6th FAMS 2025
FOOD ALLERGEN MANAGEMENT SYMPOSIUM
Collaborate, Educate, Communicate

How much gluten is too much?
Revisiting the safe gluten threshold in coeliac disease

21st May 2025

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WEHI brighter together

The Royal Melbourne Hospital

murdoch children's research institute

THE UNIVERSITY OF MELBOURNE

Disclosure Information

- I have the following relevant financial relationships to disclose:
  - Consultant for: Anatara, Anokion, Barinthus, Codexis, Chugai, Dr Falk, EVOQ Therapeutics, Equillium, Forte Biosciences, IM Therapeutics, Janssen, Mozart Therapeutics, Takeda, TEVA, Tillotts and Topas
  - Grant/Research Support from: Barinthus, Codexis, Chugai, DBV, Immunic, Kallyope, Novoviah, NHMRC, Tillotts and Topas
  - Patents relating to the use of gluten peptides in coeliac disease diagnosis and treatment

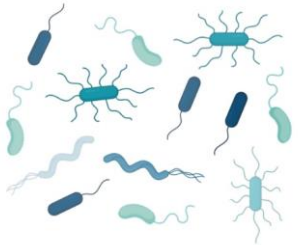
Celiac disease is common and causes widespread health effects

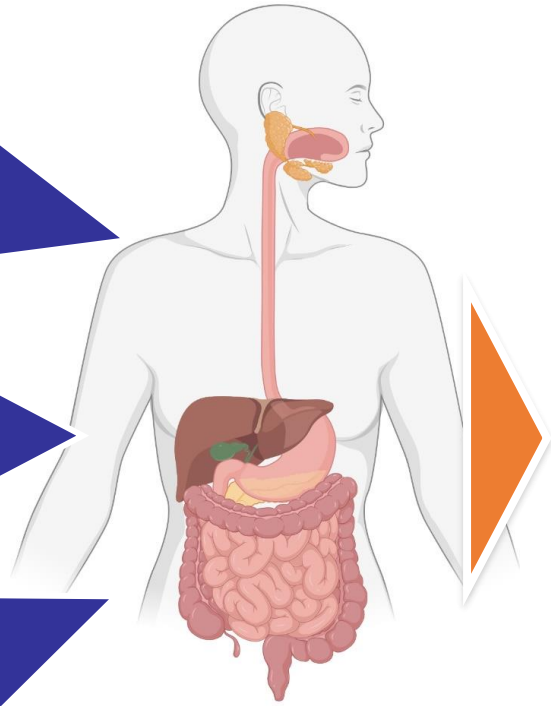
Dietary gluten

- Wheat, rye, barley

HLA-DQ2 and DQ8

Environmental factors





- Global prevalence 1.4% (0.5-3%)
- 50-80% remain undiagnosed
- In Asia, >30% increase in wheat consumption in past 10 years will likely drive increasing prevalence

Created with BioRender.com

Stahl, Lancet Child Adolesc Health 2024; Singh, CGH 2018

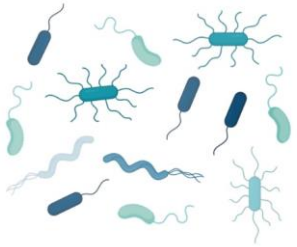
Diagnosis based on antibodies and changes of chronic gut damage

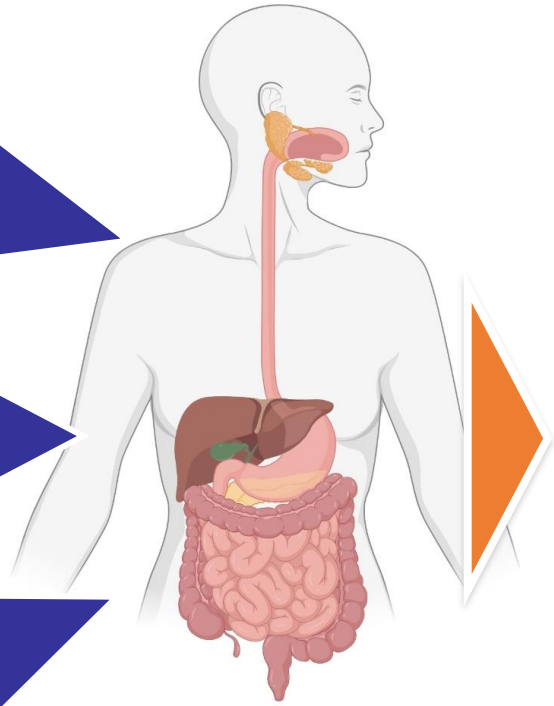
Dietary gluten

• Wheat, rye, barley

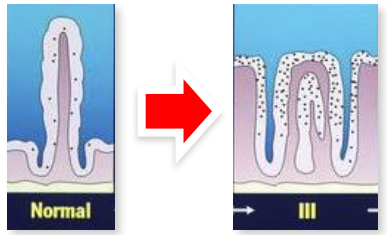
HLA-DQ2 and DQ8

Environmental factors





- **Coeliac antibodies**
  - Transglutaminase-IgA (TGA)
  - Deamidated gliadin peptide-IgG (DGP)
- **Small intestinal damage**



- Villous atrophy
- Crypt hyperplasia
- Intraepithelial lymphocytosis

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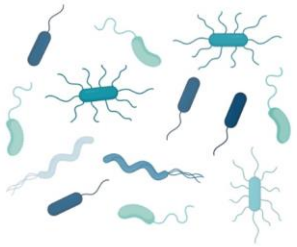
Health effects different to acute hypersensitivity responses in food allergy

