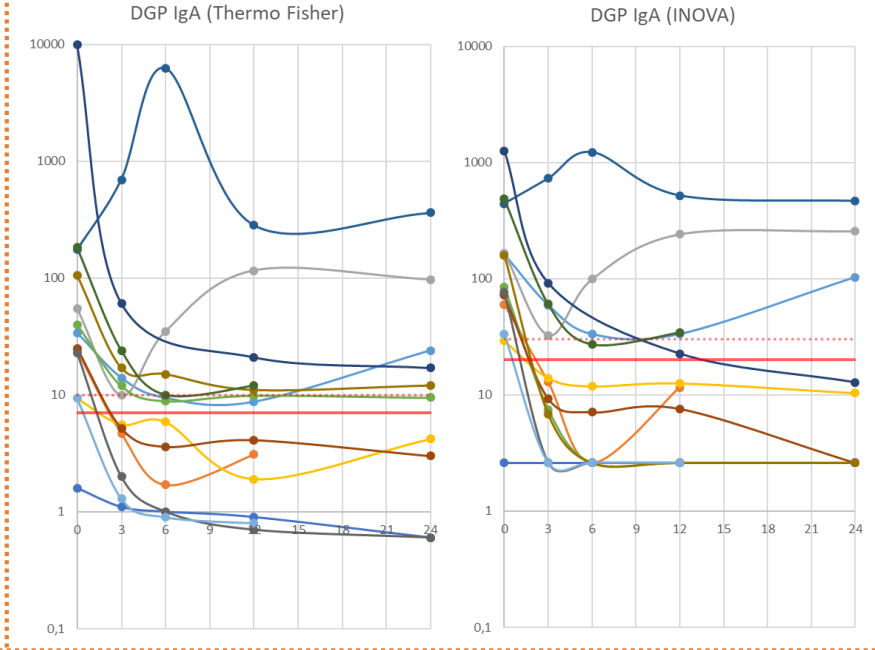
Kinetic profile of **tTG and DGP** significantly **different** for **patient 2 and 3**

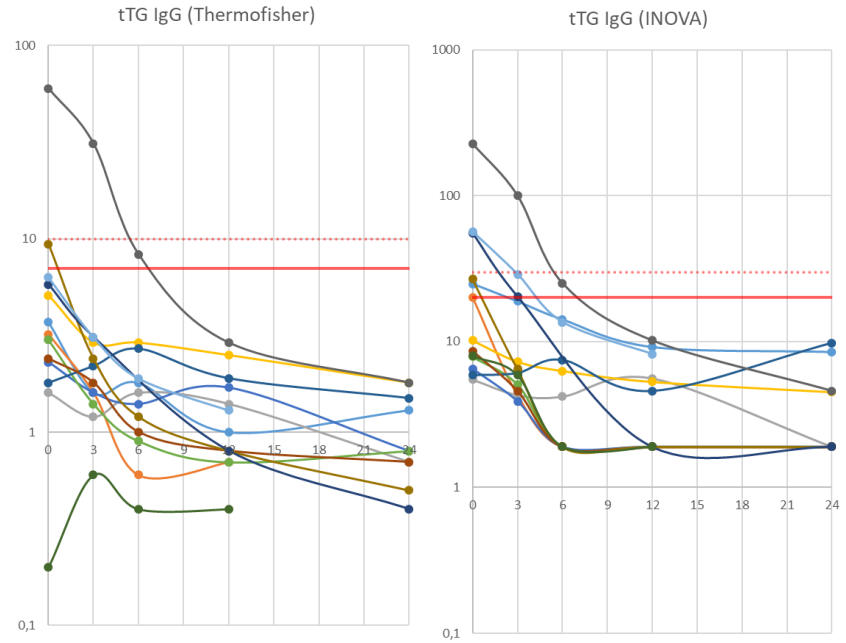
Kinetic profile different in **compliant** (100% - and partially) patient **vs. non-compliant** patients

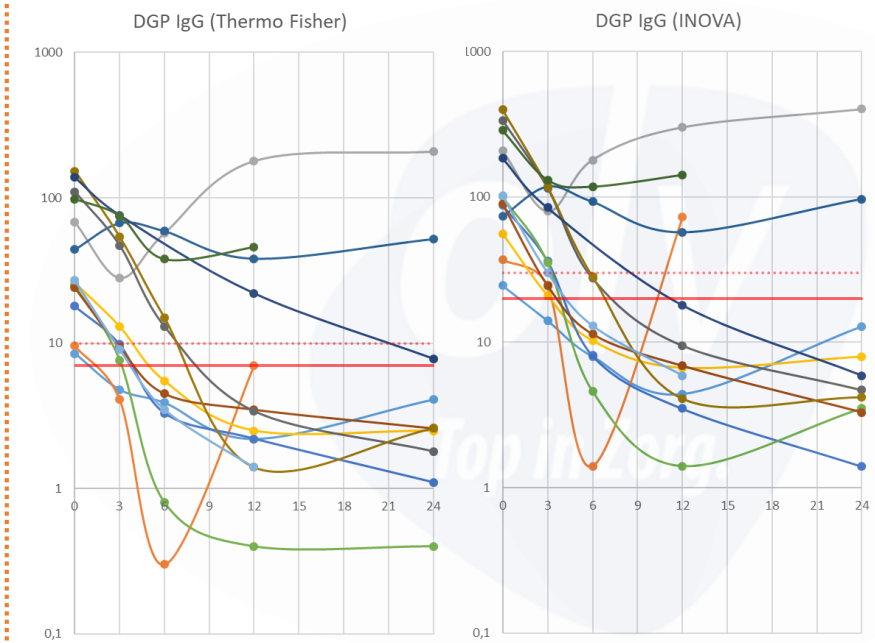
Kinetic profile **tTG IgG** less pronounced

