Case three: Thomas

Flow cytometry, IHC and TCR arrangement studies completed on small bowel biopsies = **Type 1 refractory coeliac disease.** CT/MRE did not show features of Enteropathy Assocaited T-cell Lymphoma EATL

Mistake #6: Misdiagnose RCD and other complications

	Type 1	Type 2
Severe villous atrophy	yes	yes
Autoimmune disorders	yes	no
HLA-DQ2 homozygosity	rare	common
Clonal TCR-γ/β gene rearrangement	+	++
Aberrant T-cell phenotype	≤10%IEL	≥50% IEL
Chromosomal abnormalities	no	yes
Ulcerative jejunoileitis	rare	common
Resp. to immunosuppress.	yes	no
Risk of EATL	low	60% in 5 yrs
Mortality rate	Slightly increased	5-yr survival <50%

A delayed diagnosis and a poor compliance to GFD increase the risk of complicated CD

van Gils T, Nijeboer P, et al., Nat Rev Gastroenterol Hepatol 2015; 12: 572-579

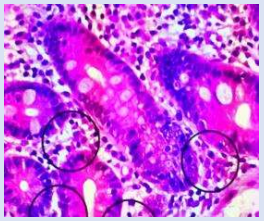
Table 1. Characteristics, therapeutic options and outcomes in refractory coeliac disease (RCD).

Condition	IEL phenotype	T-cell receptor clonality	Therapeutic options	Outcomes
Normal	>98% CD3+CD8+	Oligoclonal	N/A	N/A
Untreated coeliac	Increased numbers of γδ+TCR CD3+8+	Oligoclonal, transient clonal population may be present	Gluten-free diet (novel therapies including zonulin antagonists, oral endopeptidases and immunotherapy under trial)	Evidence to suggest overall reduced life expectancy
Type I RCD	As for untreated coeliac disease	As for untreated coeliac disease	Strict gluten restriction; oral steroid; budesonide; azathioprine; nutrition support	5-year survival 93%; progression to EATL 14% at 3 years
Type II RCD	>20% (by flow cytometry) or >40% (by immunohistochemistry) surface CD3-, intracellular CD3+, CD8+	Clonal TCR γ or β rearrangement	Strict gluten restriction; cladribine; ASCT	5-year survival 44–58%; progression to EATL 33–67% at 5 years

ASCT, autologous stem cell transplantation; EATL, enteropathy-associated T-cell lymphoma; IEL, intra-epithelial lymphocyte; TCR, T-cell receptor.

Non-coeliac gluten sensitivity NCGS

Onset of **gastrointestinal/extra-intestinal symptoms** following **consumption of gluten-containing foods** in individuals **without coeliac disease or IgE mediated wheat allergy**



Subset will have **subtle duodenal eosinophilia**
(as do subset of functional dyspepsia)
No reliable biomarker

Up to half self reported NCGS fulfil Rome criteria for functional GI disorder (e.g. IBS, functional dyspepsia)

Double-blind wheat challenge testing in self reported NCGS

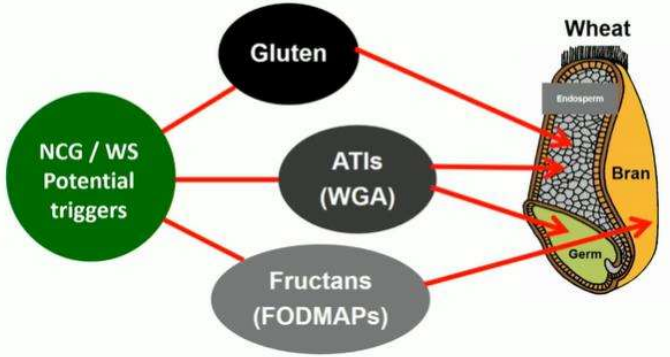
- <1/5 actually has sensitivity to wheat
- Many NCGS improve on wheat exclude actually from fructan (FODMAP) intolerance
- 2/5 respond to placebo – non-gluten physiological reaction – somatoform ill

Complete GFD not healthier and NOT required unless Coeliac disease!