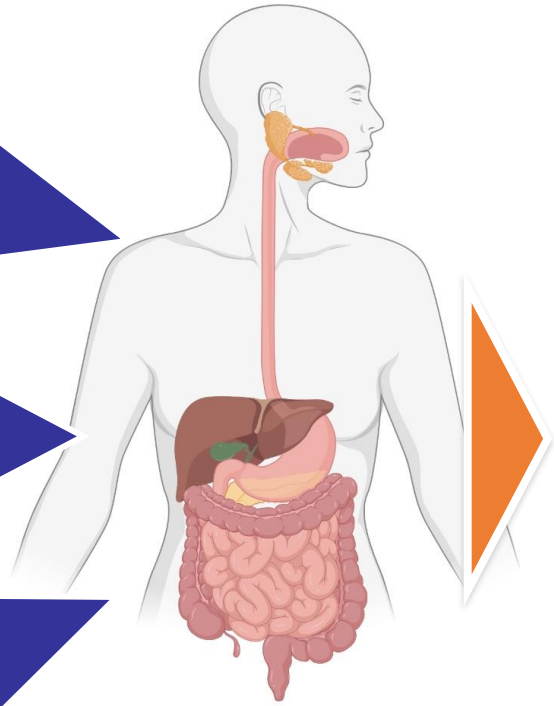
Dietary gluten

- Wheat, rye, barley

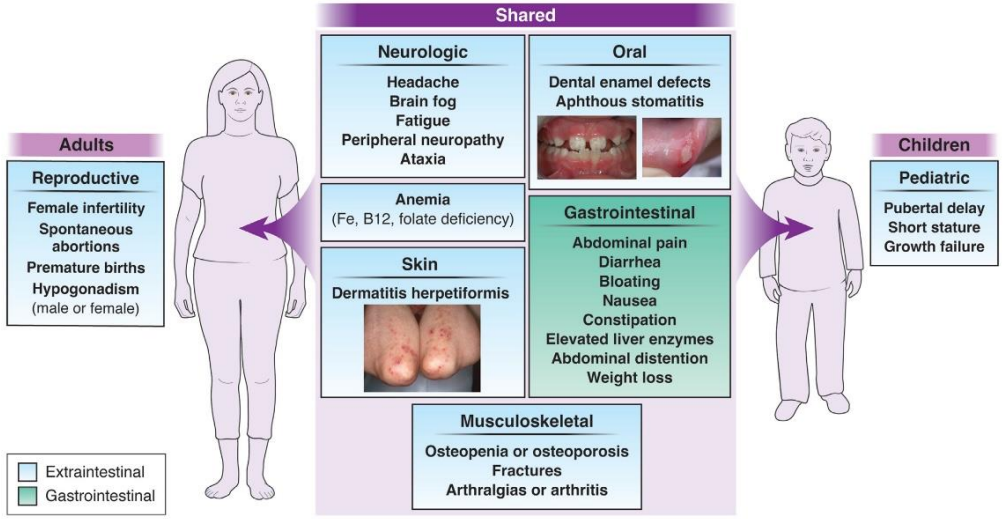
HLA-DQ2 and DQ8

Environmental factors





- **Symptoms & health effects**



Adams et al, Gastroenterology 2024

The cause

- Gluten triggers pro-inflammatory **gluten-specific CD4+ T cells**

Compared to food allergy…

- Not all patients are symptomatic
- Symptoms are a poor guide to gut damage

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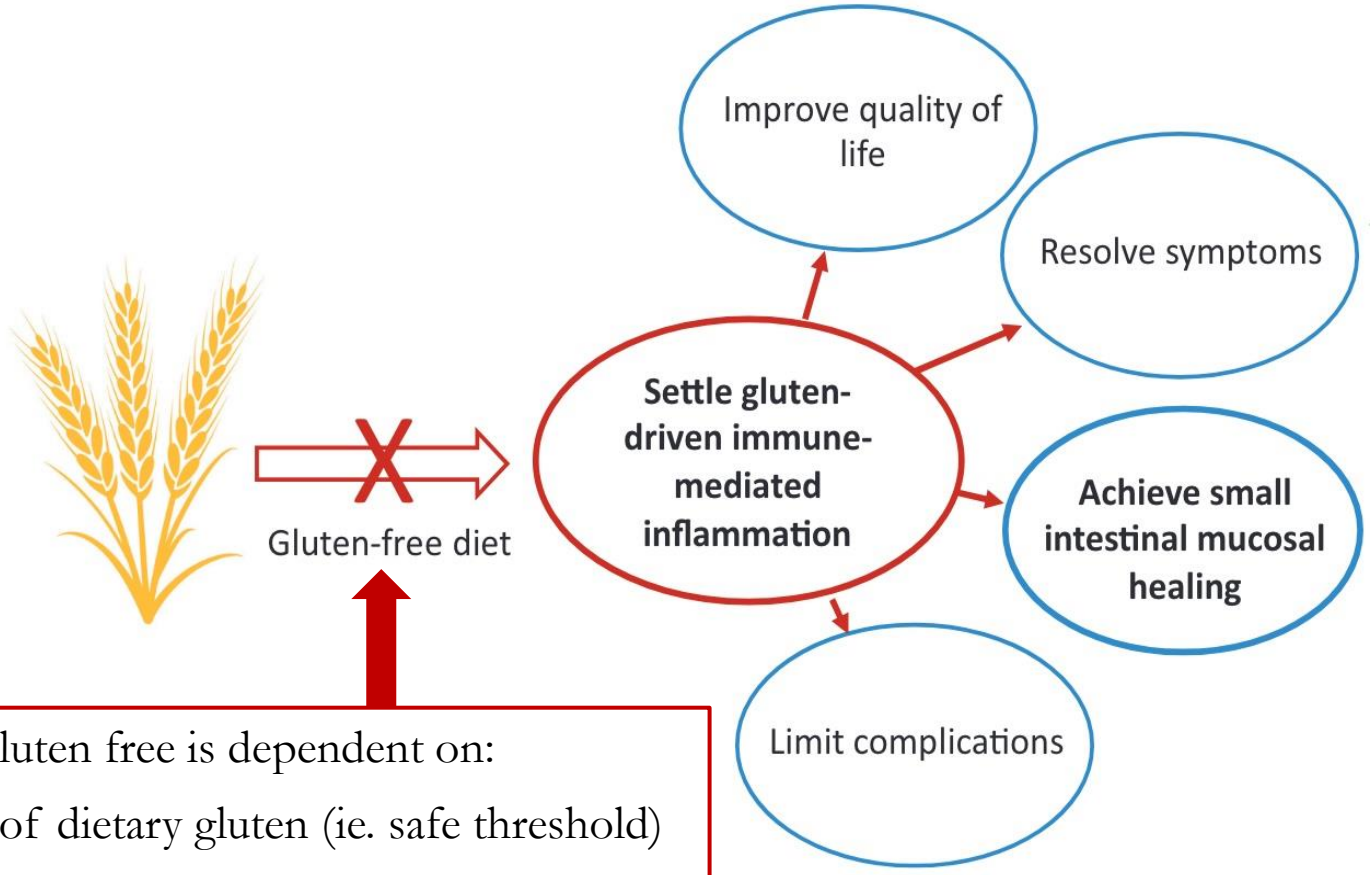
Goals of coeliac disease treatment



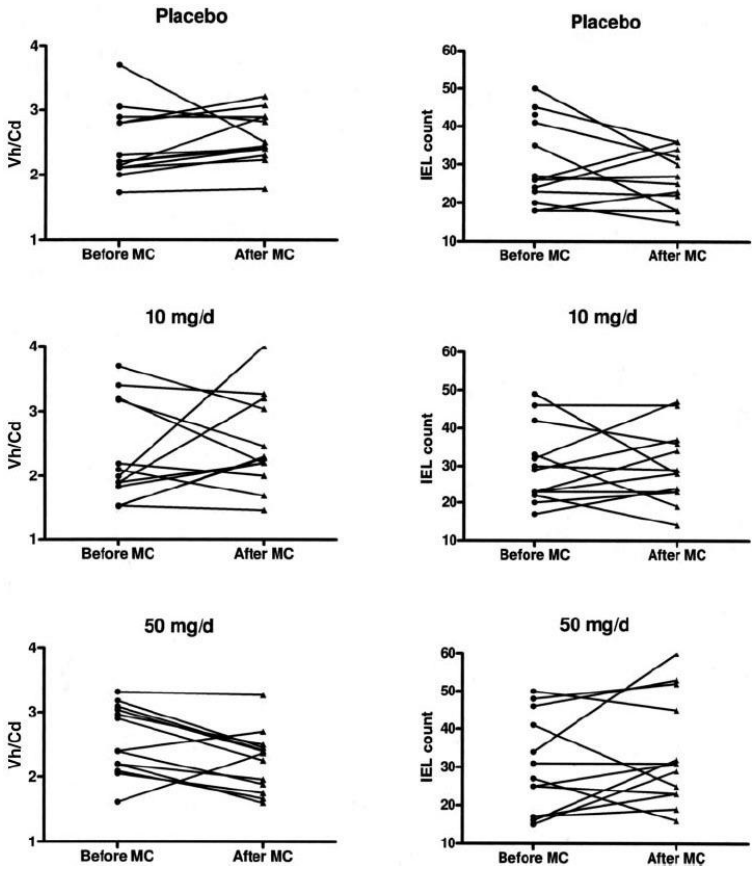
An optimal gluten free is dependent on:

- ➔ Adequate exclusion of dietary gluten (ie. safe threshold)
- ➔ Adequate access to GF food (cost, availability)
- ➔ Medical follow-up to ensure it is working

Tye-Din, APT 2022; Lebwohl, J Clin Endo Metab 2014; Lebwohl, Ann Internal Med 2013; Rubio-Tapia, Am J Gastro 2010; Lebwohl, APT 2013

The challenge of defining a safe threshold for gluten

- Only a single randomised double-blind placebo controlled feeding (RDBPCFC) study



- **3 study groups:**
  - 50 mg gluten/d (n = 13)
  - 10 mg gluten/d (n = 13)
  - placebo (n = 13)

- A significant difference in villous height:crypt depth (Vh:Cd) was observed between the **placebo and the 50 mg groups** (p = 0.029)

- **Conclusion:** The ingestion of contaminating gluten should be kept < 50mg/d in the treatment of CD

Catassi et al, Am J Clin Nutr 2007

- Meta-analyses: insufficient data to define a safe level *(Akobeng, APT 2006; Cochrane Review 2016)*
- RDBPCFC studies are expensive and logistically challenging

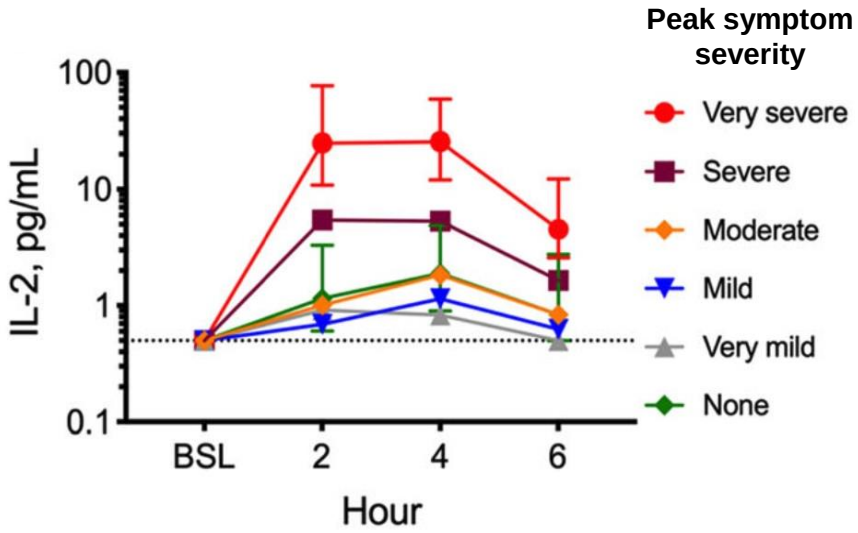
→ Is there a better/easier way?

A novel approach to detect the gluten-specific T cell

- Striking cytokine elevation in coeliac patients after injection of gluten peptides *(Goel et al, Lancet Gastro Hep 2017; Tye-Din et al, Lancet Gastro Hep 2023)*
- After single-dose ORAL gluten challenge, similar significant increase in cytokines in blood 2-4 hours later, dominated by interleukin-2 *(Goel, Science Advances 2019; Zuhlke, UEGJ 2019; Cartee, Am J Gastro 2022)*
- Earliest, most sensitive marker of gluten exposure compared to histology, ELISpot etc *(Leonard, Gastroenterology 2021)*
- IL-2 is a marker of gluten-specific T cell activation as it is produced by T cells stimulated by gluten

Ultrasensitive cytokine evaluatic

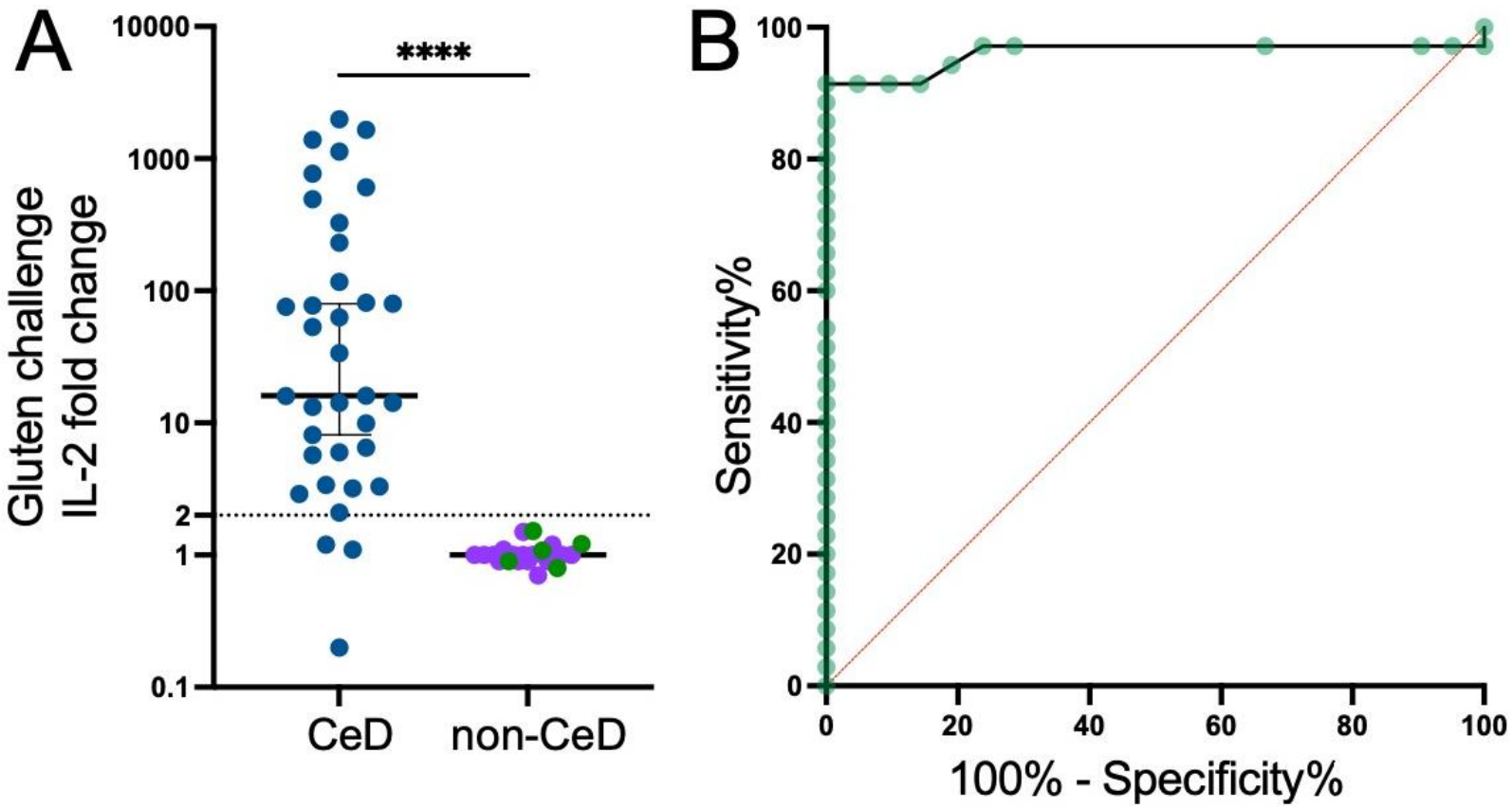
- IL-2 elevation after gluten is a **biomarker for gluten-induced symptoms**