Differences in cut-offs defined by manufacturer, result in **different clinical interpretation**









Clinical interpretation of antibody titers

All patients, n = 13

	t0			t3			t6			t12			t24		
	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN
tTG IgA TF	13	1 (7.7%)	1	13	3	7	12	10	11	13	10	12	10	9	9
tTG IgG TF	13	11 (84.6%)	*p<0.001*	13	12		12	11		13	13		10	10	
DGP IgA TF	13	1 (7.7%)		13	6		12	6		13	6		10	4	
DGP IgG TF	13	0 (0.0%)		13	2		12	7		13	8		10	7	
tTG IgA IN	13	0 (0.0%)	2	13	0	7	12	3	11	13	5	12	10	5	9
tTG IgG IN	13	7 (53.8%)	*p=0.002*	13	10		12	11		13	13		10	10	
DGP IgA IN	13	1 (7.7%)		13	8		12	8		13	8		10	7	
DGP IgG IN	13	0 (0.0%)		13	1		12	7		13	9		10	8	

CONCLUSIONS

Significantly **lower diagnostic sensitivity** of **tTG IgG** vs. tTG IgA

Clinical interpretation of antibody titers

All patients, n = 13

	t0			t3			t6			t12			t24		
	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN
tTG IgA TF	13	1 (7.7%)	1	13	3 (23.0%)	7	12	10 (83.3%)	11	13	10 (76.9%)	12	10	9 (90.0%)	9
tTG IgG TF				13	12		12	11		13	13		10	10	
DGP IgA TF	13	1 (7.7%)	*p=1.000*	13	6 (46.2%)	*p=0.225*	12	6 (50.0%)	*p=0.327*	13	6 (46.2%)	*p=0.114*	10	4 (40.0%)	***p=0.022***
DGP IgG TF				13	2		12	7		13	8		10	7	
tTG IgA IN	13	0 (0.0%)	2	13	0 (0.0%)	7	12	3 (25.0%)	11	13	5 (38.5%)	12	10	5 (50.0%)	9
tTG IgG IN				13	10		12	11		13	13		10	10	
DGP IgA IN	13	1 (7.7%)	*p=0.317*	13	8 (61.5%)	***p<0.001***	12	8 (66.7%)	***p=0.045***	13	8 (61.5%)	*p=0.249*	10	7 (70.0%)	*p=0.374*
DGP IgG IN				13	1		12	7		13	9		10	8	

CONCLUSIONS

Significantly **lower diagnostic sensitivity** of **tTG IgG** vs. tTG IgA

DGP IgA tends to **normalize sooner** compared to tTG IgA using **INOVA** assay, **not** with **TF** assay

Clinical interpretation of antibody titers

All patients, n = 13

	t0			t3			t6			t12			t24		
	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN
tTG IgA TF	13	1 (7.7%)	1	13	3 (23.1%)	7	12	10 (83.3%)	11	13	10 (76.9%)	12	10	9 (90.0%)	9
tTG IgG TF	13	11		13	12		12	11		13	13		10	10	
DGP IgA TF	13	1		13	6		12	6		13	6		10	4	
DGP IgG TF	13	0		13	2		12	7		13	8		10	7	
tTG IgA IN	13	0 (0.0%)	*p=0.317*	13	0 (0.0%)	*p=0.071*	12	3 (25.0%)	***p=0.005***	13	5 (38.5%)	*p=0.052*	10	5 (50.0%)	*p=0.057*
tTG IgG In	13	7		13	10		12	11		13	13		10	10	
DGP IgA IN	13	1		13	8		12	8		13	8		10	7	
DGP IgG IN	13	0		13	1		12	7		13	9		10	8	

CONCLUSIONS

Significantly **lower diagnostic sensitivity** of **tTG IgG** vs. tTG IgA

DGP IgA tends to **normalize sooner** compared to tTG IgA using **INOVA** assay, **not** with **TF** assay

Significantly **different interpretation** of kinetic profile **tTG IgA depending** on the **assay** used

