‘Potential’ Coeliac Disease

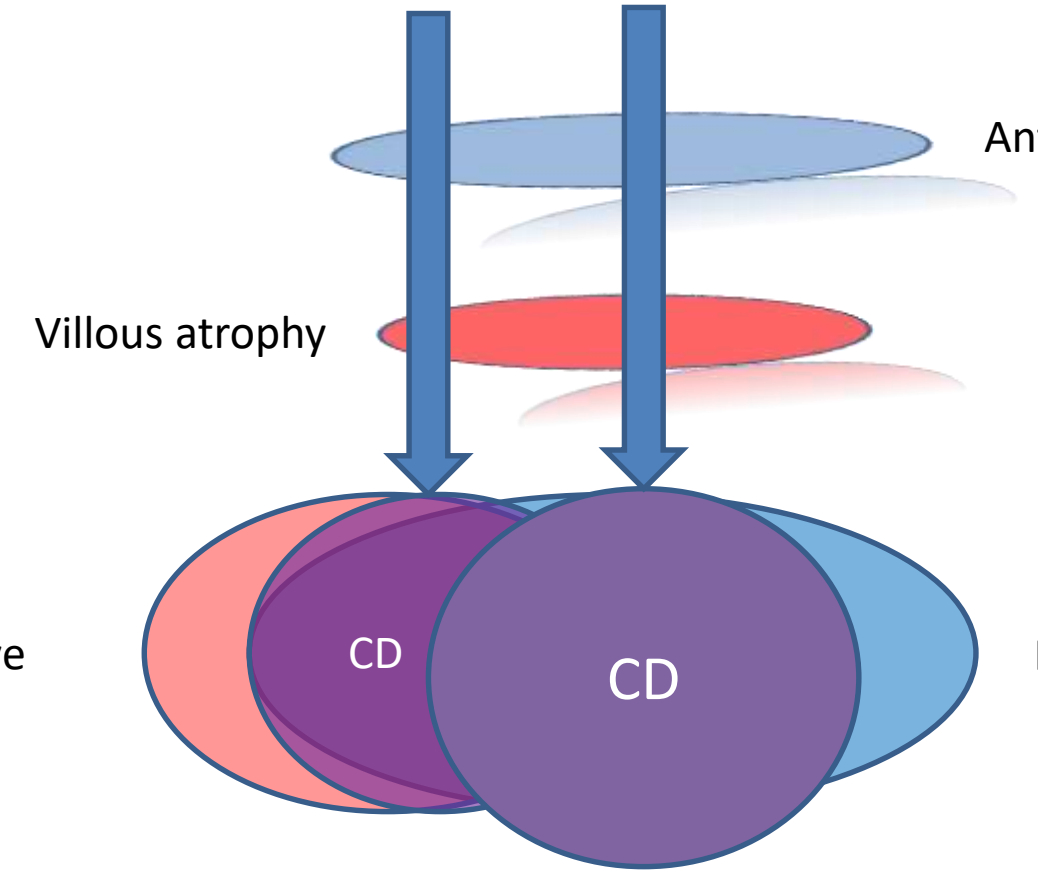
Doctor, have I got it or not?

coeliac uk
live well gluten free

‘Potential Coeliac Disease’

‘individuals with normal small intestinal mucosa who are at increased risk of developing CD as indicated by positive CD serology’

Diagnostic tests in Coeliac Disease



Seronegative

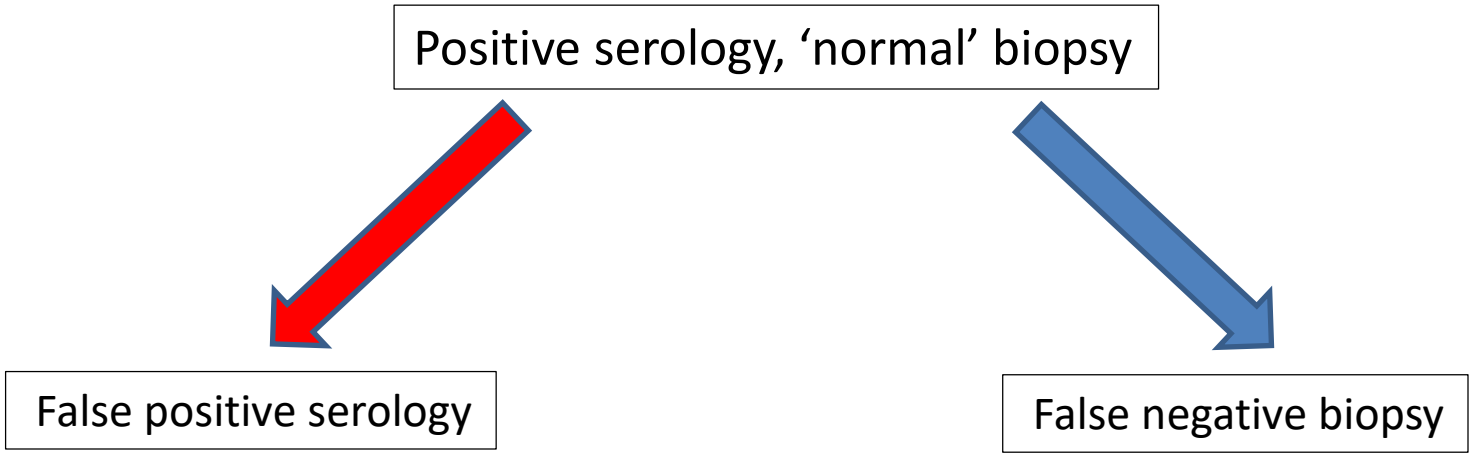
4%

Potential

16%

n = 138,
2019

Not to scale!


Positive serology, ‘normal’ biopsy
False positive serology
False negative biopsy

UK NEQAS UNITED KINGDOM NATIONAL EXTERNAL QUALITY ASSESSMENT SERVICE FOR IMMUNOLOGY, IMMUNOCHEMISTRY AND ALLERGY

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UK NEQAS for COELIAC DISEASE

IgA Tissue Transglutaminase EIA	Returns	Positive	Negative	Mean	Range
Total	**473**	**3**	**470**	**2**	**0 - 12**
A. Menarini - Zenit EIA	5	0	5	3	2 - 6
A. Menarini - Zenit RA	14	0	14	2	2 - 3
AESKU	9	0	9	1	0 - 3
BI-Diagnostika	1	0	1	1	1 - 1
Bio-Rad Bioplex 2200	11	0	11	1	0 - 1
Bio-Rad/Kallestad/Sanofi	1	0	1	1	1 - 1
Biosystems	1	0	1	0	0 - 0
Diamedix	2	0	2	2	1 - 2
Diasorin	5	0	5	0	0 - 0
Diasorin LIAISON	6	0	6	0	0 - 1
Diesse	2	0	2		-
Euroimmun	16	0	16	3	0 - 8
Eurospital	15	0	15	4	2 - 6
GA Generic Assays	1	0	1	4	4 - 4
Genesis	2	0	2	4	4 - 4
Immco	3	0	3	7	5 - 9
In House	2	0	2	45	2 - 88
Inova	30	1	29	4	0 - 12
Inova QUANTA Flash	21	0	21	2	1 - 2
Medipan	1	0	1	3	3 - 3
ORGenTec	32	0	32	1	1 - 2
ORGenTec Alegria	18	0	18	1	1 - 2
Orgentec Screen	6	0	6	4	0 - 5
Other ...	7	0	7	1	0 - 3
Phadia 100 EliA	14	0	14	1	1 - 1
Phadia 250 EliA	237	2	235	1	1 - 1
Phadia Varelisa	10	0	10	0	0 - 1
THERADIAG (BMD) Luminex technology	1	0	1	1	1 - 1

		1	2	3
IgA TTG	Sens	96%	91%	97%
	Spec	86%	91%	87%
IgA EMA	Sens	97%	85%	98%
	Spec	76%	98%	85%
IgA DGP	Sens	82%	83%	78%
	Spec	80%	80%	97%
IgG DGP	Sens	89%	83%	85%
	Spec	81%	97%	92%