- 295 adults with coeliac disease had open-label gluten challenge (10 g vital wheat gluten)
- Peak symptom severity at 3 h; nausea and vomiting hallmarks of more severe reactions

Tye-Din et al, BMC Med 2020

IL-2 elevation after gluten is sensitive and specific for coeliac disease

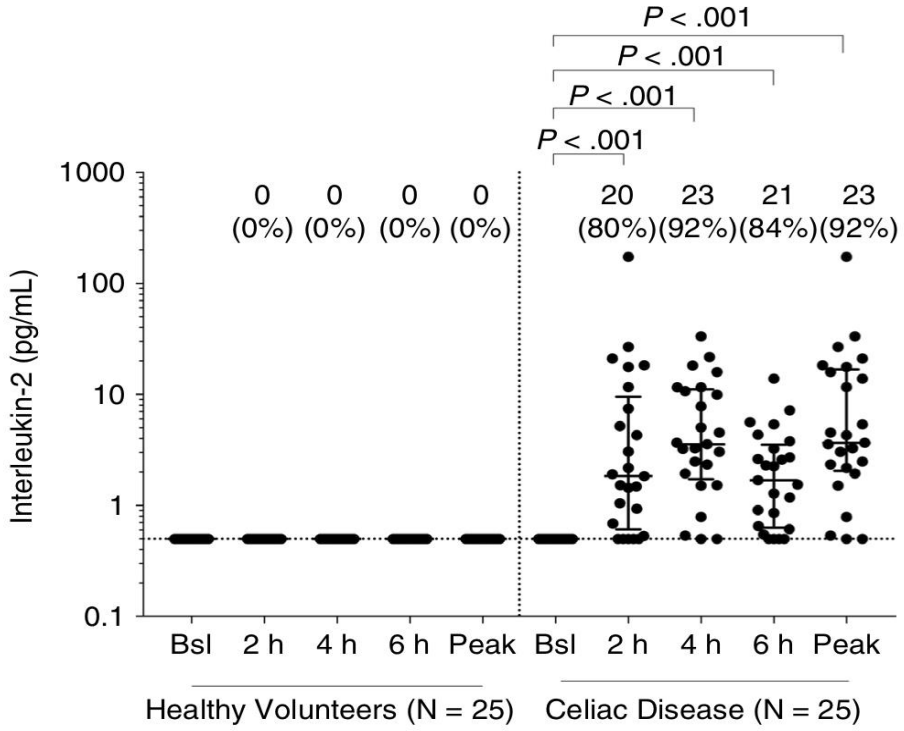


- **97% sensitivity**
- **100% specificity** for CeD

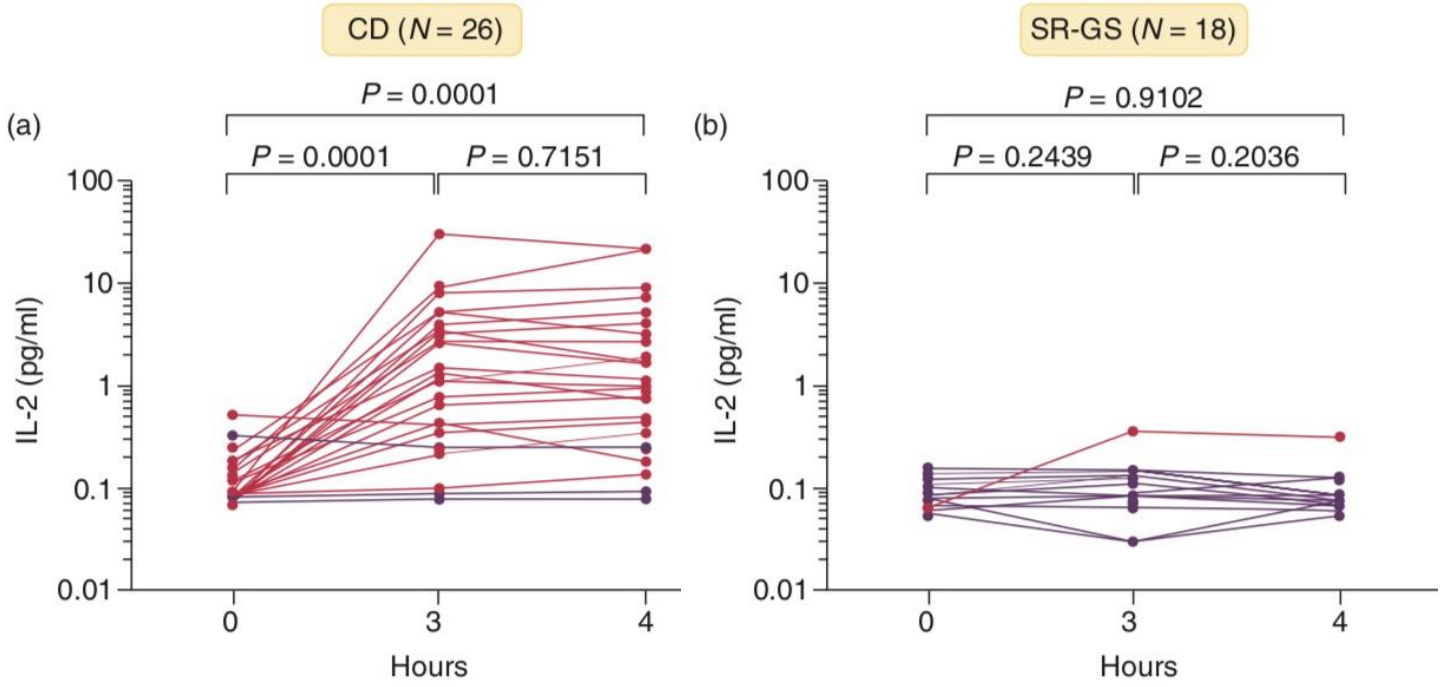
- **AUC=0·96**, p<0·0001, 95% confidence interval (CI) 0·9–1·0

Moscatelli et al, Gastroenterology 2025 (in press)

Potential role as a diagnostic test for coeliac disease

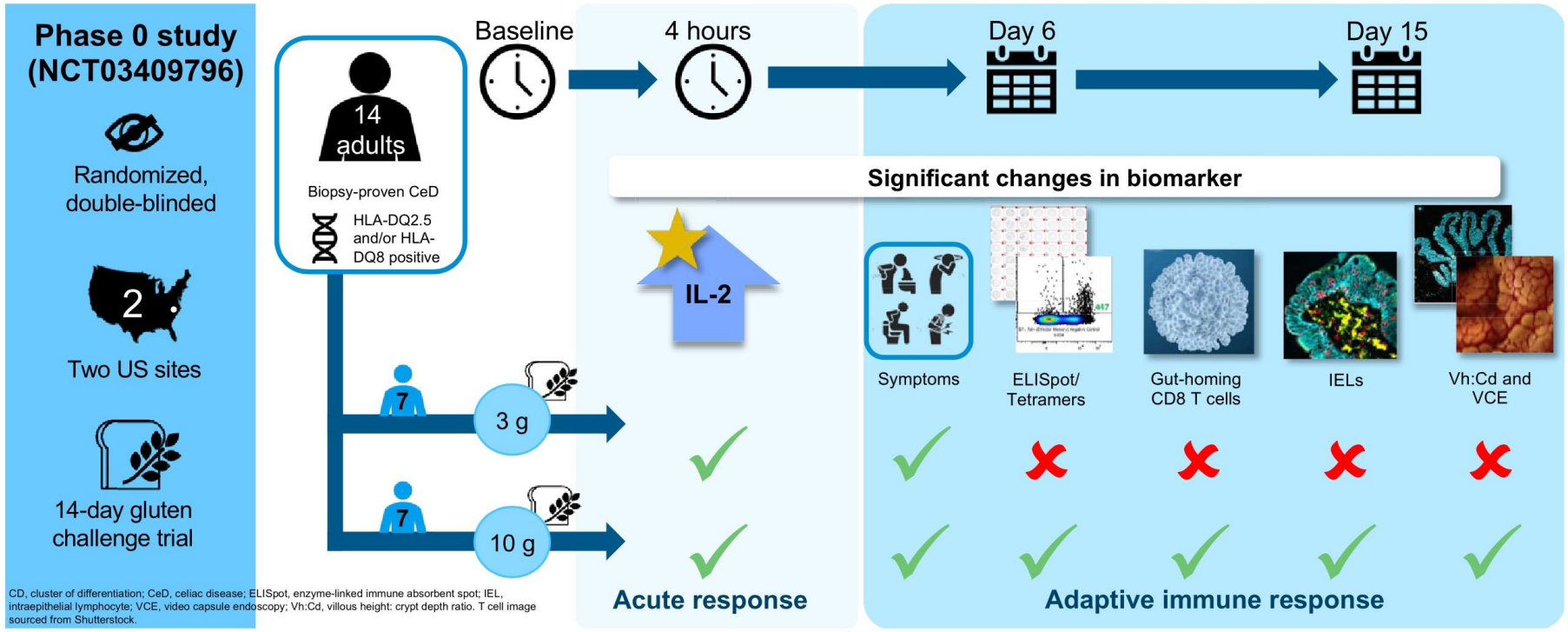


Tye-Din et al, Aliment Pharmacol Ther 2019



Tye-Din et al, United European Gastro J 2019

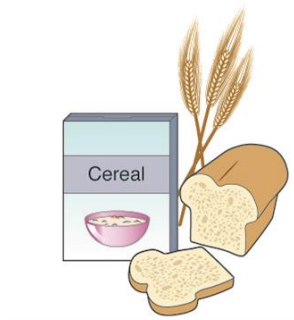
Evaluating Responses to Gluten Challenge:
A Randomized, Double-Blind, 2-Dose Gluten Challenge Trial