PART 1

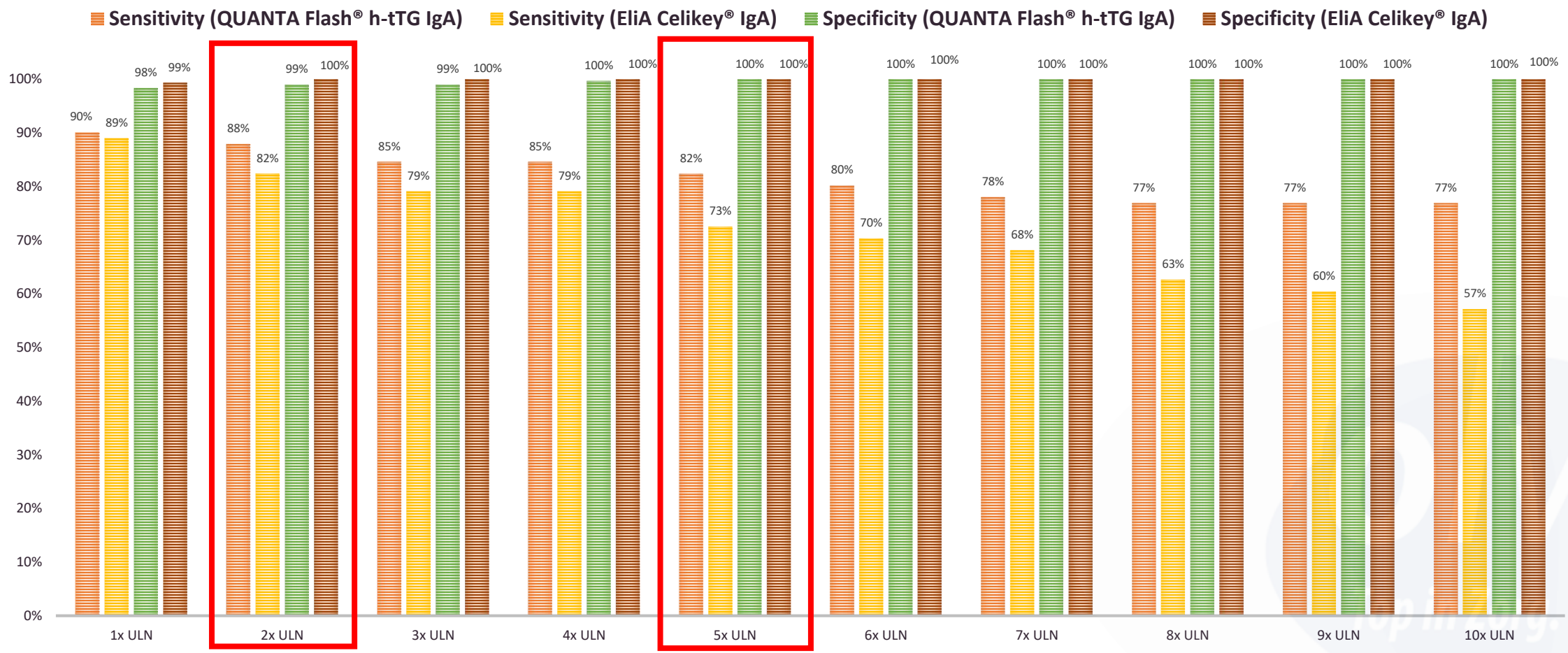
Pre- and post-test probabilities of coeliac disease

Review

Autoimmunity Reviews 19 (2020) 102513

Optimization of serologic diagnosis of celiac disease in the pediatric setting

Laura Bogaert[a,b,1], Mathieu Cauchie[c,1], Lieve Van Hoovels[a,g], Pieter Vermeersch[b], Walter Fierz[d], Gert De Hertogh[e], Ilse Hoffman[f], Xavier Bossuyt[b,g,*]



CD patients, n = 91
Controls, n = 605

Presentation master's thesis L. Bogaert, used with permission

Clinical interpretation of antibody titers

All patients, n = 13

	t0			t3			t6			t12			t24		
	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN
tTG IgA TF	13	1 (7.7%)	**1 (7.7%)**	13	3 (23.1%)	**7 (53.8%)**	12	10 (83.3%)	**11 (91.7%)**	13	10 (76.9%)	**12 (92.3%)**	10	9 (90.0%)	**9 (90.0%)**
tTG IgG TF	13	11		13	12		12	11		13	13		10	10	
DGP IgA TF	13	1		13	6		12	6		13	6		10	4	
DGP IgG TF	13	0		13	2		12	7		13	8		10	7	
tTG IgA IN	13	0 (0.0%)	**2 (15.4%)**	13	0 (0.0%)	**7 (53.8%)**	12	3 (25.0%)	**11 (91.7%)**	13	5 (38.5%)	**12 (92.3%)**	10	5 (50.0%)	**9 (90.0%)**
tTG IgG IN	13	7		13	10		12	11		13	13		10	10	
DGP IgA IN	13	1		13	8		12	8		13	8		10	7	
DGP IgG IN	13	0		13	1		12	7		13	9		10	8	

