Non-Celiac Gluten Sensitivity:
Patient Management

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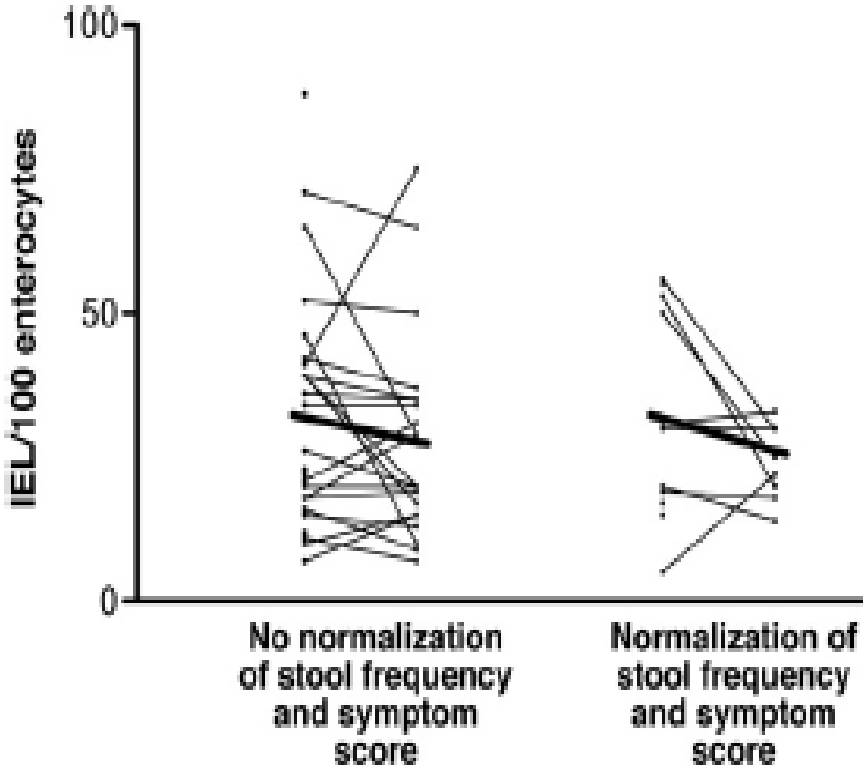
Initial Studies Suggest an Immune Mechanism for NCGS

		Normalization of		
	n	Symptom score	Stool frequency	Both
≥40 IEL/100 enterocytes				
Positive	11	5 (45%)	5 (45%)	4 (36%)
Negative	30	15 (50%)	11 (37%)	8 (27%)
DQ2				
Positive	25	17 (68%)[a]	13 (52%)[b]	11 (44%)[b]
Negative	16	3 (19%)	3 (19%)	1 (6%)
IgG (AGA/TTG)				
Positive	20	14 (70%)[b]	10 (50%)	9 (45%)[b]
Negative	21	6 (29%)	6 (29%)	3 (14%)
DQ2 and IgG (AGA/TTG)				
Positive	16	14 (93%)[a]	10 (60%)[b]	9 (60%)[b]
Negative	25	6 (23%)	6 (27%)	3 (12%)

IELs, intraepithelial lymphocytes; DQ2, expression of the HLA-DQ2 alleles A1*0501/B1*0201; AGA, anti–gliadin antibodies; TTG, anti–tissue-transglutaminase antibodies.
[a] $P < .01$ vs negative patients.
[b] $P < .05$ vs negative patients.



Wahnschaffe U, et al. CGH 2007.