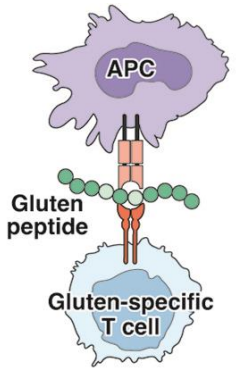
- Interleukin-2 (IL-2) response consistently measurable with low-dose gluten challenge
- Potential as an immune endpoint and symptom biomarker

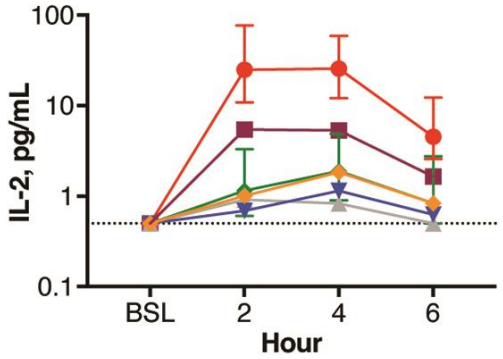
From *Leonard & Silvester et al, Gastroenterology 2021*

Acute cytokine response to gluten correlates with symptoms

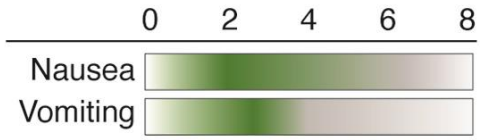


Gluten challenge in people with treated CeD





Gluten-specific T cell activation and acute interleukin-2 and cytokine/chemokine response

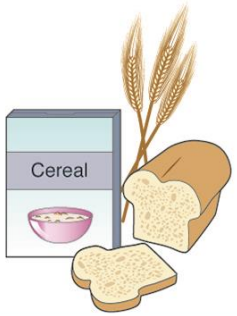


Acute response:

- **Asymptomatic (~20%)**
- **Symptomatic (~80%)**
  - Nausea, vomiting, diarrhea, abdominal pain, bloating, lethargy, headache, brain fog

Adams et al, Gastroenterology 2024

Towards a mechanistic understanding of symptoms



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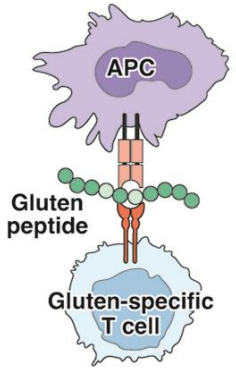

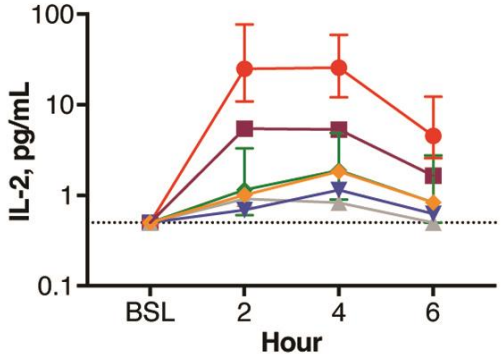

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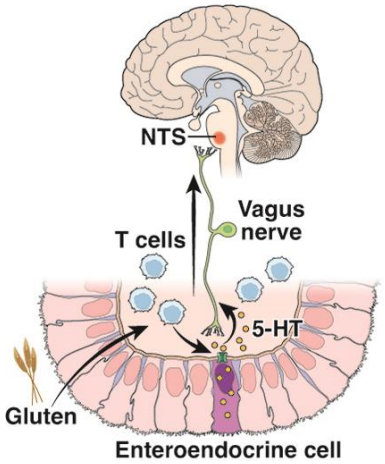
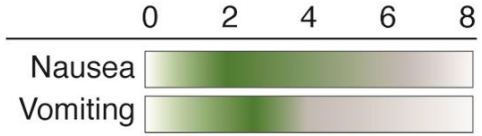


Postulated neuro-enteric effects triggered by interleukin-2 leading to release of symptom mediators such as serotonin



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Adams et al, Gastroenterology 2024

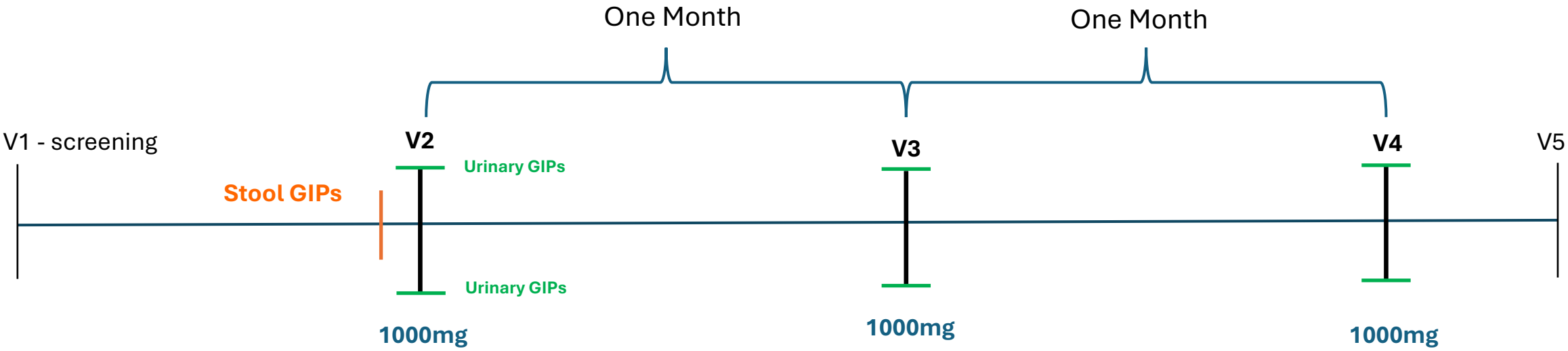
Gluten Threshold Study

A double-blind, placebo-controlled, adaptive dose-response study to assess the acute effects of gluten in adults with treated coeliac disease

- James Daveson and team at Wesley Medical Research (QLD)
- Michelle Colgrave and team (ECU)
- Jason Tye-Din and team at WEHI
- Bob Anderson (QLD)

Adaptive dose-response study

Cohort 1 (n=6)

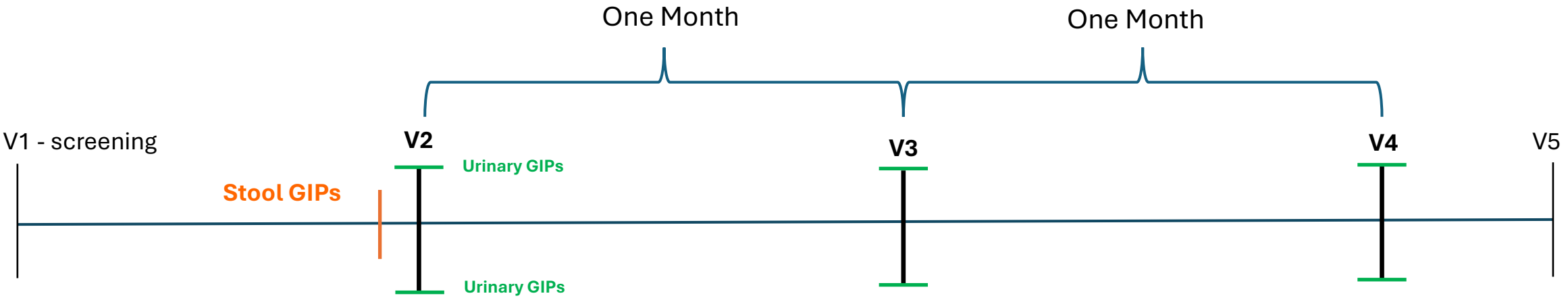


Serum IL-2 at 0, 2, 4, 6 hours | Serum IL-2 at 0, 2, 4, 6 hours | Serum IL-2 at 0, 2, 4, 6 hours

CD Serology

Hourly PRO | Hourly PRO | Hourly PRO

Cohorts 2-4 (n=15 each cohort)



610mg, 90mg, 13mg or Placebo
8mg, 5mg, 3mg or Placebo
3mg, 2mg, 1mg or Placebo

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610mg, 90mg, 13mg or Placebo
8mg, 5mg, 3mg or Placebo
3mg, 2mg, 1mg or Placebo