CONCLUSIONS

Significantly **lower diagnostic sensitivity** of **tTG IgG** vs. tTG IgA

DGP IgA tends to **normalize sooner** compared to tTG IgA using **INOVA** assay, **not** with **TF** assay

Significantly **different interpretation** of kinetic profile **tTG IgA depending** on the **assay** used

Harmonization in cut-off (based on LR CD or Spec%) **significantly improves clinical interpretation** of the **tTG IgA** CD serology **between manufacturers**

Clinical interpretation of antibody titers

All patients, n = 13

	t0			t3			t6			t12			t24		
	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN	number	< ULN (%)	< 2* or 5*ULN
tTG IgA TF	13	1 (7.7%)	1	13	3 (23.1%)	7	12	10 (83.3%)	11	13	10 (76.9%)	12	10	9 (90.0%)	9
tTG IgG TF	13	11		13	12		12	11		13	13		10	10	
DGP IgA TF	13	1 (7.7%)		13	6 (46.2%)		12	6 (50.0%)		13	6 (46.2%)		10	4 (40.0%)	
DGP IgG TF	13	0 (0.0%)		13	2 (15.4%)	*p=0.095*	12	7 (58.3%)	*p=0.690*	13	8 (61.5%)	*p=0.443*	10	7 (70.0%)	*p=0.188*
tTG IgA IN	13	0 (0.0%)	2	13	0 (0.0%)	7	12	3 (25.0%)	11	13	5 (38.5%)	12	10	5 (50.0%)	9
tTG IgG IN	13	7		13	10		12	11		13	13		10	10	
DGP IgA IN	13	1 (7.7%)		13	8 (61.5%)		12	8 (66.7%)		13	8 (61.5%)		10	7 (70.0%)	
DGP IgG IN	13	0 (0.0%)		13	1 (7.7%)	***p=0.005***	12	7 (58.3%)	*p=0.690*	13	9 (69.2%)	*p=0.686*	10	8 (80.0%)	*p=0.615*

CONCLUSIONS

Significantly **lower diagnostic sensitivity** of **tTG IgG** vs. tTG IgA

DGP IgA tends to **normalize sooner** compared to tTG IgA using **INOVA** assay, **not** with **TF** assay

Significantly **different interpretation** of kinetic profile **tTG IgA depending** on the **assay** used

Harmonization in cut-off (based on LR CD or Spec%) **significantly improves clinical interpretation** of the **tTG IgA** CD serology **between manufacturers**

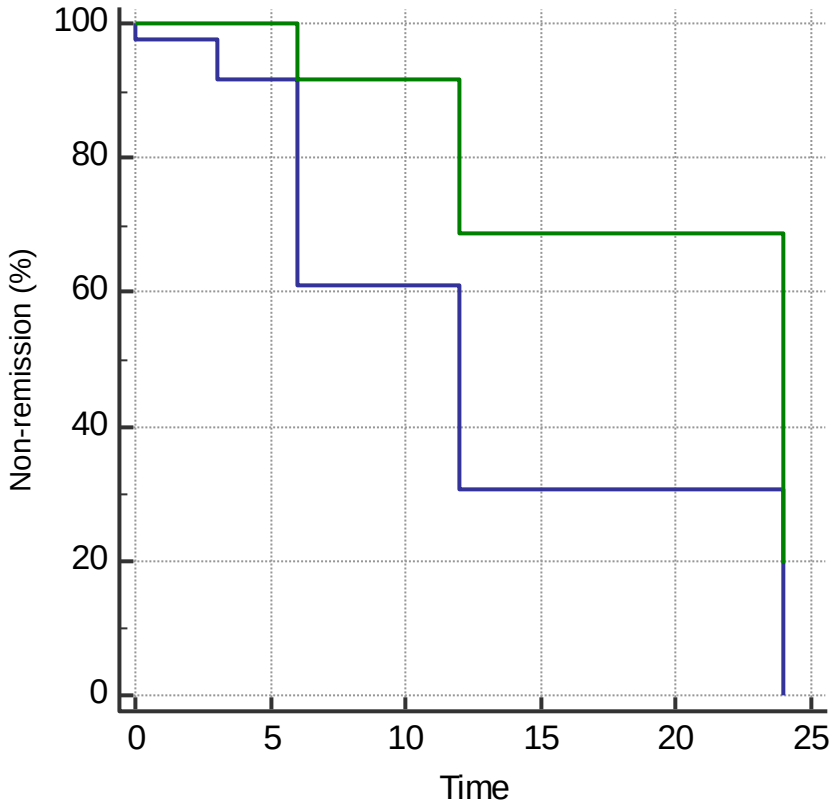
No significant differences in clinical interpretation between **DPG assays**; IgA DGP tends to normalize sooner than IgG DPG (t3)

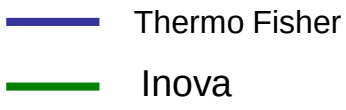
Time to serological remission of tTG IgA

100% compliant + partially compliant patients (n = 9)
Excluding: non-compliant patients (n = 2), data incomplete (n = 2)