1.Mubarak et al, 2011; Panetta et al 2011

2. Hopper et al, 2008;Volta et al 2010; Swallow et al 2012

3. Burgin-Wolff et al 2013

1. Mubarak et al, 2011 2. Volta et al 2010

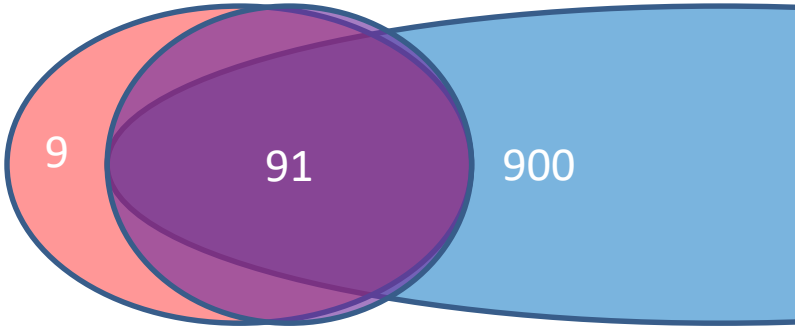
3. Burgin-Wolff et al 2013

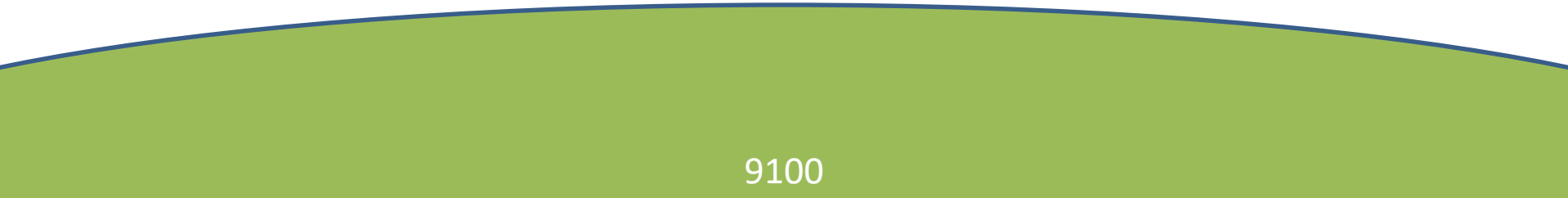
Coeliac Not Coeliac

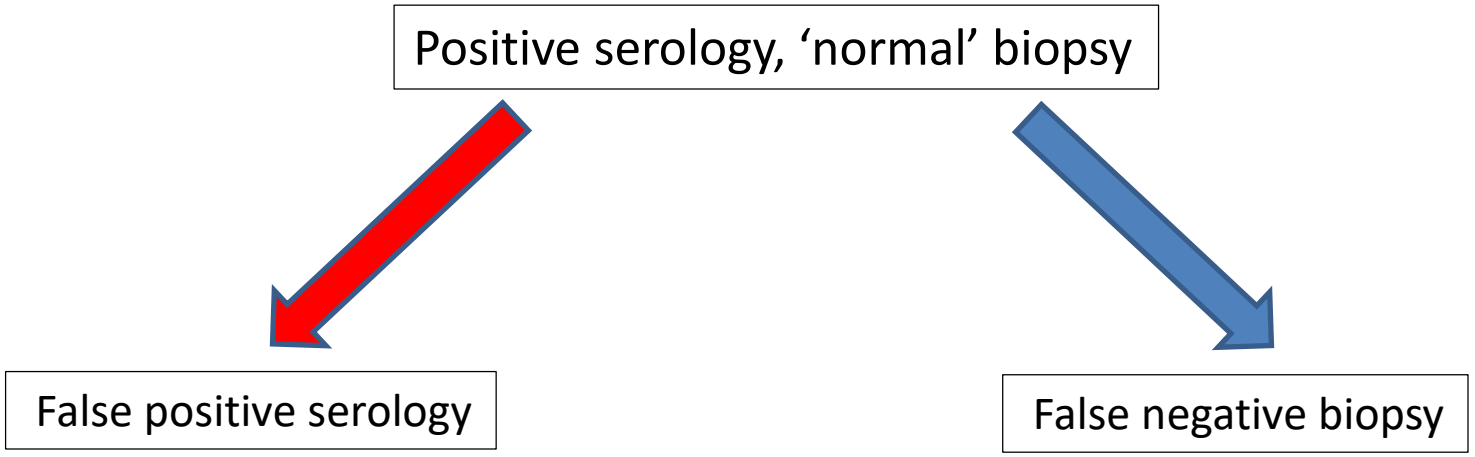
	Biopsy +ve	Biopsy -ve
Serology +ve	91	9
Serology -ve	9	91

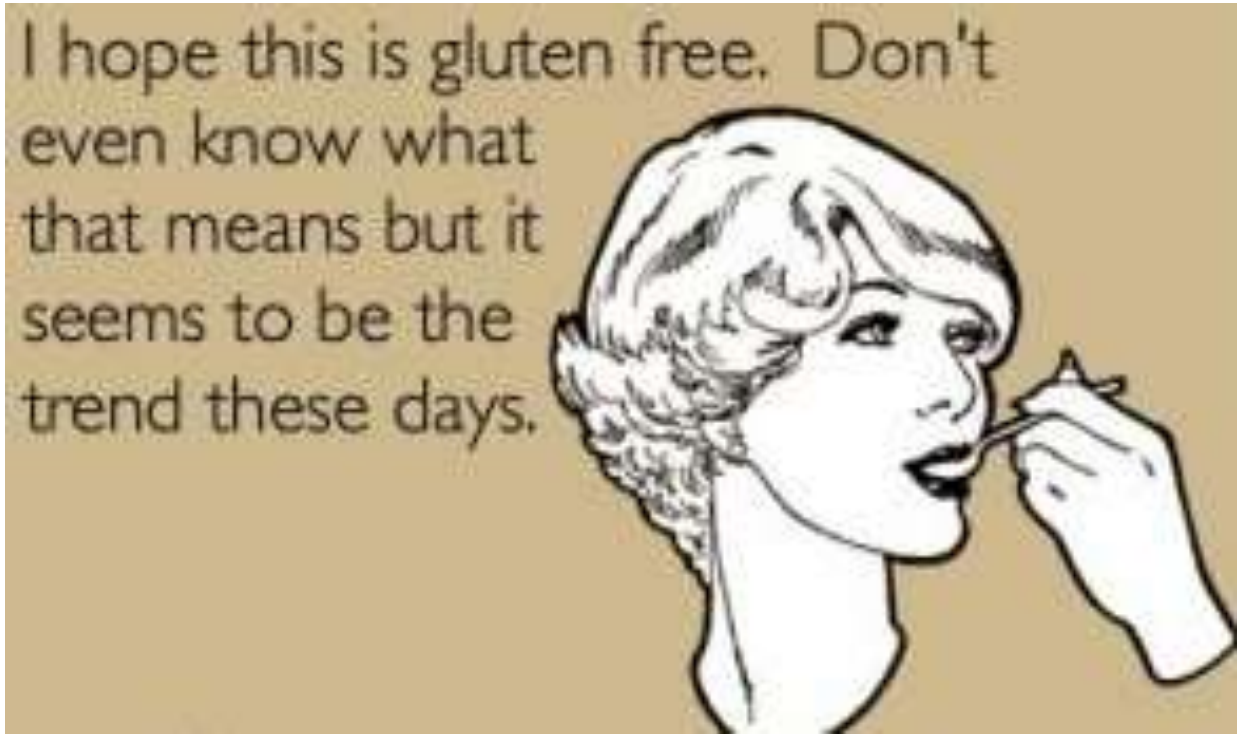
100x

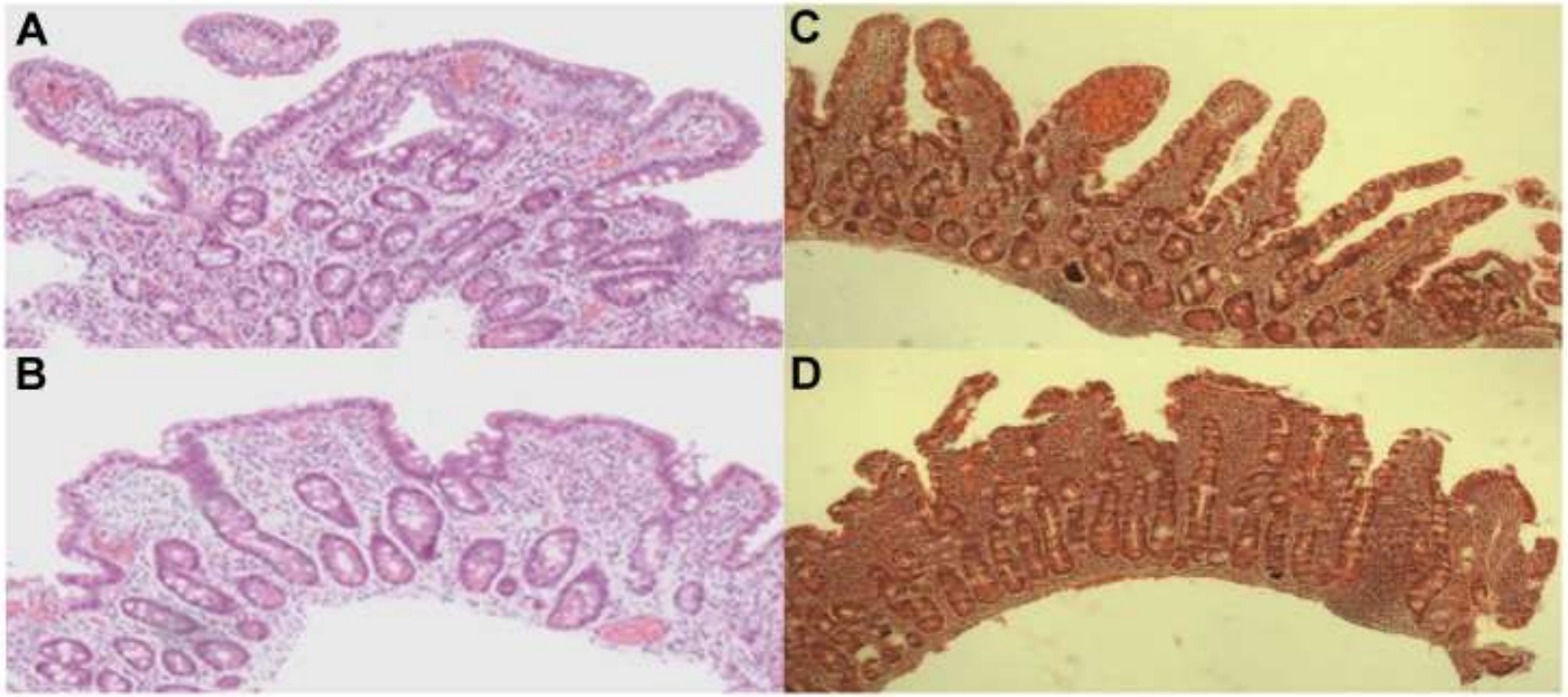
	Biopsy +ve	Biopsy -ve
Serology +ve	91	900
Serology -ve	9	9100