CD Serology

Hourly PRO | Hourly PRO | Hourly PRO

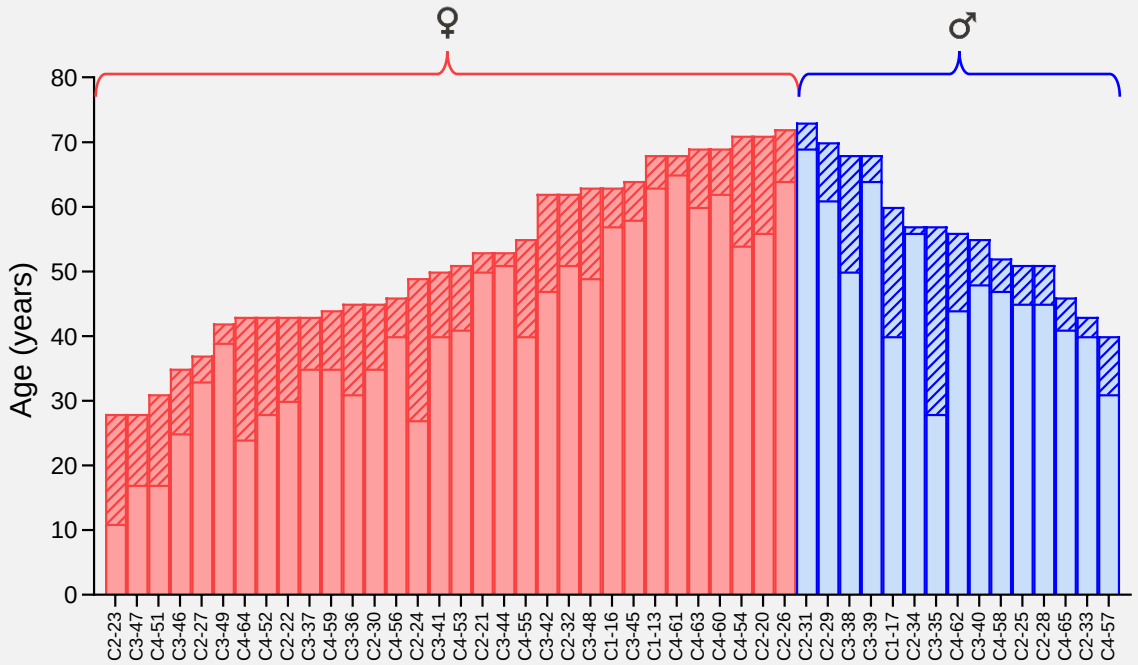
Randomised dosing plan

	Cohort 1				Cohort 2				Cohort 3				Cohort 4		
	V2	V3	V4		V2	V3	V4		V2	V3	V4		V2	V3	V4
C12	1000	1000	1000	C20	13	0	90	C35	0	8	5	C51	1	0	2
C13	1000	1000	1000	C21	13	90	610	C36	3	5	8	C52	2	1	3
C16	1000	1000	1000	C22	610	0	13	C37	8	5	0	C53	1	0	3
C17	1000	1000	1000	C23	610	13	90	C38	5	8	3	C54	0	1	3
C18	1000	1000	1000	C24	13	610	90	C39	5	3	8	C55	2	1	3
C19	1000	1000	1000	C25	13	610	90	C40	8	0	3	C56	0	2	3
				C26	13	0	90	C41	3	5	0	C57	3	0	2
				C27	0	90	610	C42	0	8	3	C58	3	0	2
				C28	90	610	13	C44	5	3	8	C59	2	3	1
				C29	90	0	610	C45	8	5	3	C60	2	1	3
				C30	610	0	13	C46	8	3	0	C61	3	2	1
				C31	90	0	610	C47	0	5	8	C62	1	0	3
				C32	13	610	0	C48	3	0	5	C63	0	2	1
				C33	90	13	13	C49	3	5	0	C64	2	1	3
				C34	13	90	610	C50	5	8	3	C65	0	2	1

1,ooomg	610mg	90mg	13mg	8mg	5mg	3mg	2mg	1mg	Placebo

- Total of 51 participants (153 individual doses)
- 73 different dosing variations allowing for investigation of roll over effect

Demographics

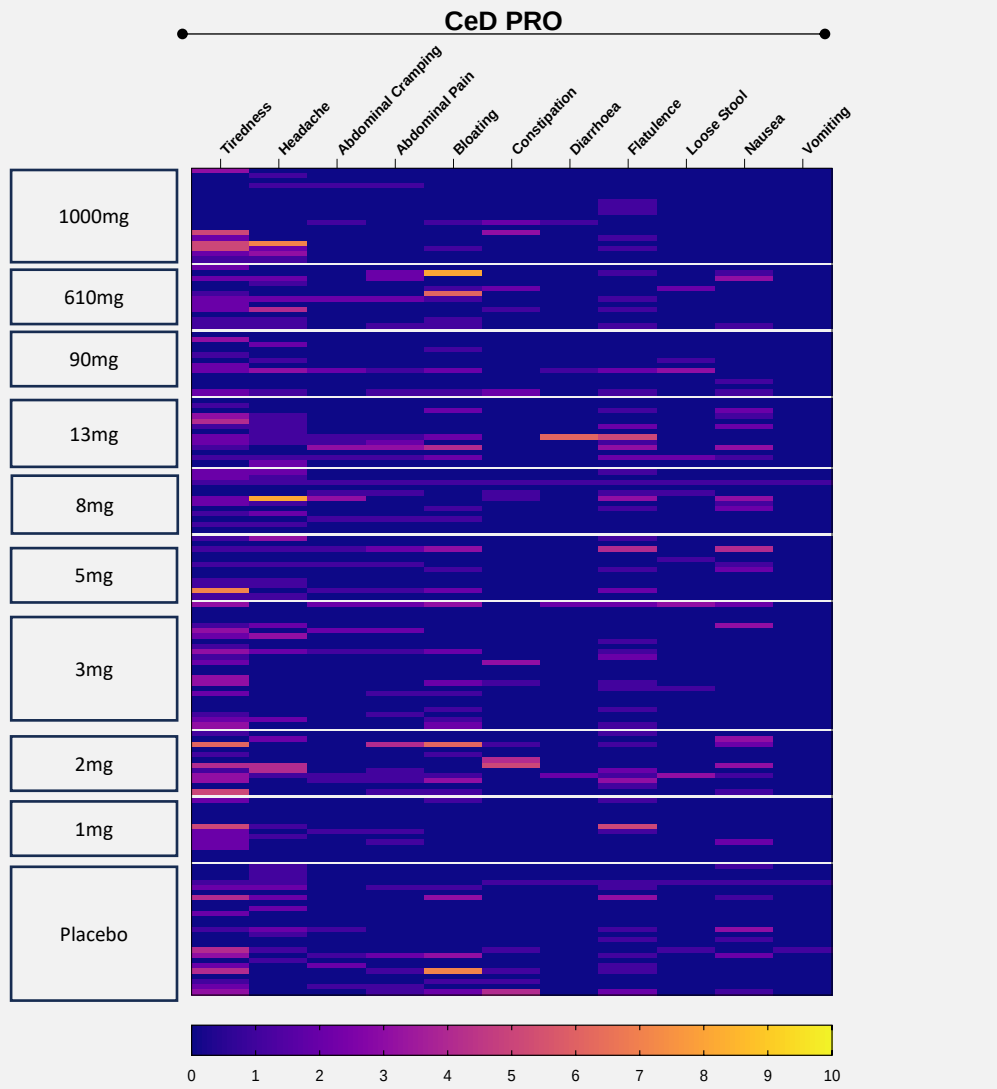


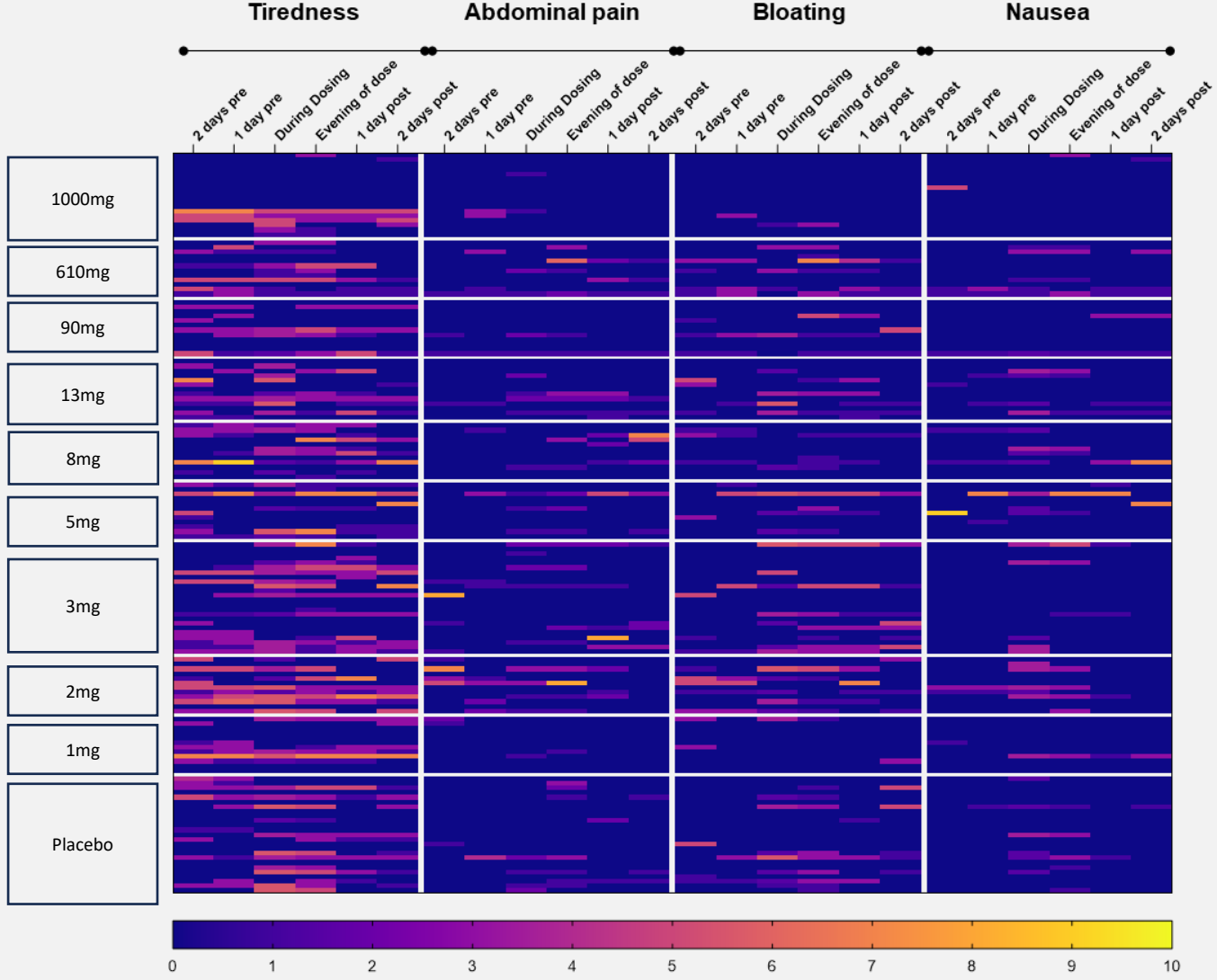
- Shaded portion = years since diagnosis
- F:M= 2.2:1

	Years	Females	Males
# participants		37	14
% participants		68.9	31.1
Median Age	53.09	51.26	56.80
1st Q	43.85	43.37	51.31
2nd Q	53.09	51.26	56.80
3rd Q	64.73	64.20	68.53
IQR	20.88	20.83	17.22
Minimum	28.65	28.65	40.41
Maximum	73.20	72.66	73.20
Range	44.55	44.01	32.79
	Total		
HLA-DQ2.2	**14/51**	**12/37**	**3/14**
HLA-DQ2.5	**42/51**	**29/37**	**11/14**
HLA-DQ8	**12/51**	**7/37**	**4/14**