Kaplan-Meier curve analysis

Manufacturer's cut-off





Mean time to remission (months)	95% CI mean
Thermo Fisher 13.0	10.0-16.0
INOVA 19.8	16.7-22.8

p=0.001

Kaplan-Meier curve analysis

Harmonized cut-offs (100% Spec)*

Mean time to remission (months)	95% CI mean
Thermo Fisher 11.9	9.1-14.8
INOVA 11.9	9.1-14.8

p=1.000

*Bogaert *et al*. AIR 2020; 19: 102513

Fallacies and Facts

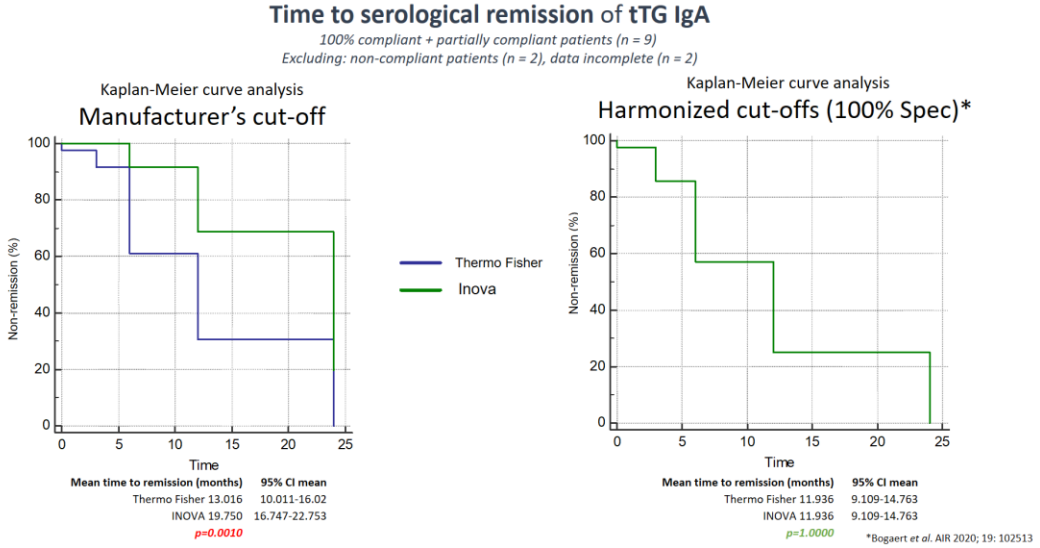
Prospective study results

Discussion

Discussion

1) *How does the **kinetic profile** differ between the **different serological assays** (tTG IgA/IgG vs. DGP IgA/IgG)?*
2) *Is the **clinical interpretation dependent** on the **assay** that is used (Thermo Fisher vs. INOVA)?*
3) *How does serological status, complaints and routine laboratory test differ between strictly, partially and non-compliant CD patients?*

Data-analysis



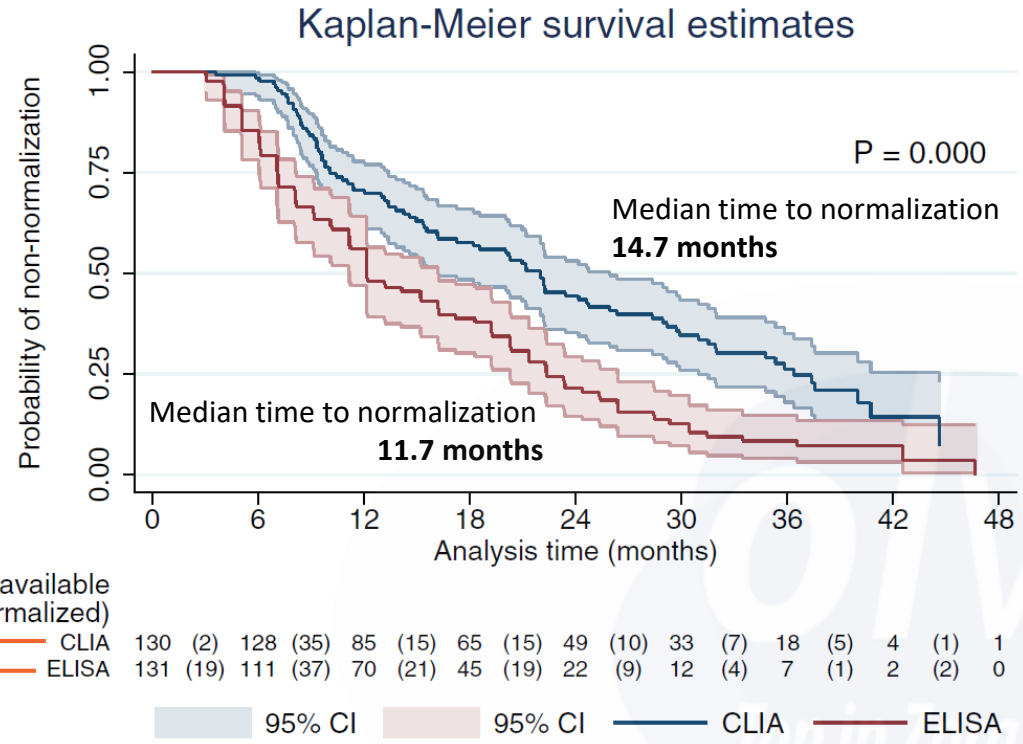


FIGURE 1. Kaplan-Meier analysis demonstrating rate and time of antitissue transglutaminase (atTG) normalization over time after starting gluten-free diet. CI = confidence interval; CLIA = chemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay.