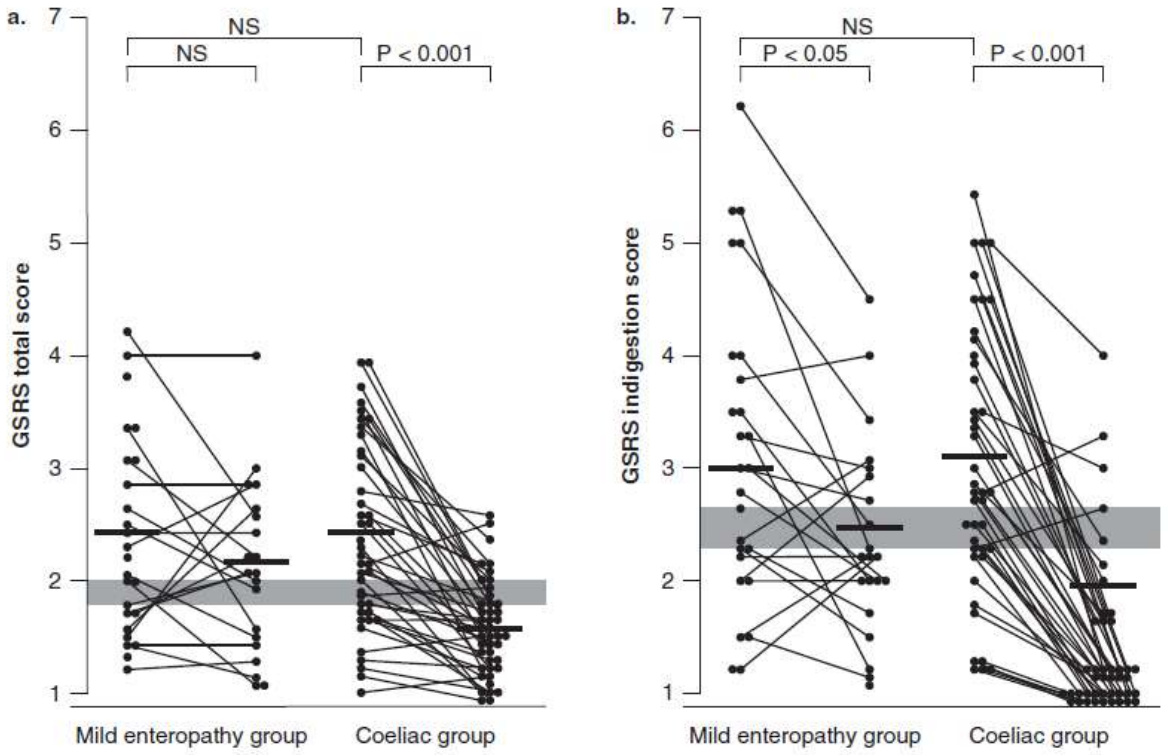

Positive serology, ‘normal’ biopsy
False positive serology
False negative biopsy


I hope this is gluten free. Don't even know what that means but it seems to be the trend these days.

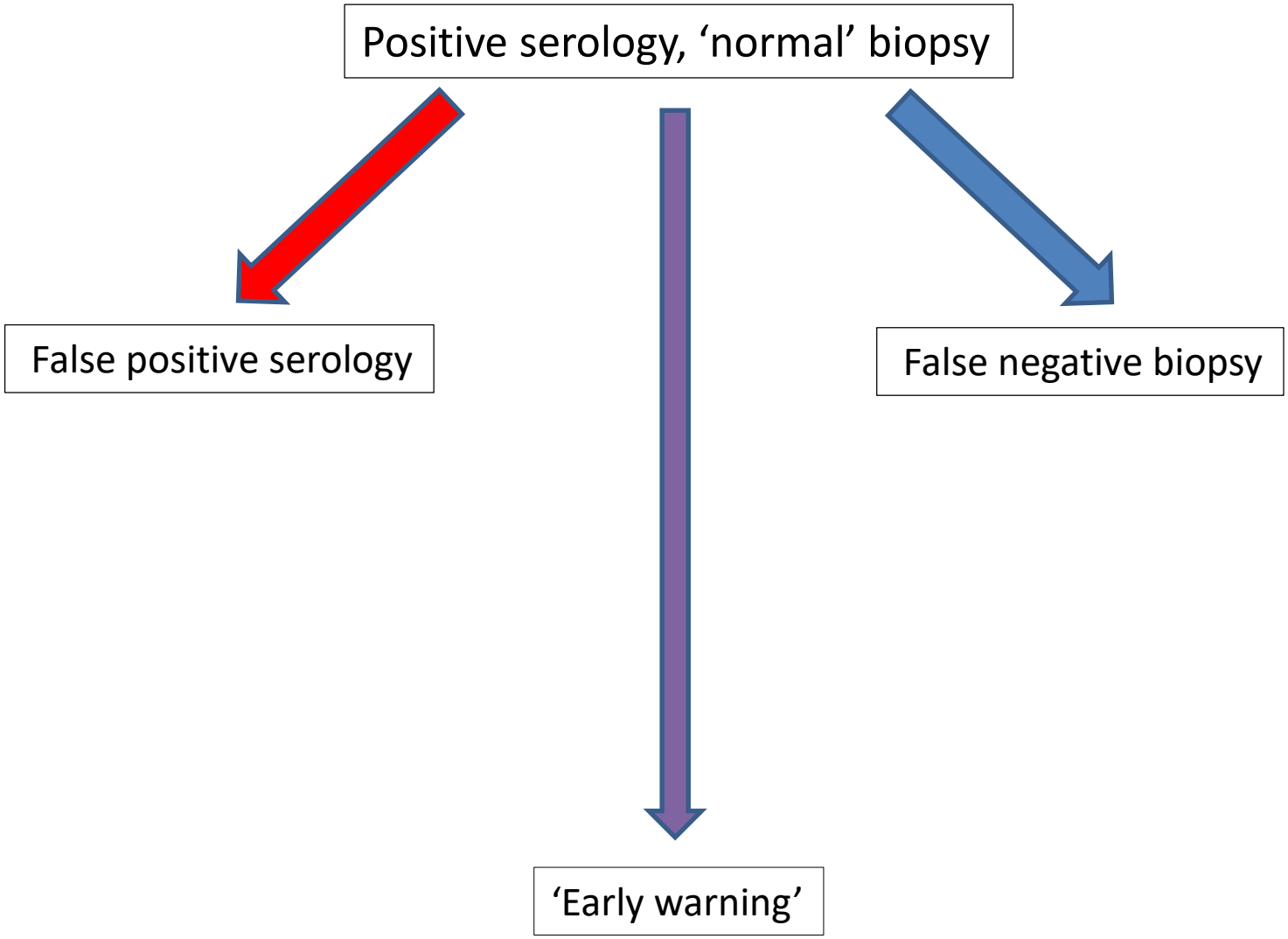


Taavela et al, 2013

Histological definition of Coeliac Disease



Kurppa et al, 2010


Positive serology, ‘normal’ biopsy
False positive serology
‘Early warning’
False negative biopsy

	7 years	Villous atrophy
TTG –ve, Marsh I	→	3/16
TTG +ve, Marsh 0/I	→	13/18

Salmi et al 2006

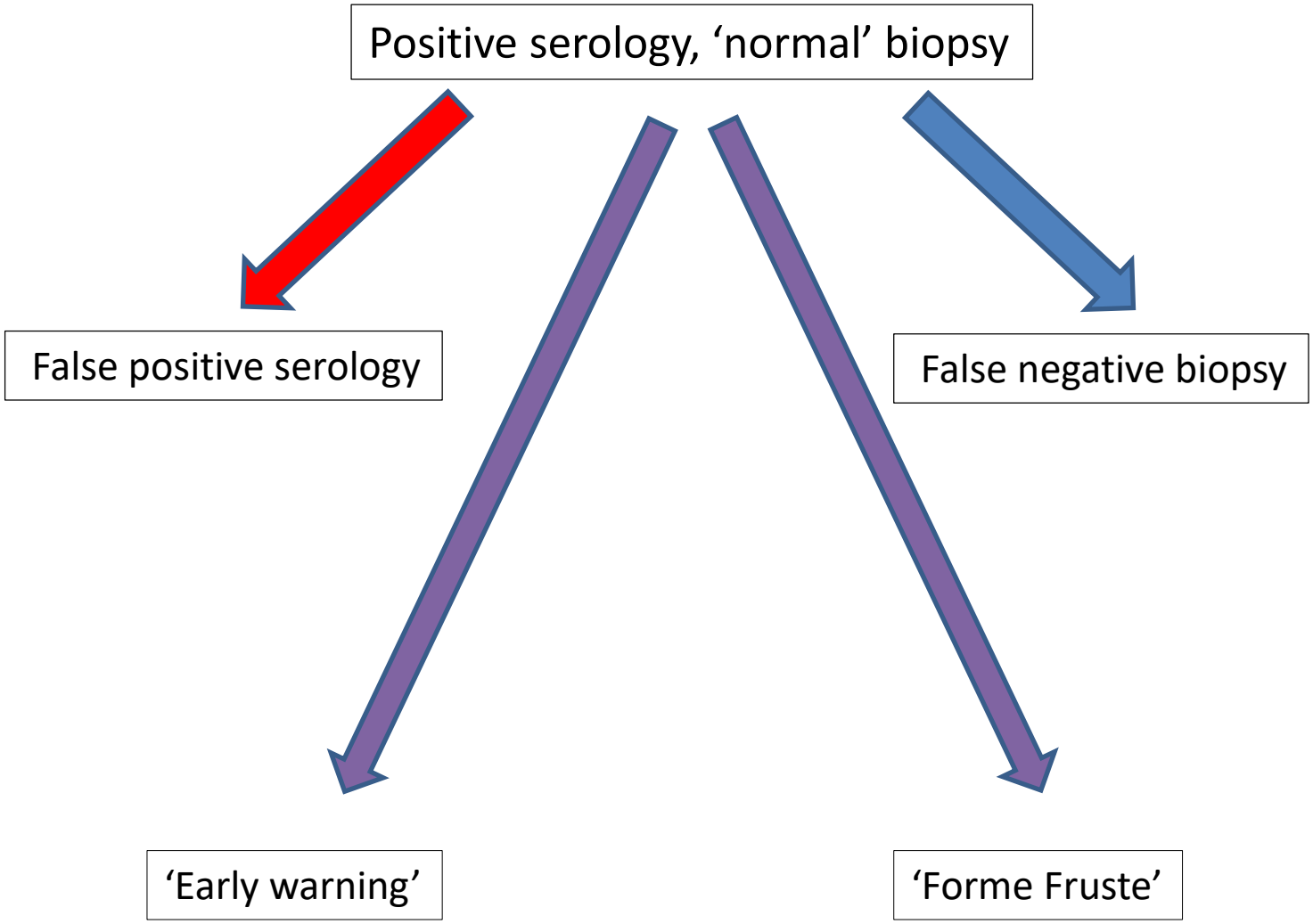
Article

Long-Term Outcome of Potential Celiac Disease in Genetically at-Risk Children: The Prospective CELIPREV Cohort Study