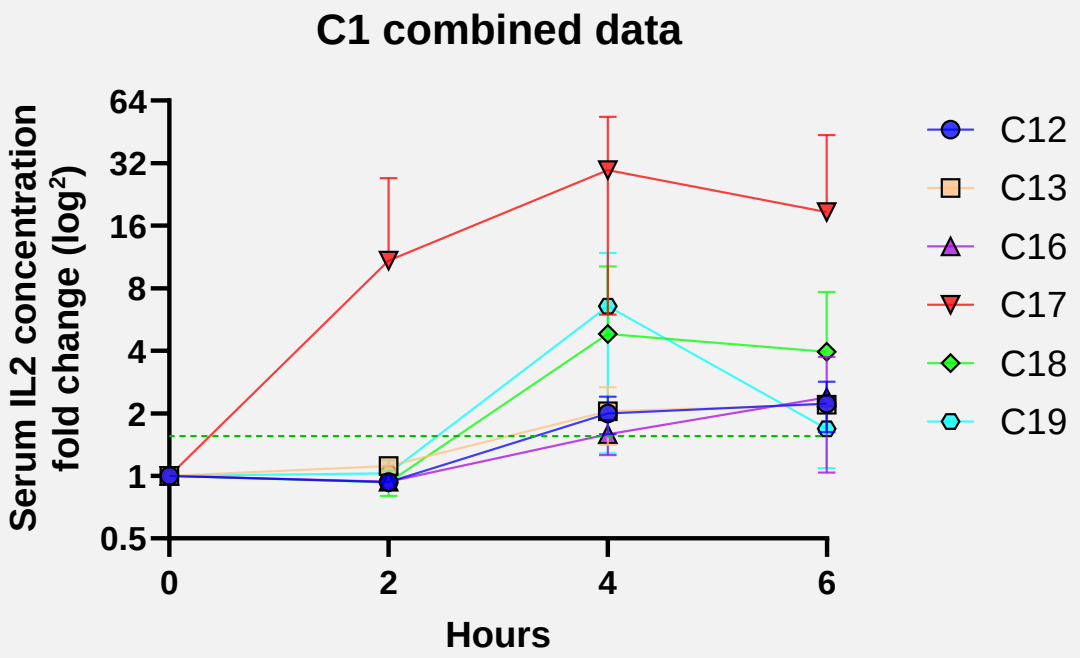
Coeliac Disease Patient Reported Outcome Measures

- No observed difference in symptoms between placebo and lower doses of gluten exposure



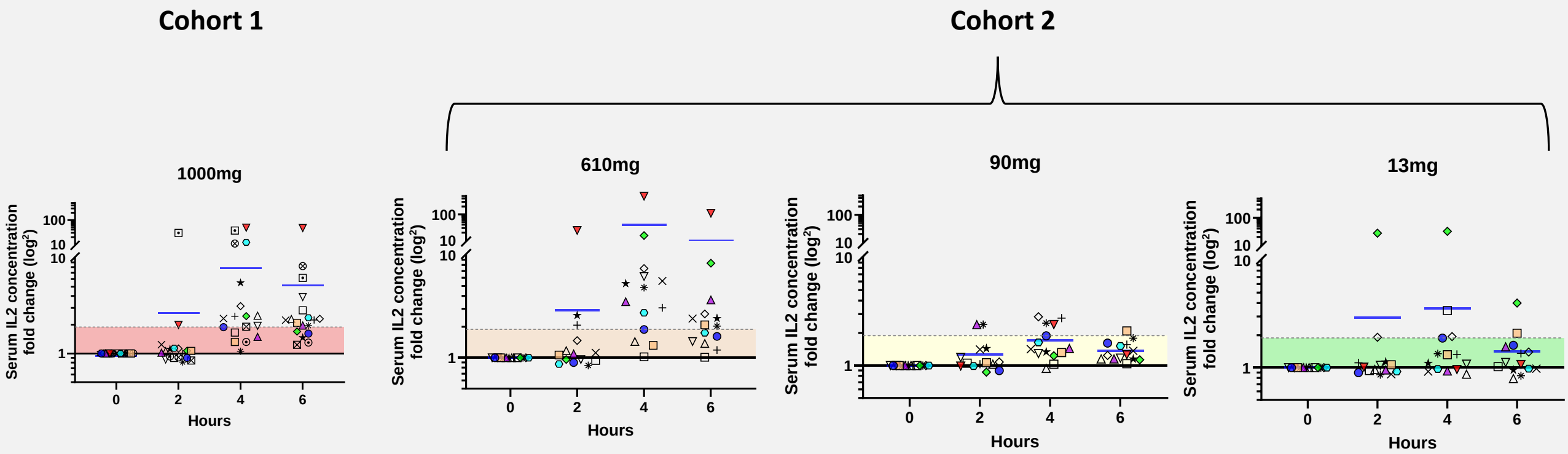


Cohort 1: Combined IL-2 response at 2, 4 & 6 hours



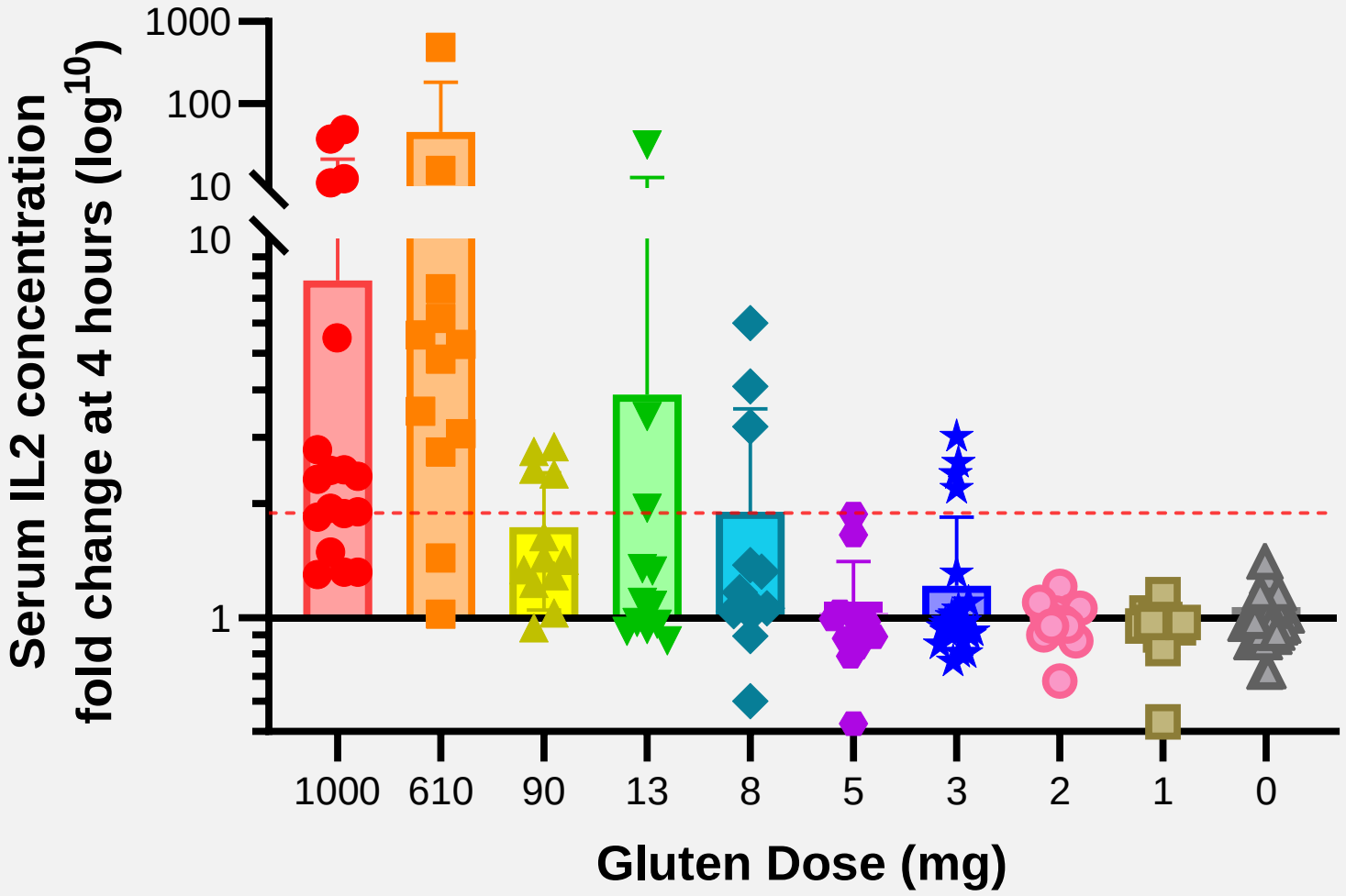
Log2 positive fold change:
1.89362 (dotted line)