	Celiac disease	Non celiac gluten sensitivity	Wheat allergy
Prevalence	0,5-1% of population; it has been duplicated in the last 20 years	There are no population studies. 20-40% of patients with irritable bowel syndrome	0,5-9% in children
Pathogenia	Autoimmune. Acquired immunity. Gastrointestinal and systemic inflammatory reaction.	Innate immune response	Type I and IV hypersensitivity (type I reactions are better characterized)
Most frequent gastrointestinal symptoms	Abdominal pain Constipation or chronic diarrhea. Abdominal distension	Abdominal pain Chronic diarrhea Abdominal distension	Vomits, diarrhea immediately after wheat ingestion

Non-celiac gluten / wheat sensitivity (NCG/WS): A 'mixed bag' with many potential culprits...

...wheat contains gluten and non-gluten proteins as well as FODMAPs...



Volta U & De Giorgio R., Exp Rev Gastroenterol Hepatol 2017, 11:9-18

Q: Which of these statements are incorrect?

1) There is an overlap between NCGS and functional GI disorders
2) **There is no risk to being on a gluten free diet as it is considered healthy**
3) There are no easily obtainable biomarkers to test for NCGS
4) A subset of NCGS have subtle duodenal eosinophilia
5) There is no established criteria for the diagnosis of NCGS

Regular follow-up is recommended

Follow-up is typically more frequent in the first year following a diagnosis of coeliac disease, e.g. ideally every three to six months, while the patient is becoming established on a gluten-free diet.[1, 28] Initially, this may be with the gastroenterologist, but for most patients, ongoing follow-up occurs in primary care. Once the patient is successfully established on a gluten-free diet and symptoms have resolved, reviews can be conducted annually.[1] People with coeliac disease should also be reviewed during pregnancy.

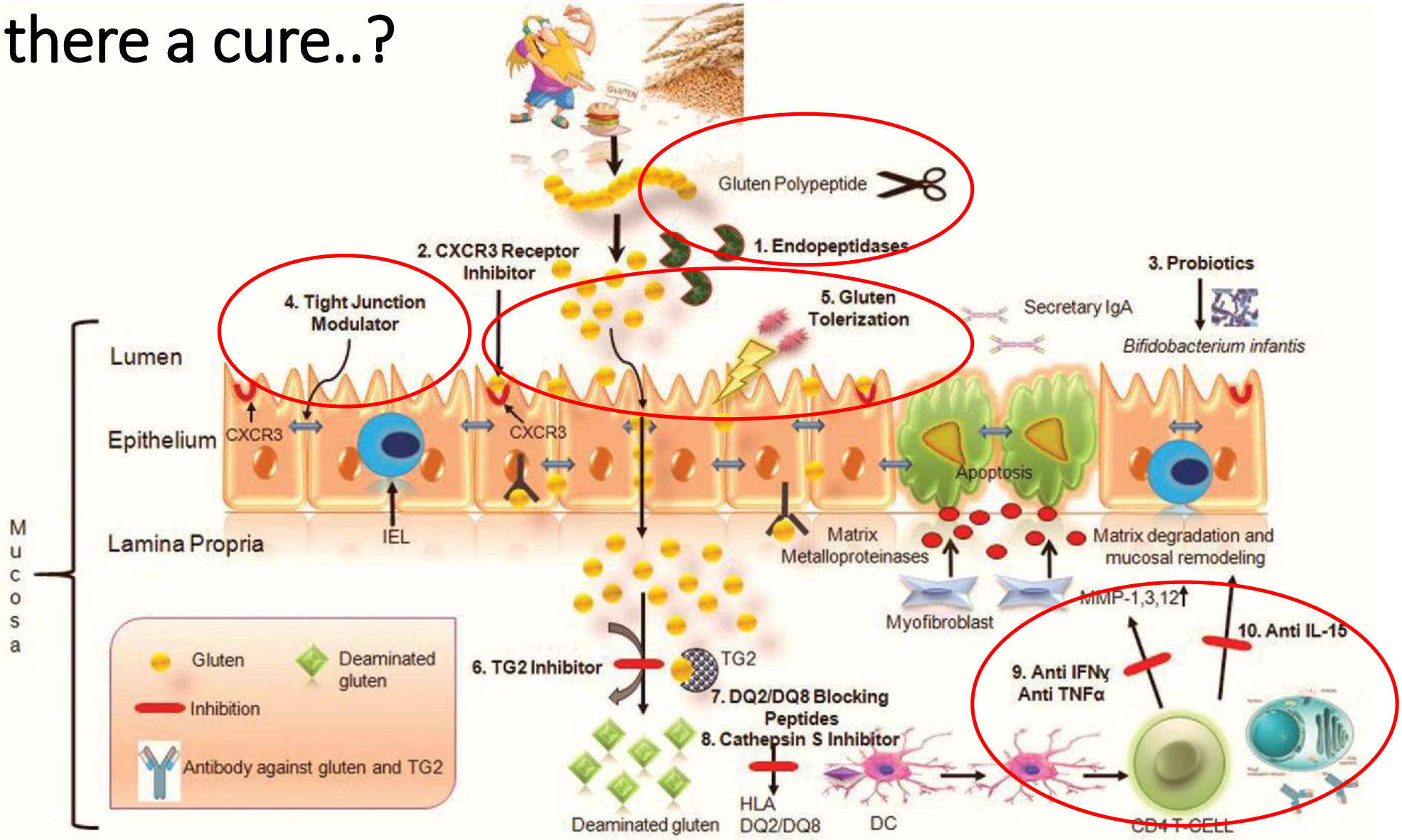
Suggested approach to follow-up appointments:[1, 9]