Inova Diagnostics
A Werfen Company

ThermoFisher SCIENTIFIC

SANSOTTA et al. J Pediatr Gastroenterol Nutr. 2020;70(1):37-41

Discussion

1) *How does the **kinetic profile** differ between the **different serological assays** (tTG IgA/IgG vs. DGP IgA/IgG)?*
2) *Is the **clinical interpretation dependent** on the **assay** that is used (Thermo Fisher vs. INOVA)?*
3) *How does **serological status**, **complaints** and **routine laboratory test** differ between **strictly, partially and non-compliant CD patients**?*

surrogate marker?

Table 6. Positive (PPV) and negative predictive values (NPV) for fair to poor gluten-free diet (GFD) adherence

Test	PPV	NPV	PPV GFD ≥ 12 months	NPV GFD ≥ 12 months
IgA anti-tTG ≥ 20 (n = 49)	30.6%	83.2%	53.8%	84.5%
IgA DGP ≥ 20 (n = 46)	30.6%	81.7%	50.0%	86.7%
IgG DGP ≥ 20 (n = 29)	31.0%	80.5%	42.8%	82.5%
IgA-IgG DGP ≥ 20 (n = 35)	31.4%	82.1%	55.6%	83.9%
Self-report ≠ highly adherent (n = 28)	42.9%	86.5%	42.1%	84.8%
Self-report ≠ highly adherent + IgA anti-tTG ≥ 20 (n = 15)	60.0%	87.6%	80.0%	86.7%

DGP, deamidated gliadin peptides; tTG, transglutaminase. (ELISA, INOVA)

?

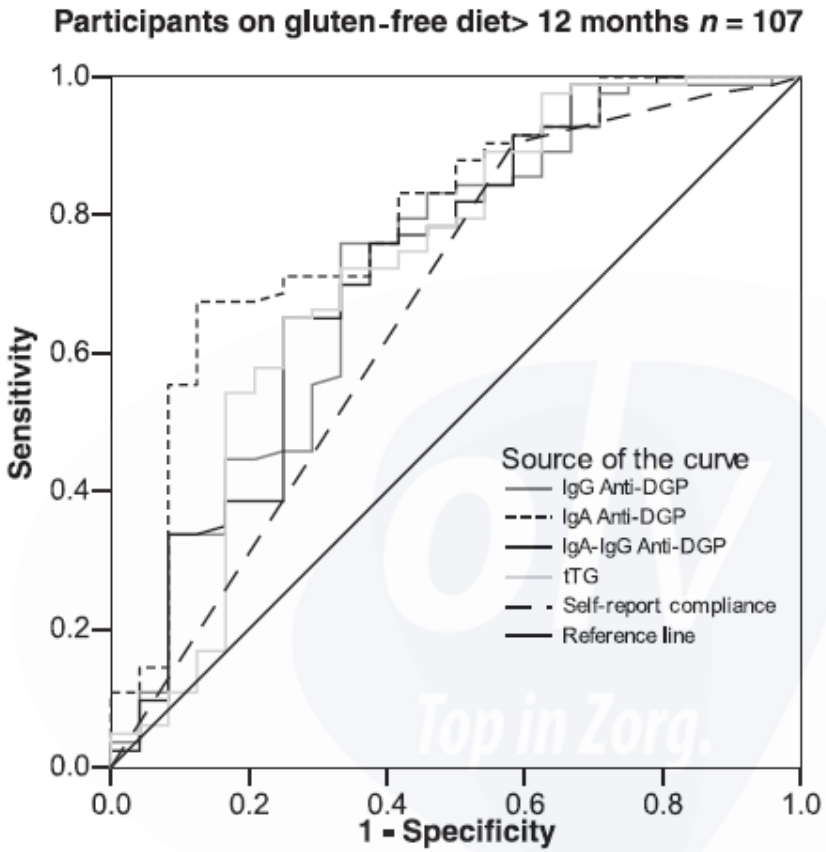
ORIGINAL ARTICLE

Annals of Gastroenterology (2020) **33**, 1-7

Testing for fecal gluten immunogenic peptides: a useful tool to evaluate compliance with gluten-free diet by celiacs

Brunetta Porcelli[a], Fabio Ferretti[b], Ivano Biviano[c], Alessia Santini[c], Francesca Cinci[a], Marina Vascotto[d], Elisabetta Grande[d], Francesco Quagliarella[d], Lucia Terzuoli[a], Nicola Bizzaro[e], Mario Marini[c], Silvia Rentini[c]