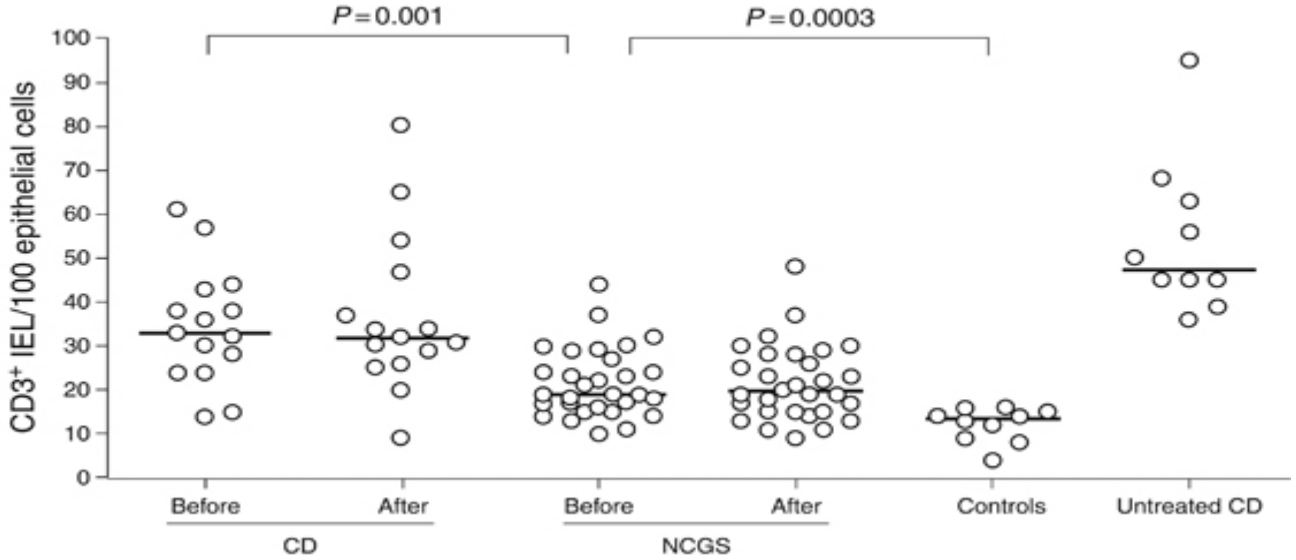
Serologic Tests

- IgG AGA
  - Found in 40-70% of patients with NCGS
  - 80-90% of celiac disease
  - 5-25% of controls
- IgA AGA
  - Found in 10% of NCGS
  - 75-80% of celiac disease
  - 2-10% of controls
- DGP
  - <5% of NCGS
  - >85% of celiac disease
- EMA/tTG negative by definition

Volta U, JCG 2012, Leffler D, AJG 2010, Kull K, JG 1999,
Jaeger C, Diabetes Care 2001

Histologic Findings

- Villous architecture should be normal
- IELs may be increased; mean ~20-25
- Possible other findings include:
  - Deposition of T lymphocyte clusters