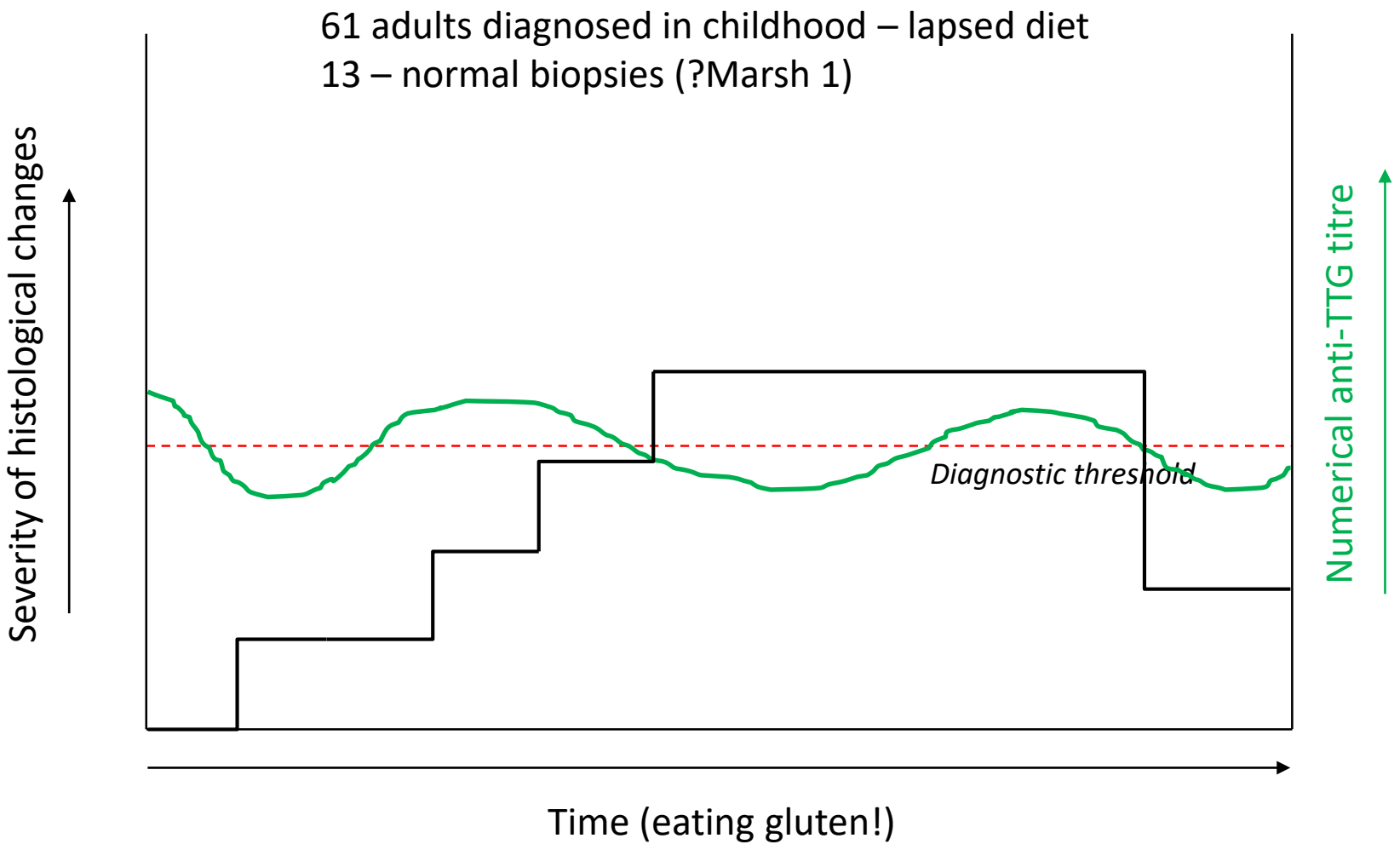
2019

Elena Lionetti [1,*], Stefania Castellaneta [2], Ruggiero Francavilla [3], Alfredo Pulvirenti [4], Giulia Naspi Catassi [1], Carlo Catassi [1,5] and The SIGENP Working Group of Weaning and CD Risk