Cohorts 1 & 2: Combined IL-2 response at 2, 4 & 6 hours



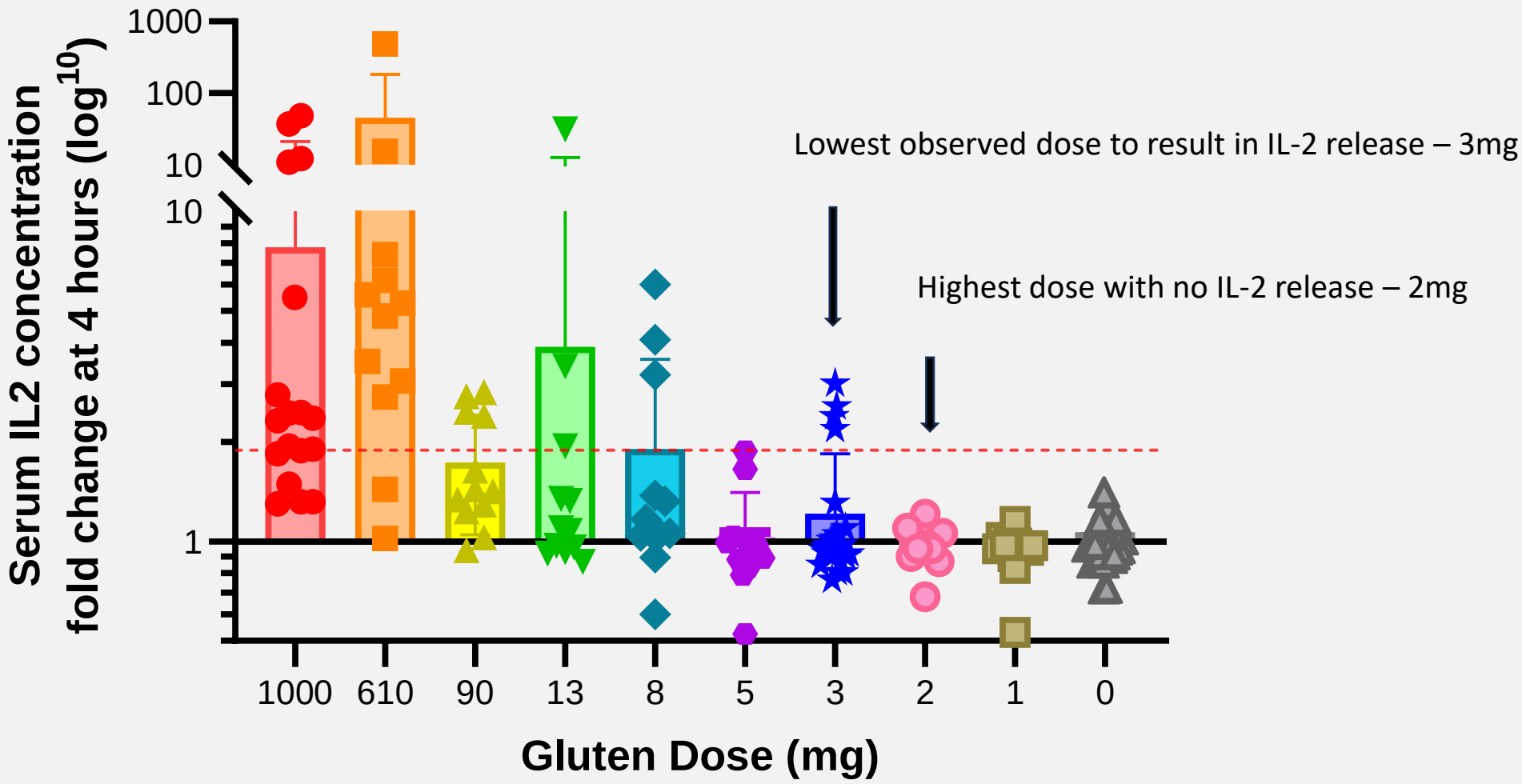
Log2 positive fold change:
1.89362 (dotted line)

Combined cohorts 1-4 (all) IL-2 at 4 hours

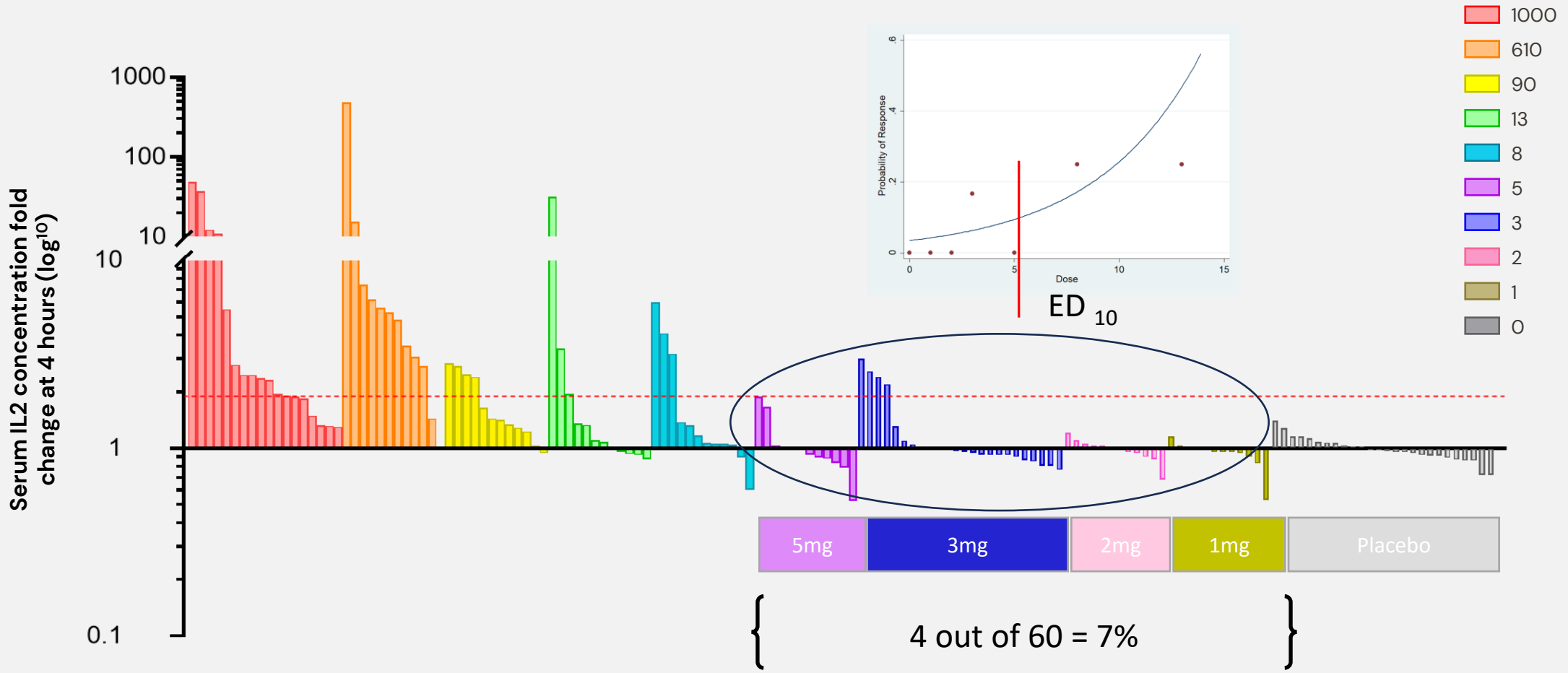


VWG Dose (mg)	# participants	"Log2 +ve" fold change: +ve responders	"Log2 +ve" fold change: % responders
1000	18	12	67%
610	12	10	83%
90	12	4	33%
13	12	3	25%
8	12	3	25%
5	12	0	0.0
3	24	4	17%
2	12	0	0.0
1	12	0	0.0
0	26	0	0.0

Combined cohorts 1-4 (all) IL-2 at 4 hours



Towards an ED05 for gluten

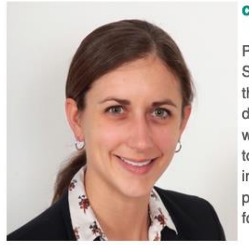


ISSCD
International Society for the Study of Celiac Disease

Gluten Safety & Standards Committee

co-Chair: Prof Jason Tye-Din (Australia)

Associate Professor Jason Tye-Din is an adult gastroenterologist who heads the Coeliac Research Lab in the Immunology Division of the Walter and Eliza Hall Institute, Melbourne, Australia. His research focuses on examining the basis for gluten immunity to improve the diagnosis, treatment and management of people with coeliac disease. In addition to research he runs a dedicated coeliac disease clinic at the Royal Melbourne Hospital and chairs the Medical Advisory Committee of Coeliac Australia, working closely with them to promote evidence based practice and medical and public awareness of coeliac disease.



co-Chair: Prof Katharina Scherf (Germany)

Prof Katharina Scherf leads a team at the TUM School of Life Sciences, Germany. Prof. Scherf's main research interests are the protein composition of food crops as well as wheat related disorders including celiac disease and wheat allergy. Together with her team, her mission is to develop new analytical strategies to study the complex interplay between structure, functionality, immunological and chemosensory activity of food proteins and peptides. The fundamental insights help to improve food security, food quality and food safety..

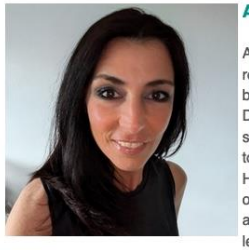
She leads the research group Food Biopolymer Chemistry at the Leibniz Institute for Food Systems Biology at the TUM and also holds the Professorship of Food Biopolymer Systems at the TUM.

Carlo Catassi

Carlo Catassi, MD, is professor of pediatrics at the Polytechnic University of Marche, Ancona, Italy and adjunct faculty at the Massachusetts General Hospital, Harvard Medical School, Boston, USA. He is past president of the Italian Society for Pediatric Gastroenterology and Nutrition (SIGENP) and scientific consultant for the Instituto Superiore di Sanità in Rome, Italy, for the D1Ce pilot study on pediatric screening for celiac disease and type 1 diabetes. His primary research interests are celiac disease and other gluten related disorders, particularly the worldwide epidemiology, the clinical spectrum, pediatric screening and safe threshold of gluten intake.

Ludvig Sollid

Ludvig Sollid is a Professor at the University of Oslo and a senior consultant at the Oslo University Hospital - Rikshospitalet. Also director of the KG Jebsen Coeliac Disease Research Centre, Norway. Professor Sollid's research interests are focused around genetics and immunology of autoimmune diseases in general and celiac disease in particular. His group has made important contributions to the understanding of the molecular basis of celiac disease, in particular the role of HLA genes, the existence of gluten reactive (HLA-DQ restricted) T cells in the celiac intestinal lesion, the identification of immunotoxic gluten peptide sequences and the involvement of the transglutaminase 2 in the pathogenesis of the disease. His group is currently working on the characterization of the antigen receptors of T cells and B cells that recognize the celiac disease relevant antigens gluten and transglutaminase 2.

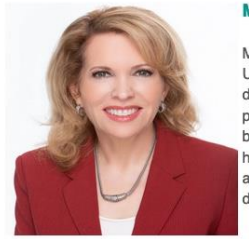


Alessandra Costigliola

Alex Costigliola, MSc, is an accomplished scientific and regulatory affairs professional with a background in dietetics, bringing nearly two decades of expertise within the food industry. During her career, defined by a blend of technical expertise and strategic advocacy, she has consistently provided critical insights to support the review of relevant legislation and guidance. As the Head of Food Policy at Coeliac UK, Alex champions the interests of individuals with celiac disease, striving to ensure their needs are accounted for in regulations at both national and international level. In addition to her policy work, she oversees the UK Gluten Free Accreditation scheme within the hospitality sector, helping to raise standards and ensure a safe dining experience for celiac consumers.