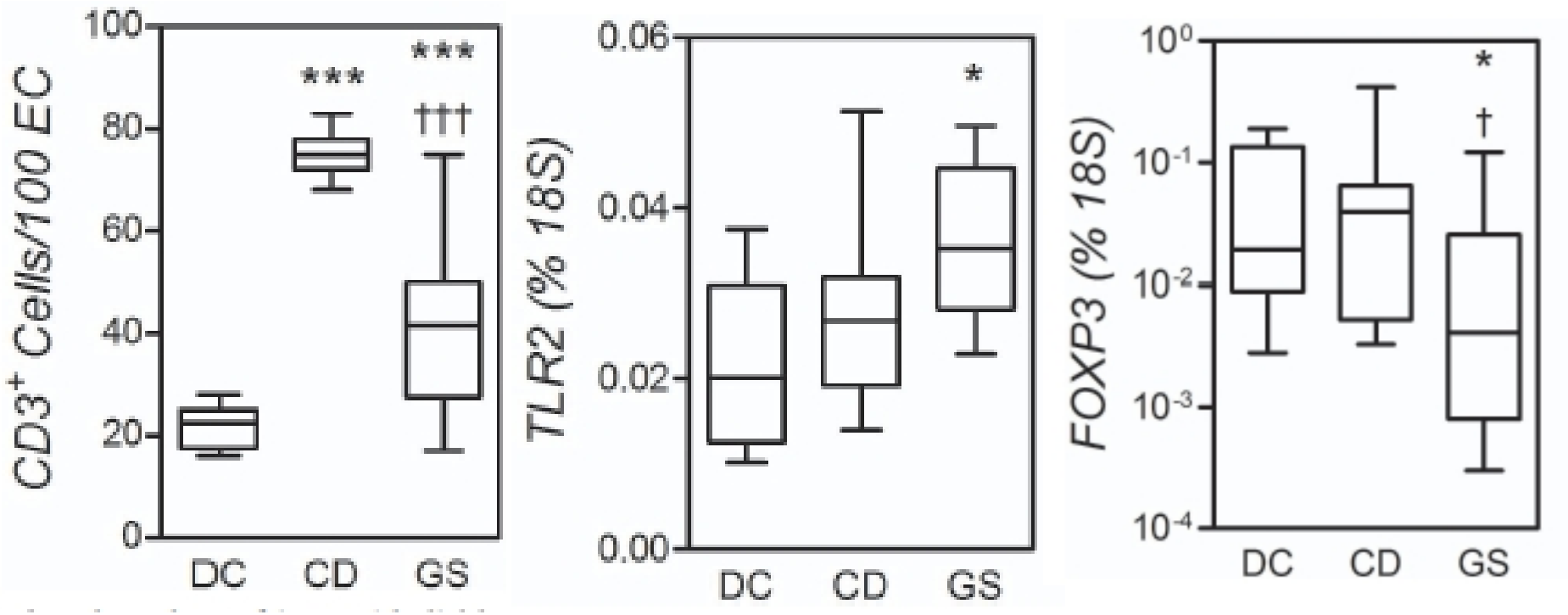
Villanacci V, AJG 2013, Brottveit M, AJG 2013

Miscellaneous Tests

- In vitro basophil activation with increased CD63 expression
- Double blind placebo controlled challenge
- Oral patch test
- HLA testing

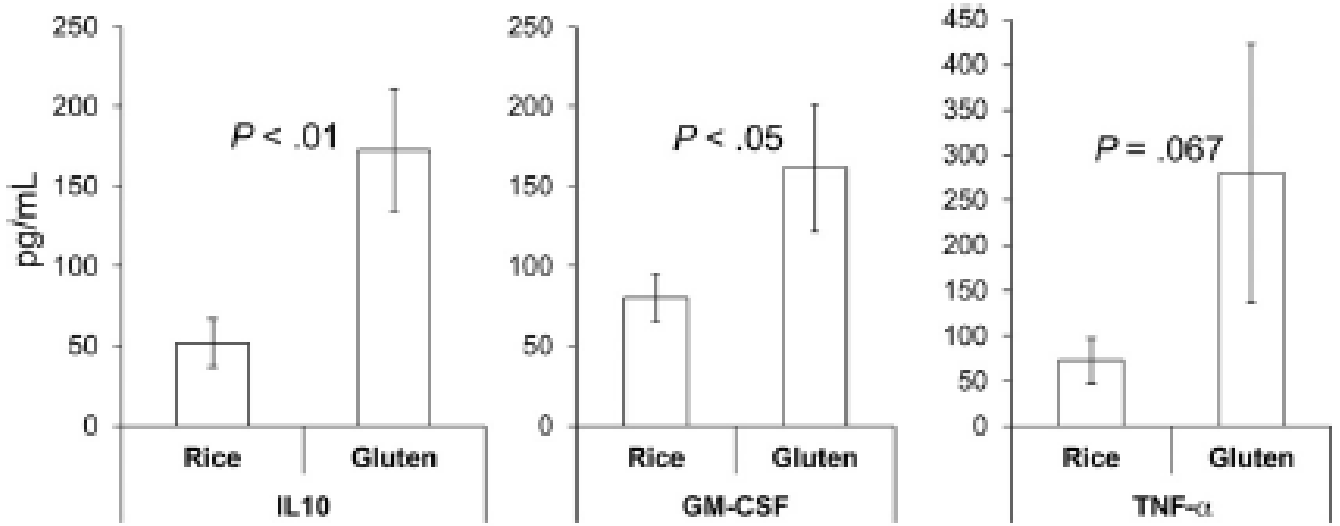
Carroccio I, et al CCLM 2013, Saneian H, IJP