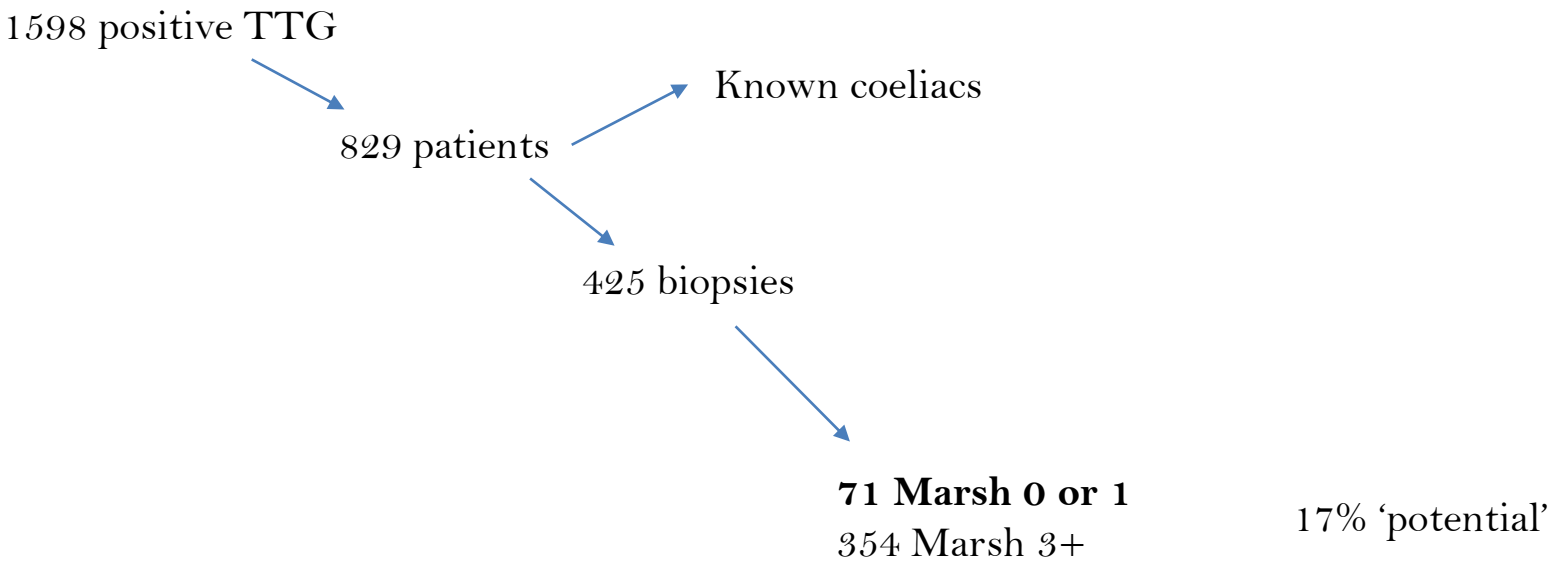
13% at 10 years

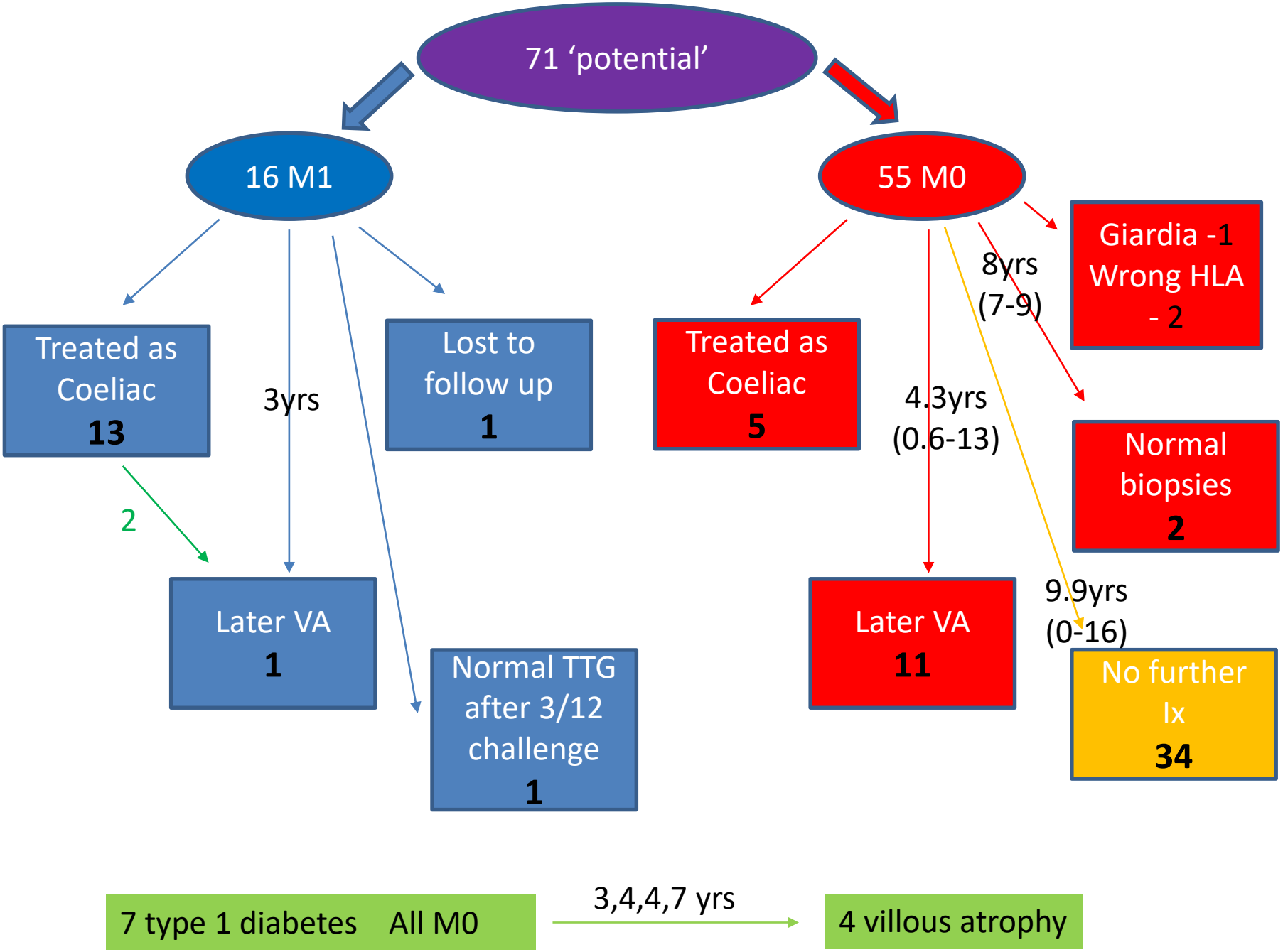

Positive serology, ‘normal’ biopsy
False positive serology
False negative biopsy
‘Early warning’
‘Forme Fruste’

Matysiak-Budnik et al, 2007



Cambridge 2003 - 2008




71 'potential'
16 M1
55 M0
Treated as Coeliac 13
3yrs
Lost to follow up 1
2
Later VA 1
Normal TTG after 3/12 challenge 1
Treated as Coeliac 5
4.3yrs (0.6-13)
Later VA 11
8yrs (7-9)
Giardia -1 Wrong HLA - 2
Normal biopsies 2
9.9yrs (0-16)
No further Ix 34
7 type 1 diabetes All M0
3,4,4,7 yrs
4 villous atrophy

The importance of clear diagnosis

Marsh 1 and +ve TTG → **HLA** → Treat as Coeliac

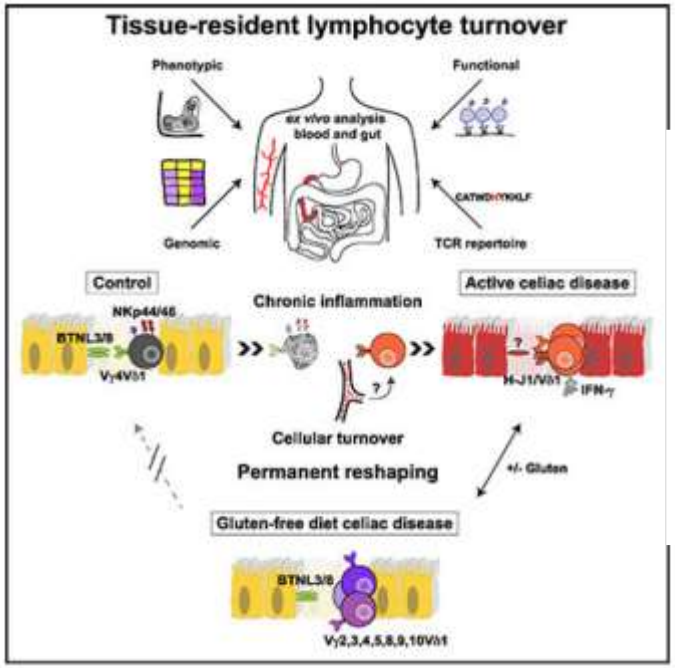
Marsh 0 and +ve TTG → HLA → ? Patient choice

Repeat biopsy
If willing

- Continue gluten and 2 yearly biopsy
- Treat as Coeliac
- Different test?

Nijeboer P et al, 2019

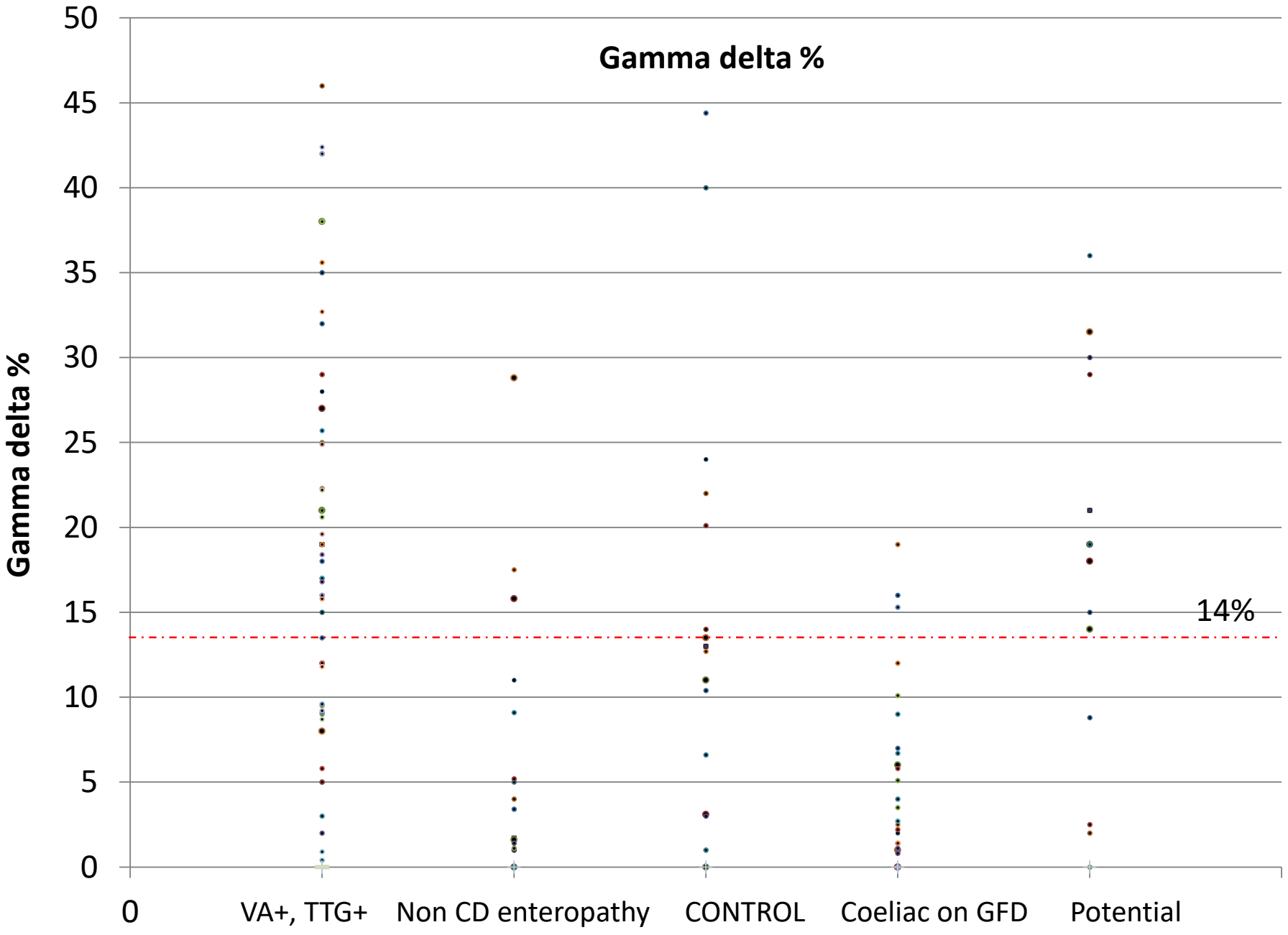
A cut-off value of 14% for CD3TCRγδ IEL resulted in 66.3% sensitivity and 96.6% specificity for CD diagnosis (area under the curve, 88.6%).
Conclusions: A percentage of ≥14% CD3TCRγδ IEL has a high specificity for CD diagnosis and can be of diagnostic help in cases where diagnosis is not straightforward.