Università degli Studi di Siena; Azienda Ospedaliera Universitaria Senese, Siena, Azienda Sanitaria Universitaria Integrata di Udine, Tolmezzo, Italy



LEFFLER et al. Aliment Pharmacol Ther. 2007;26(9):1227-35

Discussion

1) *How does the **kinetic profile** differ between the **different serological assays** (tTG IgA/IgG vs. DGP IgA/IgG)?*
2) *Is the **clinical interpretation dependent** on the **assay** that is used (Thermo Fisher vs. INOVA)?*
3) *How does **serological status**, **complaints** and **routine laboratory test** differ between **strictly, partially and non-compliant CD patients**?* → **surrogate marker?** → detecting **persistent villous atrophy** in patients on a GFD?

Table 5. Sub-group Analysis of Factors Associated With Assay Performance

tTG IgA				EMA IgA			
Subgroup	Sensitivity (95% CI)	Specificity (95% CI)	AUC	Subgroup	Sensitivity (95% CI)	Specificity (95% CI)	AUC
All studies (n=13)	0.42 (0.32–0.53)	0.83 (0.79–0.87)	0.764	All studies (n=20)[a]	0.45 (0.34–0.57)	0.91 (0.87–0.94)	0.871
Age				Age			
Pediatric (n=2)	0.70 (0.38–0.90)	0.87 (0.80–0.91)	0.879	Pediatric (n=5)	0.74 (0.35–0.94)	0.78 (0.66–0.87)	0.806
Adult (n=9)	0.38 (0.27–0.51)	0.80 (0.75–0.85)	0.720	Adult (n=16)	0.39 (0.50–0.71)	0.93 (0.90–0.95)	0.906

Supplementary Table 1. Sensitivity and Specificity of DGP IgG and DGP IgA Antibody Tests for Persistent Villous Atrophy in Patients With Celiac Disease Following a Gluten-Free Diet

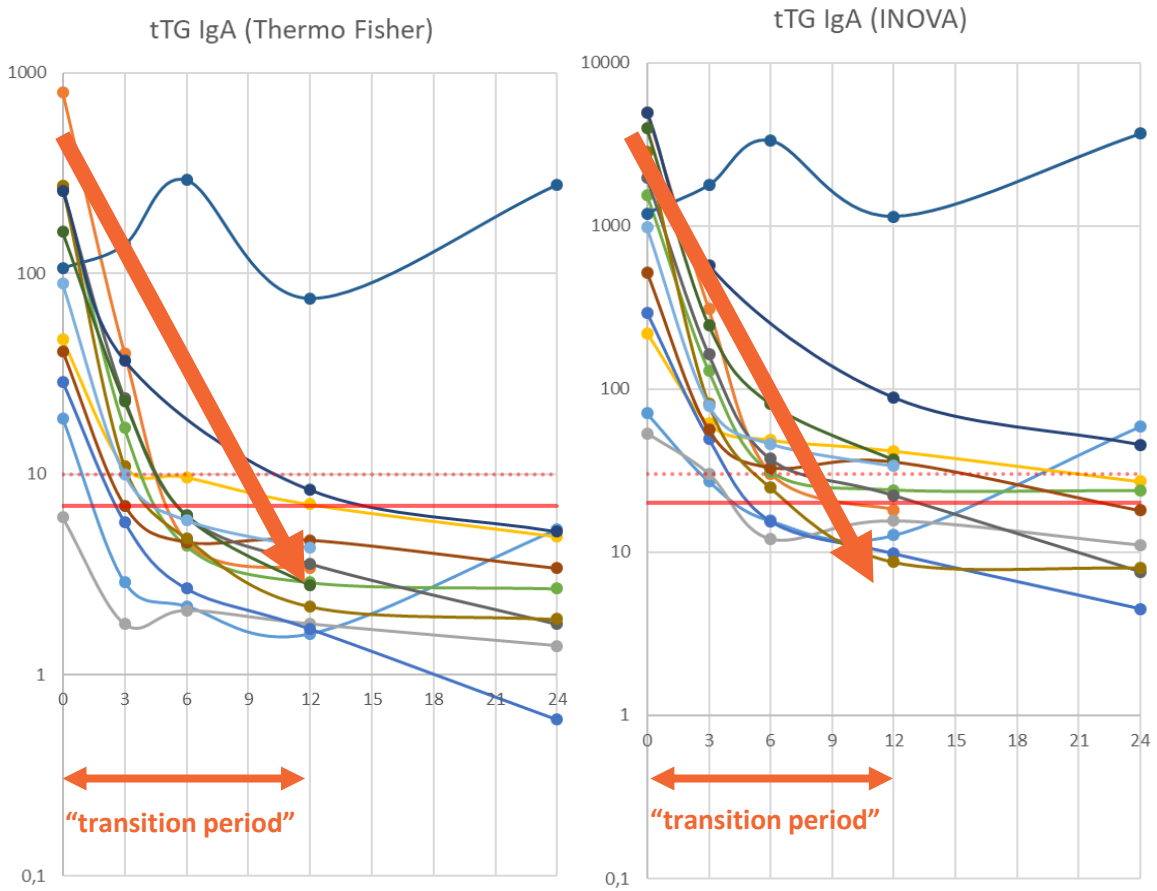
Study	No. of Subjects	Persistent Villous Atrophy n (%)	Sensitivity	Specificity
DGP IgG				
Bannister et al, 2014[24]	150[a]	8 (5)	0.29	0.96
Vécsei et al, 2014[41]	53	6 (11)	0.83	0.79
Volta et al, 2008[28]	53	15 (28)	0.60	0.90
DGP IgA				
Vécsei et al, 2014[41]	53	6 (11)	0.67	0.66
Volta et al, 2008[28]	53	15 (28)	0.67	0.79