Penny Dellsperger

Penny, is an Accredited Practising Dietitian, she has dedicated nearly 20 years to Coeliac Australia, leading the organisation's policy, advocacy, research, and knowledge translation efforts. Her lived experience with celiac disease fuels her commitment to empowering those affected by the condition. She provides expert, evidence-based support to Coeliac Australia's education and advocacy programs, while working closely with the food industry, legislators, and enforcement bodies to champion consumer focused food policies.



Marilyn Geller

Marilyn G. Geller is the CEO of the Celiac Disease Foundation, USA where she has led the organization's efforts for over a decade to accelerate research, improve diagnosis, and enhance patient support for the millions affected by celiac disease. With a background in health technology and patient advocacy, Marilyn has been a pioneering voice in advancing patient centric research and forging strategic collaborations to drive progress in celiac disease treatment and potential cures globally.

Markus Lacorn

Markus Lacorn is a Research & Development department Head Deputy, overseeing all internal and external validation studies on R-Biopharm products from the food & feed area. His interdisciplinary team works collaboratively to validate products prior to launch.

He also works for and within various approval bodies such as AOAC and ICC to achieve external certifications for R-Biopharm products and represents the perspective of method developers within key groups such as AOAC, ICC, Eurachem, OIV, ISO, CEN, DIN, and Codex Alimentarius. For nearly two decades, Markus has belonged to an international network on allergen and gluten analysis which seeks to improve the quality of life of patients.

Dan Leffler

Daniel Leffler, MD, MS, AGAF is a gastroenterologist caring for patients with celiac disease and other gastrointestinal disorders and is a founding member of the Celiac Center at Beth Israel Deaconess Medical Center. He is an associate professor of medicine at Harvard Medical School, has received multiple National Institute of Health, foundation and industry sponsored grants and has published over 200 articles in peer reviewed literature. Dr Leffler joined Takeda Pharmaceuticals in 2016 where he serves as the global clinical lead for celiac disease.

Jacqueline Pante

Jacqueline Pante has been the Global Director Nutrition Service at Dr Schär for nearly 30 years. Aiming to become a vet, she jumped during her studies into the fascinating world of nutrition and dietetics. With a team of dietitians, nutritionists and other professionals, she is connecting healthcare professionals (HCP), patient advocacies and retailers within the food industry. Focused on identifying evidence based solutions and strategies to promote awareness and knowledge of gluten related disorders. An ultimate aim to connect and bring back "joie de vivre" to patients and create accessible information for HCPs to master the diagnosis of gluten related disorders and the gluten free diet.

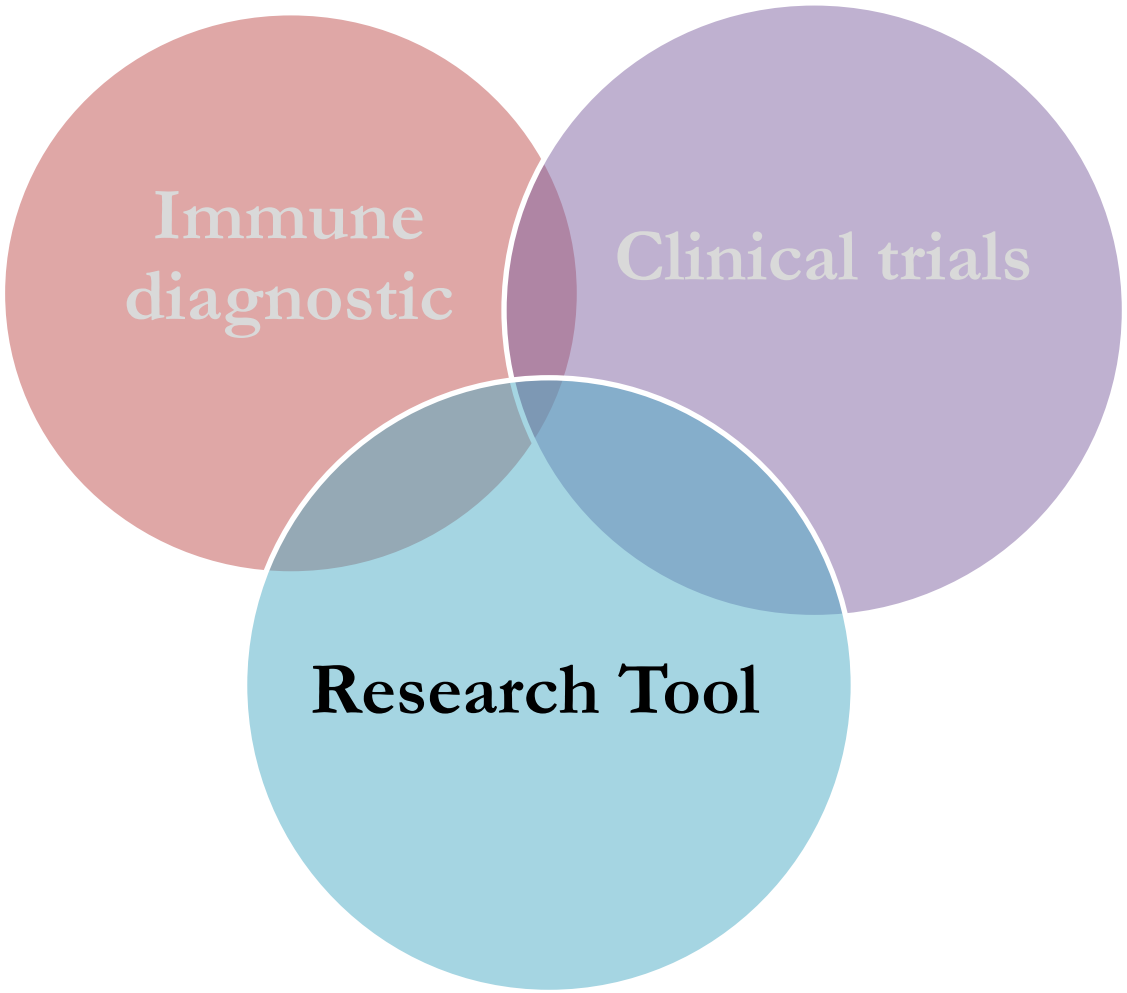
Jennifer Sealey-Voyksner, PHD

Jennifer is an analytical chemist and entrepreneur. She has more than 30 years of experience in government and industry-based R&D, traversing pharmaceutical, food and environmental sciences. She is a pioneering mass spectrometrist focused on allergenic protein marker discovery and analysis. She received her honors B.Sc. in Chemistry from McMaster University, Canada and her MSc and Ph.D. in analytical chemistry at the University of North Carolina at Chapel Hill.

Most recently she served as SVP for R&D for Entero Therapeutics. Previously, she co-founded and served as Chief Scientific Officer for ImmunogenX and co-founded and served as Senior Director for R&D for LCMS Limited in North Carolina, an independent analytical laboratory.

Jennifer was diagnosed with celiac disease in 2002. Since her diagnosis, she has dedicated both her professional and personal lives to bettering the lives of those who suffer from food-related diseases.

Implications of our novel cytokine release platform



Evaluation of other diseases e.g.

- Type 1 diabetes (*Lacorcia et al, Science Transl Med* 2025)

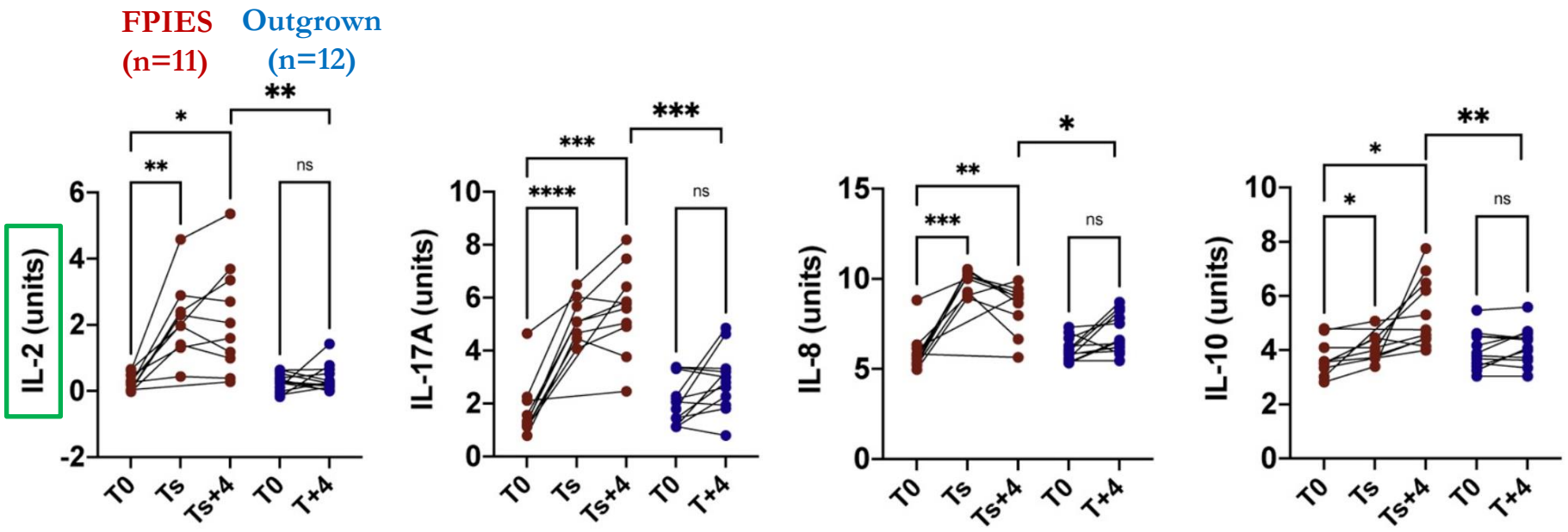
& other autoimmune disease

- Cancer
- COVID-19 & other infections
- Transplantation immunology
- **Food allergy (IgE and non-IgE)**

→ Food challenge platform

- Study underway

Children with FPIES show similar acute cytokine responses after offending food challenge



- FPIES children aged 1.5-16 years
- Oral food challenge (milk, rice, wheat, fish, prawn)

Berin et al, JACI 2021

Acknowledgements

All the volunteers who take part in our research

Coeliac (Tye-Din) Lab

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ICDS International Celiac Disease Symposium

Melbourne, Australia 17 – 20 Nov 2026

THE GLUTEN-FREE DIET AND BEYOND • TOWARDS NEW TREATMENTS

SAVE -THE- DATE

ISSCD International Society for the Study of Celiac Disease