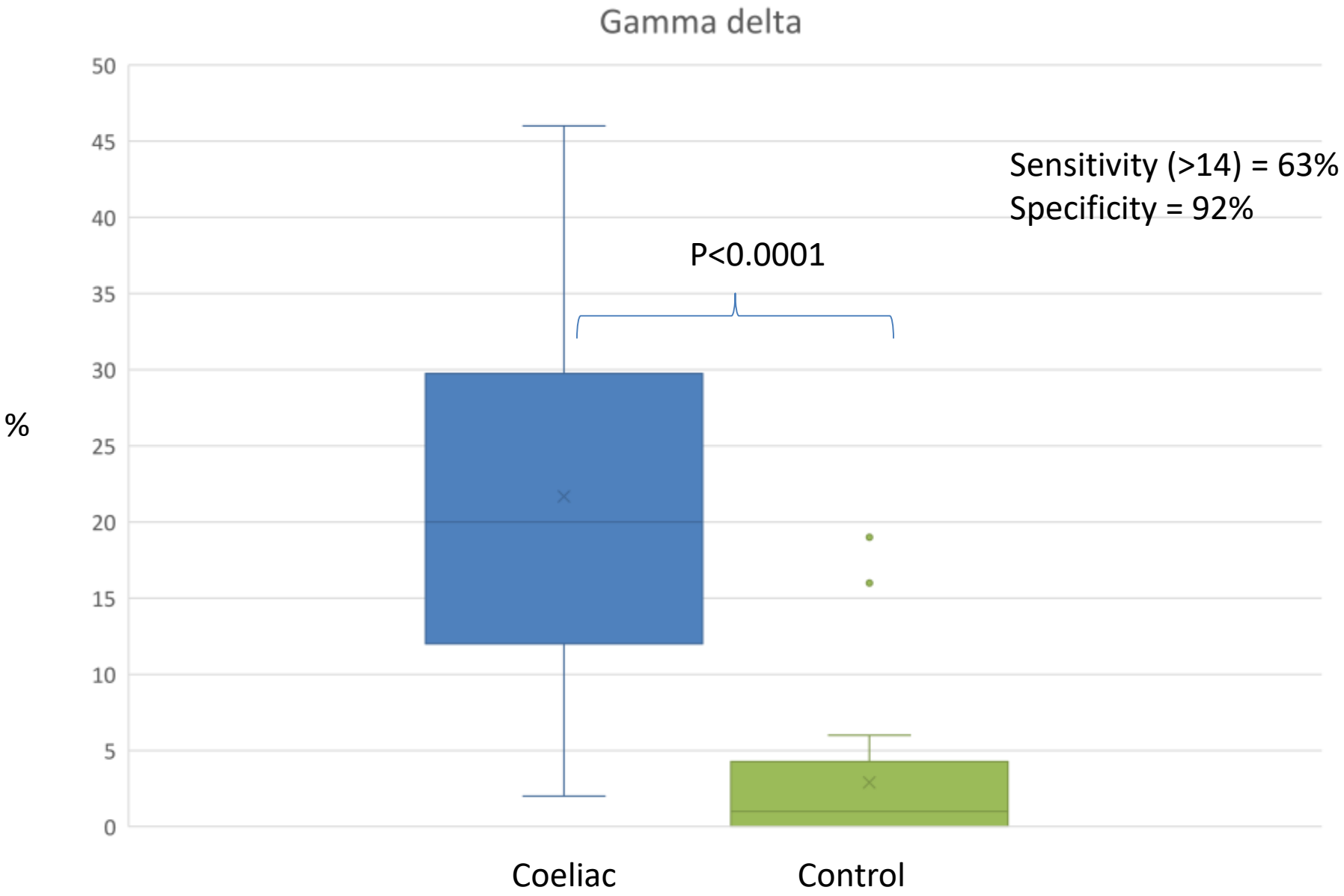


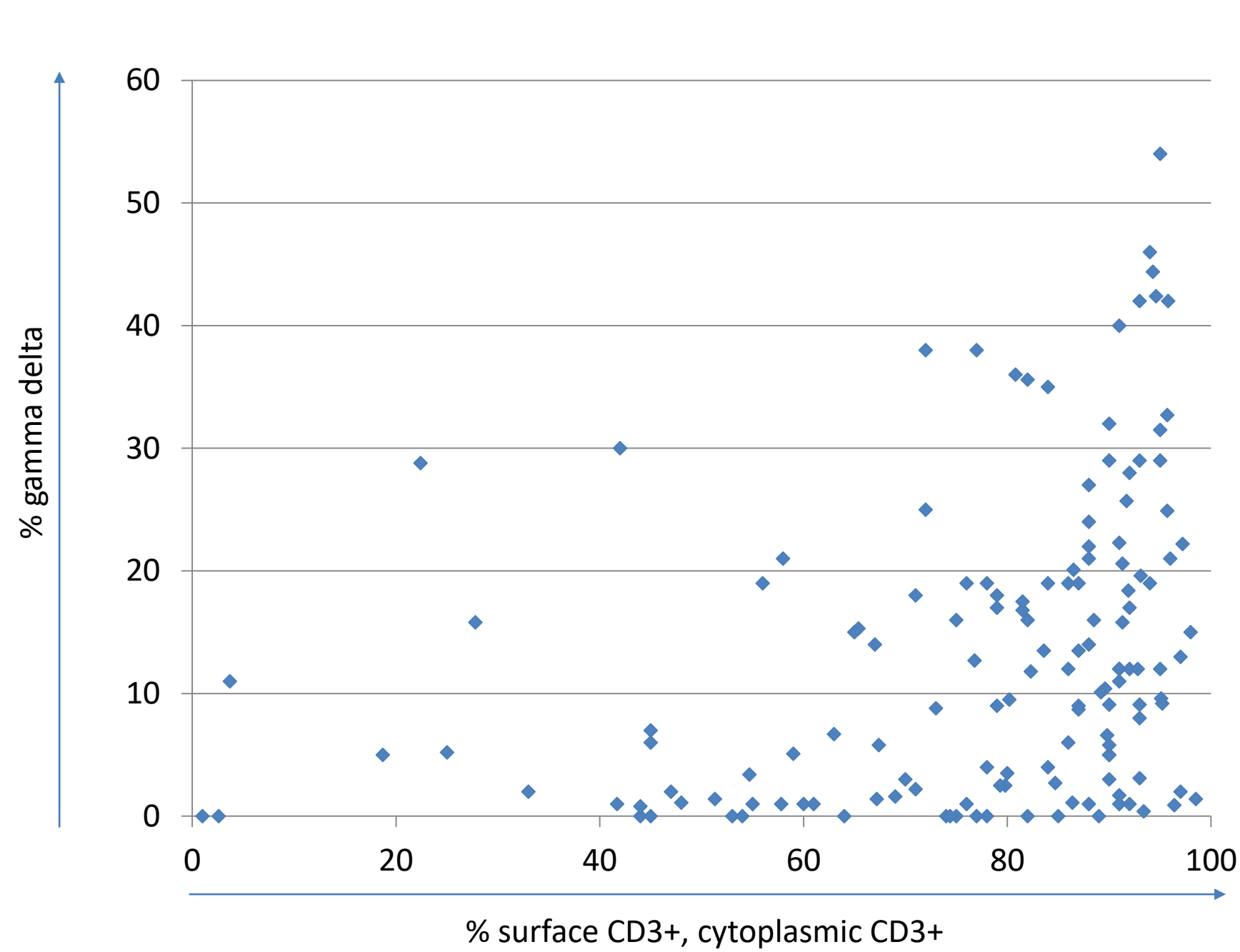
Cell. 2019 February 21; 176(5): 967–981.e19. doi:10.1016/j.cell.2018.12.039.

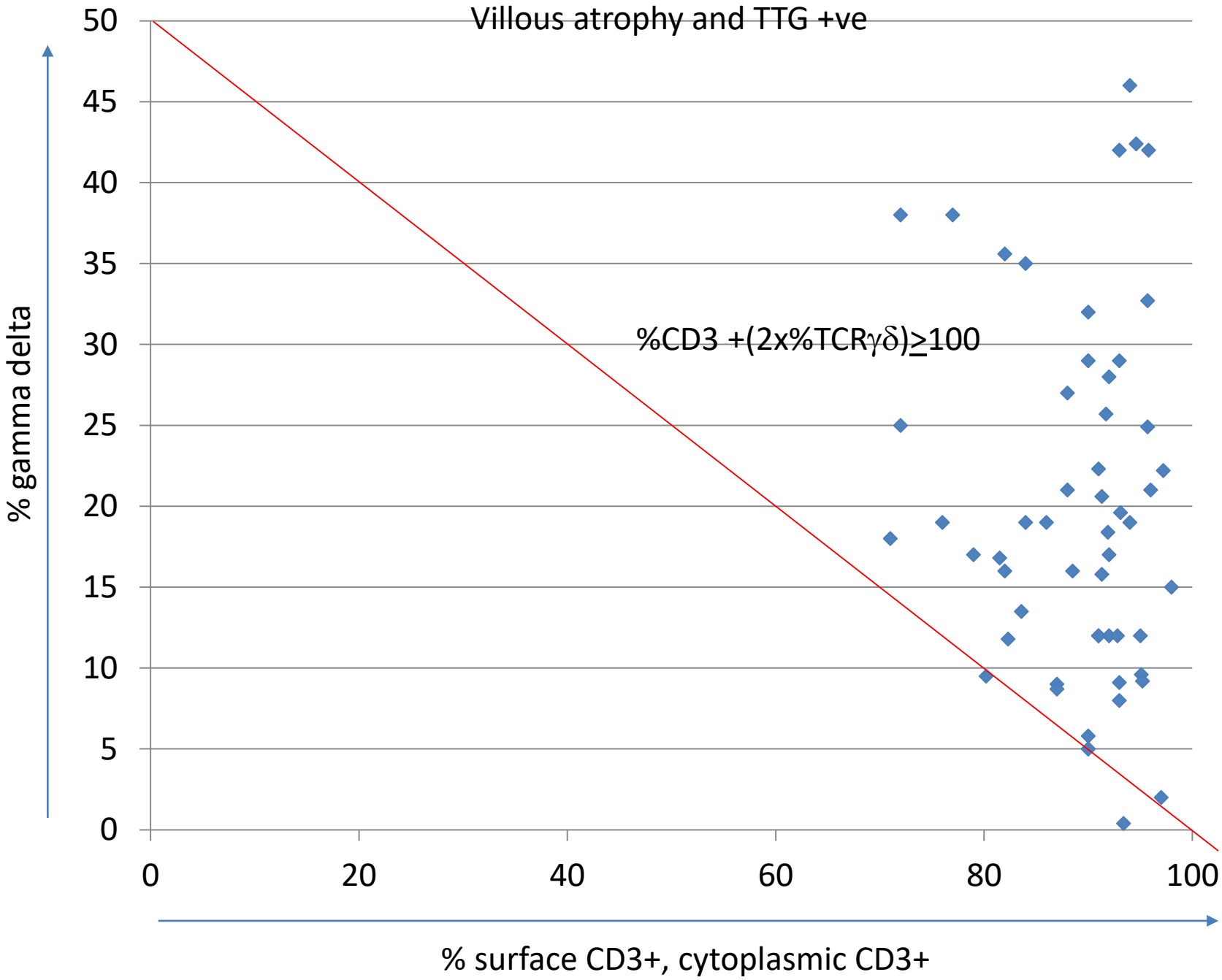
Chronic Inflammation Permanently Reshapes Tissue-Resident Immunity in Celiac Disease