Suggestions of Alteration in Immune Regulation



Sapone; BMC Med 2011

	GFD	GCD	*P* value, effect of diet	HLA+	HLA−
Δ cumulative urine mannitol 0–2 h, *mg*	−48.6 ± 12.3	83.0 ± 70.9	.028	.586	.01
Δ cumulative urine lactulose 0–2 h, *mg*	3.7 ± 4.0	−3.5 ± 2.5	.207	.150	.708
Δ lactulose:mannitol ratio 0–2 h	0.008 ± 0.004	−0.005 ± 0.004	.0012	.006	.043
Δ cumulative urine mannitol 8–24 h, *mg*	−21.6 ± 13.4	−35.2 ± 12.7	.358	.999	.203
Δ cumulative urine lactulose 8–24 h, *mg*	−1.71 ± 3.22	−5.25 ± 4.98	.858	.540	.396
Δ lactulose:mannitol ratio 8–24 h	0.027 ± 0.022	0.059 ± 0.024	.531	.445	.919
ZO-1 fold-change, SB	1.57 ± 0.24	1.11 ± 0.24	.065	.119	.218
Occludin fold-change, SB	1.14 ± 0.07	1.03 ± 0.08	.28	.017	.490
Claudin fold-change, SB	1.64 ± 0.31	1.13 ± 0.12	.24	.32	.41
ZO-1 fold-change, colon	1.97 ± 0.56	1.04 ± 0.26	.025	.038	.161
Occludin fold-change, colon	1.47 ± 0.16	0.96 ± 0.13	.004	.006	.178
Claudin fold-change, colon	1.63 ± 0.23	1.01 ± 0.15	.036	.015	.203
Colonic transit, GC 24 h	3.2 ± 0.19	2.6 ± 0.2	.182	.364	.251
Colonic transit, GC 48 h	4.4 ± 0.16	4.0 ± 0.2	.304	.352	.548