- Check BMI or monitor growth in children
- Ask about any persistent or new symptoms. If indicated, perform a physical examination, e.g. abdominal palpation for any tenderness, mass or another abnormality.
- Check how the patient is coping with the gluten-free diet. If there are concerns about inadvertent exposure, repeat coeliac serology and consider re-engagement with a dietitian. Coeliac serology should be repeated after 12 months of a gluten-free diet regardless of symptoms.
- Repeat laboratory tests, e.g. ferritin, folate and vitamin B12, particularly if there were abnormal biochemistries at diagnosis and if symptoms suggest, check for other laboratory evidence of autoimmune conditions, e.g. with LFTs, TSH. If nutritional deficiencies have not normalised or improved after one year of a gluten-free diet (or earlier as appropriate, e.g. older age), consider supplementation.
- Discuss ways to optimise bone health. Bone densitometry scans can be requested on a case-by-case basis, e.g. aged > 55 years or with additional risk factors for osteoporosis.[23]

Vaccination: People with coeliac disease should be vaccinated against pneumococcus (not funded) due to the increased risk of hyposplenism; the benefit of other vaccinations such as *Haemophilus influenzae* type b (not funded), meningococcus (not funded) and annual influenza vaccine (funded) to people with coeliac disease are less clear, although may be considered.[1, 28]

Recommendation
In adults, follow-up should be scheduled every 3-6 month during the first year and then every 1-2 yr
A normal TGA level at the follow-up does not predict recovery of villous atrophy
On the contrary, persistently positive serology 12 mo after starting a GFD strongly suggests gluten contamination
The follow-up should include at least a dietary interview, serology, and laboratory tests evaluating absorption.
Follow-up biopsy is not universally recommended but may be reasonable after 2 yr of GFD in high-risk patients
In children, follow-up should be scheduled every 3-6 mo during the first year and then every year until the end of development
Newly diagnosed patients should be referred to a dietitian for management
Primary care physicians or dietitians with experience in dealing with CD may take responsibility for the follow-up
Follow-up should also include periodical bone densitometry, vaccinations and psychological support

Is there a cure..?



Optimal
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We exist to improve everyday lives for current and future patients in need; contributing to knowledge and providing outstanding research experiences.

- A leading ISO 9001 quality certified Phase 1b-3 research centre in Asia-Pacific based in Auckland
- Commercial trials across various therapeutic areas
- Team of over 80 research professionals, specialist research doctors and consultants, dedicated to providing outstanding research experiences to patients
- Optimal's clinical team monitors participant’s health throughout the study, but the patient’s GP remains in charge of their overall care
- All clinical trials reviewed and approved by NZ’s HDEC and Medsafe
- Informed consent of patients is at the forefront of all research

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Insights

61% of New Zealanders say that health research is part of the solution to reducing health care costs

82% of New Zealanders are either somewhat interested or very interested in health and medical research