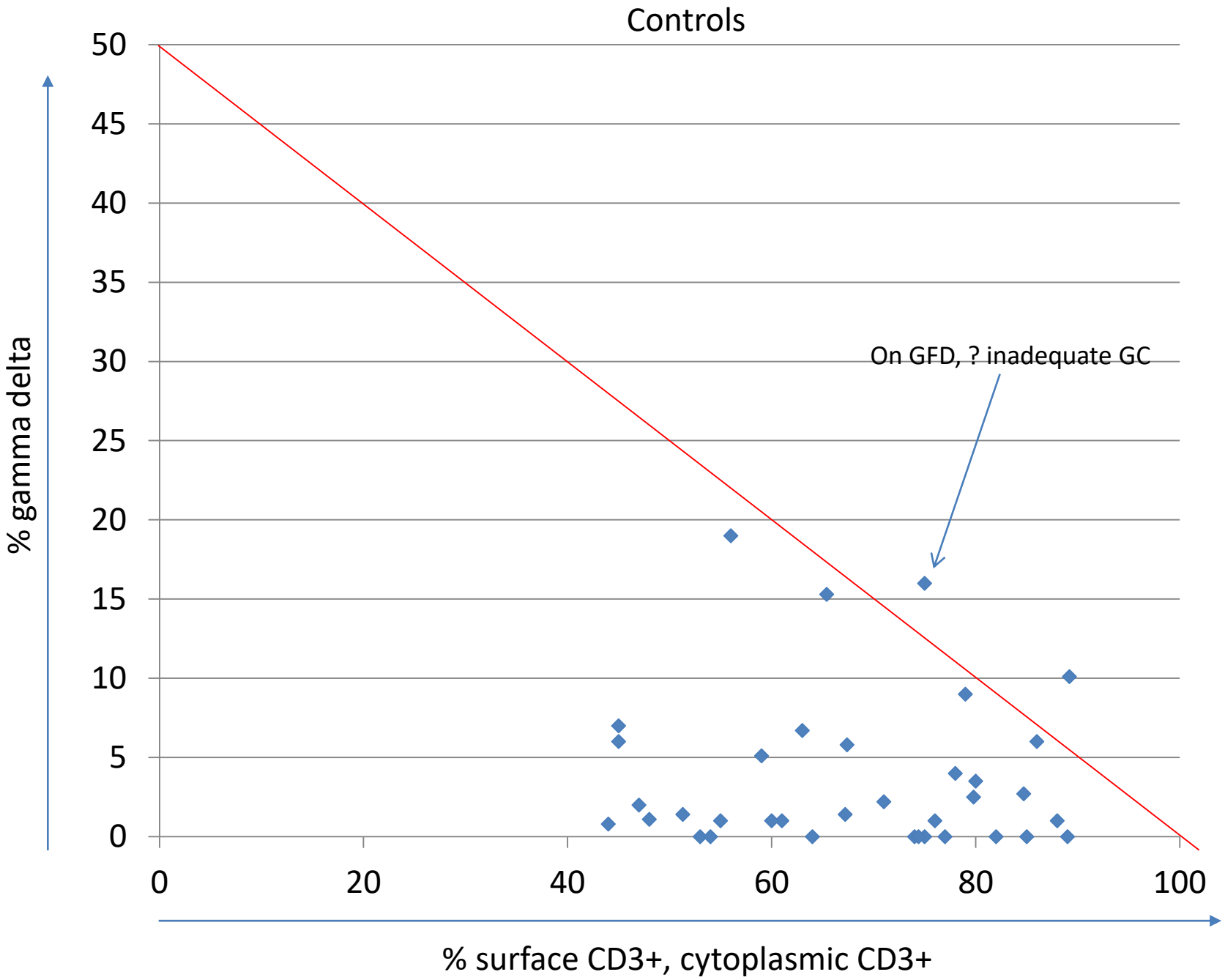
Toufic Mayassi[1,2], Kristin Ladell[3], Herman Gudjonson[4,5], James E. McLaren[3], Dustin G. Shaw[1,2], Mai T. Tran[6], Jagoda J. Rokicka[2], Ian Lawrence[2], Jean-Christophe Grenier[7], Vincent van Unen[8], Cezary Ciszewski[2], Matthew Dimaano[2], Hoda E. Sayegh[2], Vinod Kumar[9], Cisca Wijmenga[9], Peter H.R. Green[10], Ranjana Gokhale[11,12], Hilary Jericho[11,12], Carol E. Semrad[2,12], Stefano Guandalini[11,12], Aaron R. Dinner[4,5,13], Sonia S. Kupfer[2,11], Hugh H. Reid[6,14], Luis B. Barreiro[7], Jamie Rossjohn[3,6,14], David A. Price[3,16,*], Bana Jabri[1,2,15,16,17,*]

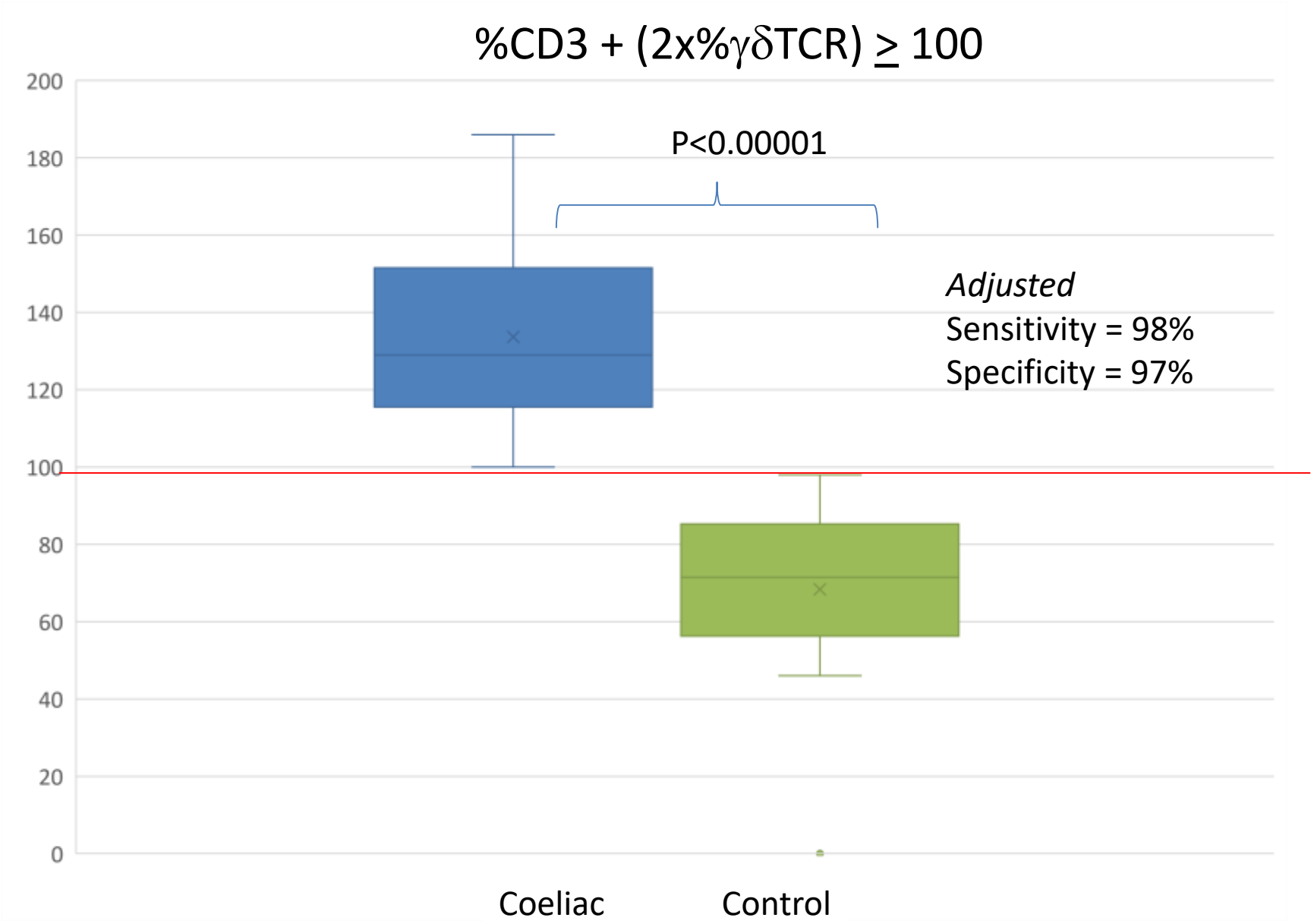

Gamma delta %
Gamma delta %
50
45
40
35
30
25
20
15
10
5
0
14%
0
VA+, TTG+
Non CD enteropathy
CONTROL
Coeliac on GFD
Potential