[a]Sensitivity and specificity calculations exclude 8 patients with indeterminate results (Marsh 0: 5, Marsh 1: 2, Marsh 3: 1).

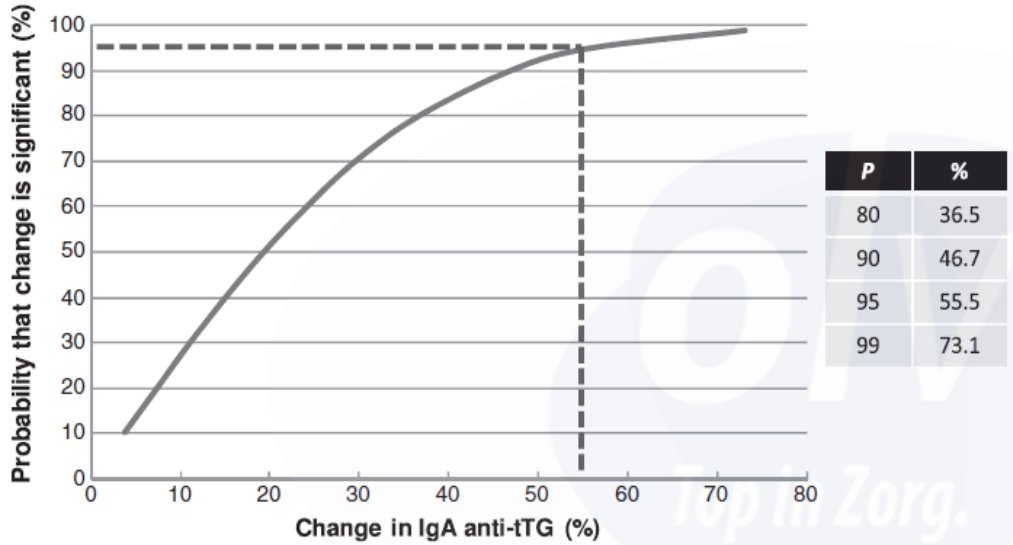
SILVESTER et al. Gastroenterology 2017;153(3):689-701

Discussion

1) *How does the **kinetic profile** differ between the **different serological assays** (tTG IgA/IgG vs. DGP IgA/IgG)?*
2) *Is the **clinical interpretation dependent** on the **assay** that is used (Thermo Fisher vs. INOVA)?*
3) *How does **serological status**, **complaints** and **routine laboratory test** differ between **strictly, partially and non-compliant CD patients**?*



A proposed reference change value for an IgA anti-tissue transglutaminase immunoassay to improve interpretation of serial results in celiac patients



P	%
80	36.5
90	46.7
95	55.5
99	73.1

Fig. 2. Curve generated from the RCV equation relating the percentage of change between two consecutive results of IgA anti-tTG to the probability that this change is significant. The dashed line marks the percentage variation between two IgA anti-tTG determinations needed to reach a 95% statistical significance level. The table on the right indicates the percentage of change (%) needed for statistical significance at different probability thresholds (*P*).

LASERNA-MENDIETA et al. Clinical Chimica Acta 2013;421:12-16

OVERALL CONCLUSIONS

1) *How does the **kinetic profile** differ between the **different serological assays** (tTG IgA/IgG vs. DGP IgA/IgG)?*

tTG IgG lower CD **diagnostic sensitivity** and of **less pronounced kinetic profiling** in GFD FU

2) *Is the **clinical interpretation dependent** on the **assay** that is used (Thermo Fisher vs. INOVA)?*

Clinical interpretation differs signficantly by using manufactur's cut-off, but can be **harmonized** by using CD **LR or specificity based cut-offs**

3) *How does **serological status**, **complaints** and **routine laboratory test** differ between **strictly, partially and non-compliant CD patients**?*

Multidisciplinary approach!

UZ LEUVEN | LABORATORIUMGENEESKUNDE

olv Top in Zorg.

Apr. Lieve VAN HOOVELS

Prof. Xavier BOSSUYT

Stefanie VAN DEN BREMT – Laura HOFMAN