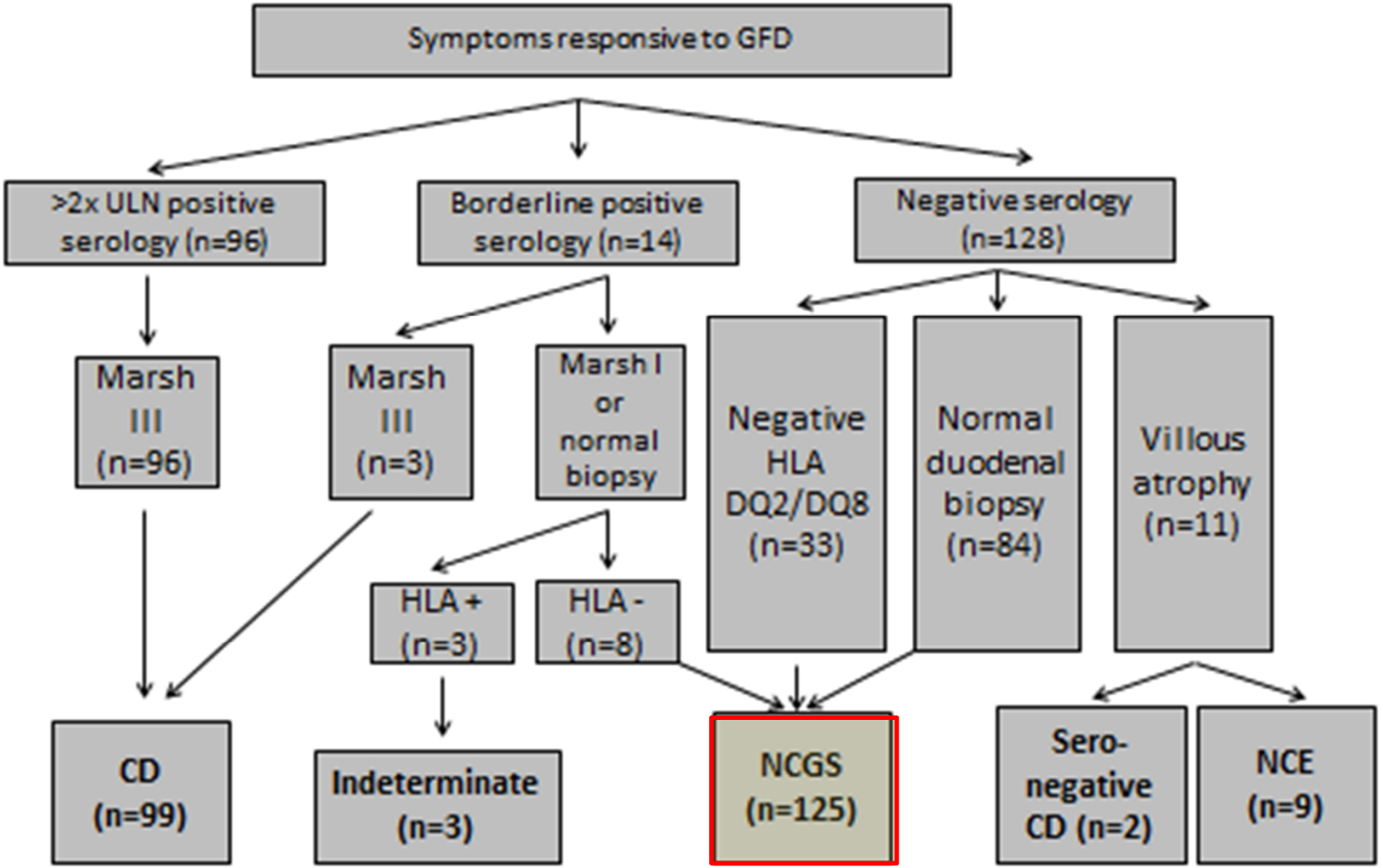
Camilleri; Gastro 2013

Evaluation of Gluten Responsive Symptoms in Clinical Practice

- 238 patients presenting for evaluation of gluten responsive symptoms without prior evaluation for celiac disease
- Evaluated:
  - Final clinical diagnosis
  - Demographics
  - Presenting symptoms
  - Serologic, genetic and histologic data
  - Nutrient deficiencies
  - Personal history of autoimmune disease
  - Family history of celiac disease