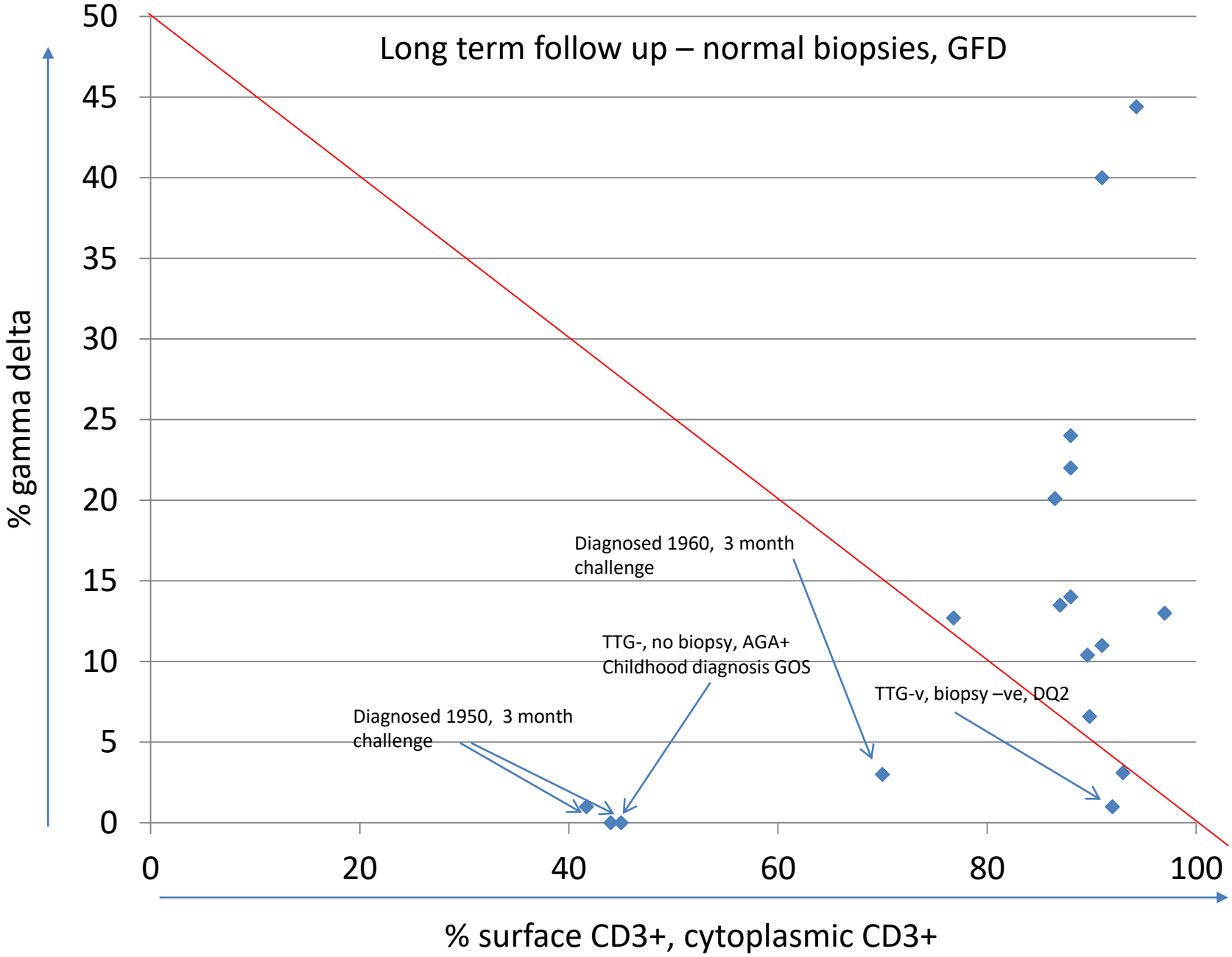

Gamma delta
50
45
40
35
30
25
20
15
10
5
0
%
Sensitivity (>14) = 63%
Specificity = 92%
P<0.0001
Coeliac
Control

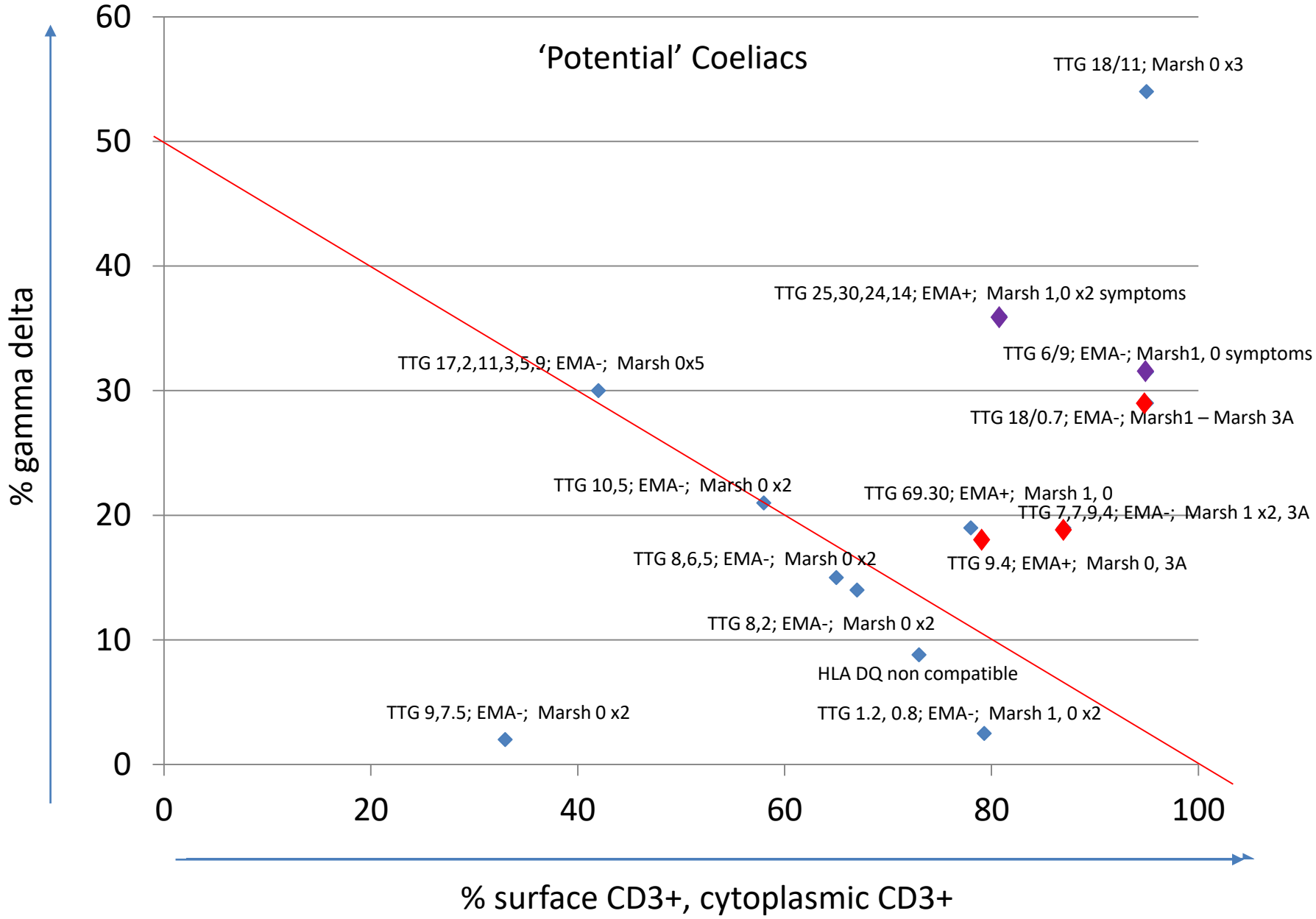

60
50
40
30
20
10
0
% gamma delta
0
20
40
60
80
100
% surface CD3+, cytoplasmic CD3+


Villous atrophy and TTG +ve
%CD3 +(2x%TCRγδ)≥100
% gamma delta
% surface CD3+, cytoplasmic CD3+
0
5
10
15
20
25
30
35
40
45
50
0
20
40
60
80
100


Controls
50
45
40
35
30
25
20
15
10
5
0
% gamma delta
On GFD, ? inadequate GC
0
20
40
60
80
100
% surface CD3+, cytoplasmic CD3+

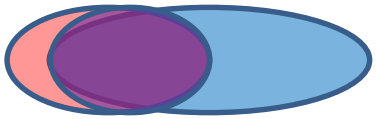

%CD3 + (2x%γδTCR) ≥ 100
200
180
160
140
120
100
80
60
40
20
0
P<0.00001
Adjusted
Sensitivity = 98%
Specificity = 97%
Coeliac
Control


Long term follow up – normal biopsies, GFD
% gamma delta
50
45
40
35
30
25
20
15
10
5
0
0
20
40
60
80
100
% surface CD3+, cytoplasmic CD3+
Diagnosed 1960, 3 month challenge
TTG-, no biopsy, AGA+ Childhood diagnosis GOS
TTG-v, biopsy –ve, DQ2
Diagnosed 1950, 3 month challenge


'Potential' Coeliacs
TTG 18/11; Marsh 0 x3
TTG 25,30,24,14; EMA+; Marsh 1,0 x2 symptoms
TTG 6/9; EMA-; Marsh1, 0 symptoms
TTG 18/0.7; EMA-; Marsh1 – Marsh 3A
TTG 17,2,11,3,5,9; EMA-; Marsh 0x5
TTG 10,5; EMA-; Marsh 0 x2
TTG 69.30; EMA+; Marsh 1, 0
TTG 7,7,9,4; EMA-; Marsh 1 x2, 3A
TTG 9.4; EMA+; Marsh 0, 3A
TTG 8,6,5; EMA-; Marsh 0 x2
TTG 8,2; EMA-; Marsh 0 x2
HLA DQ non compatible
TTG 9,7.5; EMA-; Marsh 0 x2
TTG 1.2, 0.8; EMA-; Marsh 1, 0 x2
% gamma delta
% surface CD3+, cytoplasmic CD3+
0
10
20
30
40
50
60
0
20
40
60
80
100

Potential Coeliac Disease
Summary

- Know your TTG assay!



- Some ‘Potential Coeliacs’ are genuinely ***false positive*** serology

- Some ‘Potential Coeliacs’ are gluten restricting and have undergone inadequate gluten challenge – consider re-biopsy

- Marsh 1 or 2, TTG+ are Coeliac

- ‘Early warning’ or ‘forme fruste’ requires long term follow up and further study

- The importance of a definitive diagnosis and clear messages

- Flow cytometry may provide a useful tool

- **Coeliac Disease redefinition required – OSLO II?**