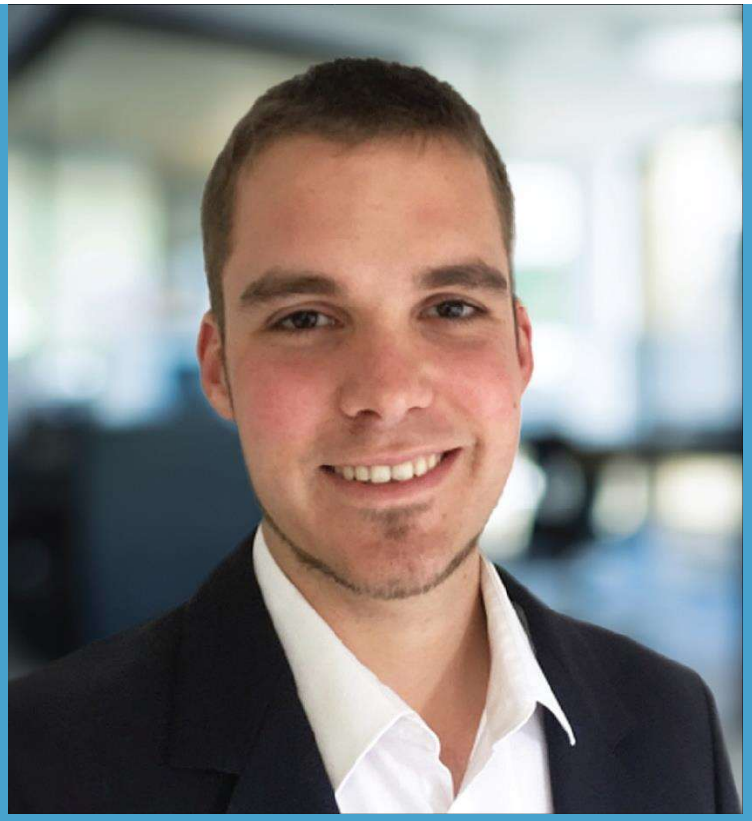
72% are willing to participate in a clinical trial for new medicine

Only 8% have participated in a clinical trial

Source: 2020 Kantar NZHR Opinion Poll

Coeliac Disease Treatment Studies

- Dr Falk - Coeliac Study CEC-4 and CEC-13
- Pfizer-Coeliac-Anokion-C5281001
- Takeda-Coeliac disease-TAK-101-2001



"I'm participating in a coeliac disease clinical study at Optimal because it's the right thing to do."

- Kenneth

- Currently, there is no approved cure
- Managing symptoms typically involves a strict gluten-free diet which can be hard and expensive to follow
- Affects around 1-2% of New Zealanders
- Impacting lifestyle choices and quality of life - can lead to malnourishment and other complications (osteoporosis, infertility, certain types of cancer, developmental delays in children)

Who can take part?

- Aucklanders 18 to 80 years (inclusive)
- Diagnosed with coeliac disease at least 12 months ago (Diagnosis made following a biopsy by a gastroenterologist)
- Adhered to a gluten-free diet for at least 12 months

What is the duration of the study?

- Several months
- Include visits to our Central Auckland or North Shore clinics

More information

- Clinical staff will monitor participant's health throughout the study
- Eligible volunteers required to undergo endoscopies and biopsies
- Some volunteers will be required to consume some gluten
- Female volunteers who are of childbearing potential will need to be on appropriate contraception to participate in the trial - also applicable to the female partner of a male participant
- Participants will be reimbursed stipend

For more information:

Go to bit.ly/optimal-coeliac **(please share with your patients)**

Or email:

Dr Penny Montgomery - Medical Director penny@optimalclinicaltrials.com

Dr Tina Baik – Principal Investigator tina@optimalclinicaltrials.c

optimalclinicaltrials.com
0800 73 73 27

Summary

- Clinical **presentations of Coeliac disease has changed** over time, often asymptomatic, minimal or atypical symptoms. *No longer just with diarrhoea, weight loss and malabsorption*

- **No universal protocol for gluten challenge;** *4x slices of wheat based bread or equivalent 4-8 weeks – Coeliac NZ*

- **Vigorous evaluation** should be applied before committing to the diagnosis of Coeliac disease
  - *Serology and small bowel biopsies*
  - *HLA-DQ2/DQ8 is a **rule out** test*

- **Serology is unlikely to be normal by 6 months** *and sometimes take up to 2-3 years to normalize.*

- **Mucosal healing can lag serological response**

- 7% of Coeliac patients have IgA deficiency. **DGP (deamidated gliadin peptides) IgG** would be the next step

- **Refractory Coeliac disease is rare** but associated with **poor outcomes**

- There are (often under recognized) **risks of being on a strict gluten free diet** and should be avoided unless there is a diagnosis of Coeliac disease

- **Clinical trials** will hopefully pave the way for a cure for this often under-recognized condition