Kabbani T, *under review*

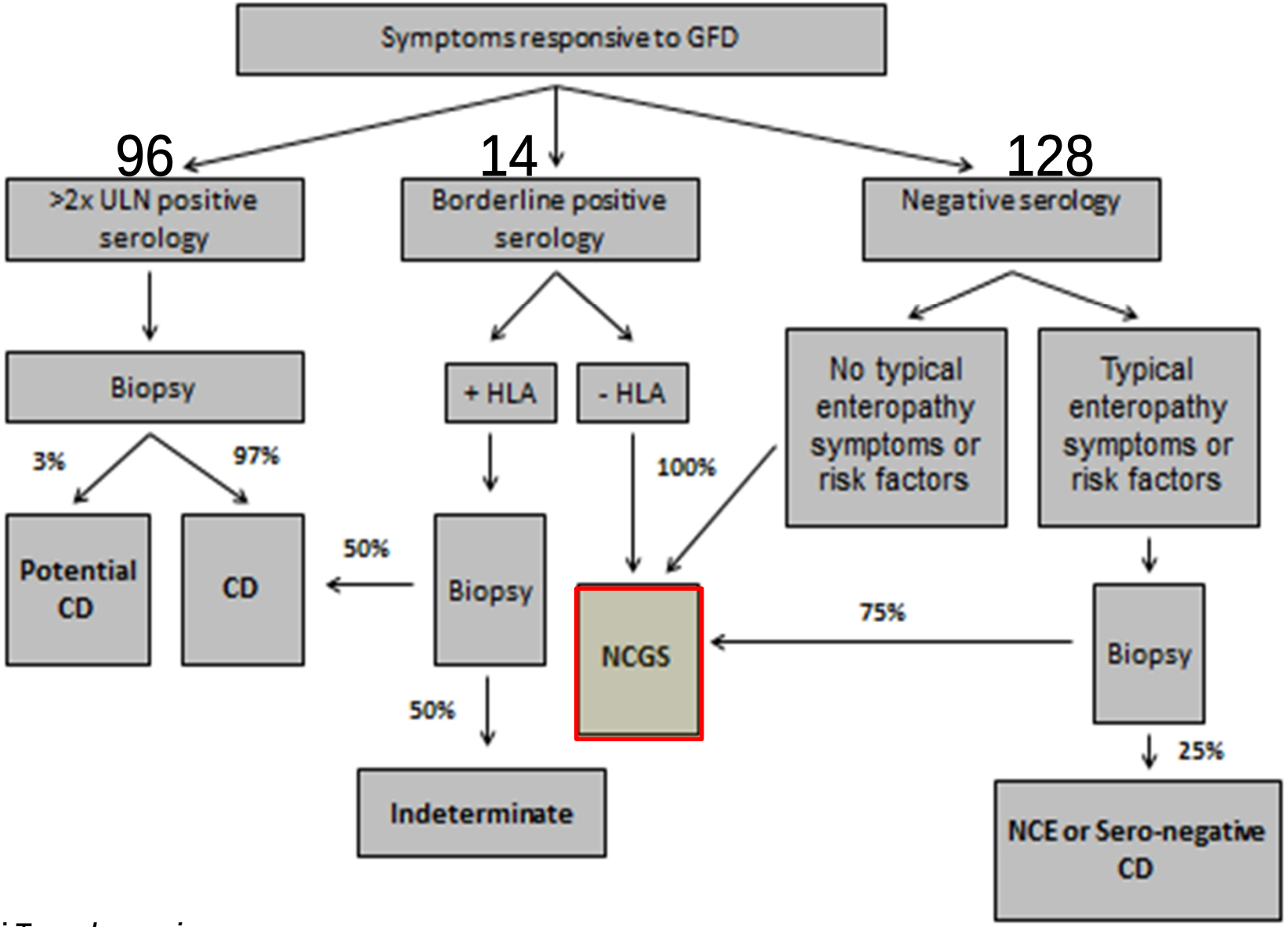
Results of Evaluation / Clinical Diagnosis



NCE; Non-Celiac Enteropathy, CD; Celiac Disease, NCGS; Non-Celiac Gluten Sensitivity

Kabbani T, *under review*

NCGS: Currently Diagnosis of Exclusion



Kabbani T, *under review*

Conclusions

- Gluten sensitivity appears to be common but true prevalence is unknown
- Presence of tTG, EMA and likely DGP antibodies should preclude a diagnosis of NCGS
- Elevated AGA titers appear to be more common in NCGS but clinical utility is unclear
- Some promising biomarkers of NCGS but currently non validated
- Role of blinded oral challenge for diagnosis is unclear, possible role in research, unlikely in clinical practice
- Clinically, currently NGGS should be a diagnosis of exclusion in individuals with reliable response to gluten exposure and withdrawal in whom celiac disease has been excluded