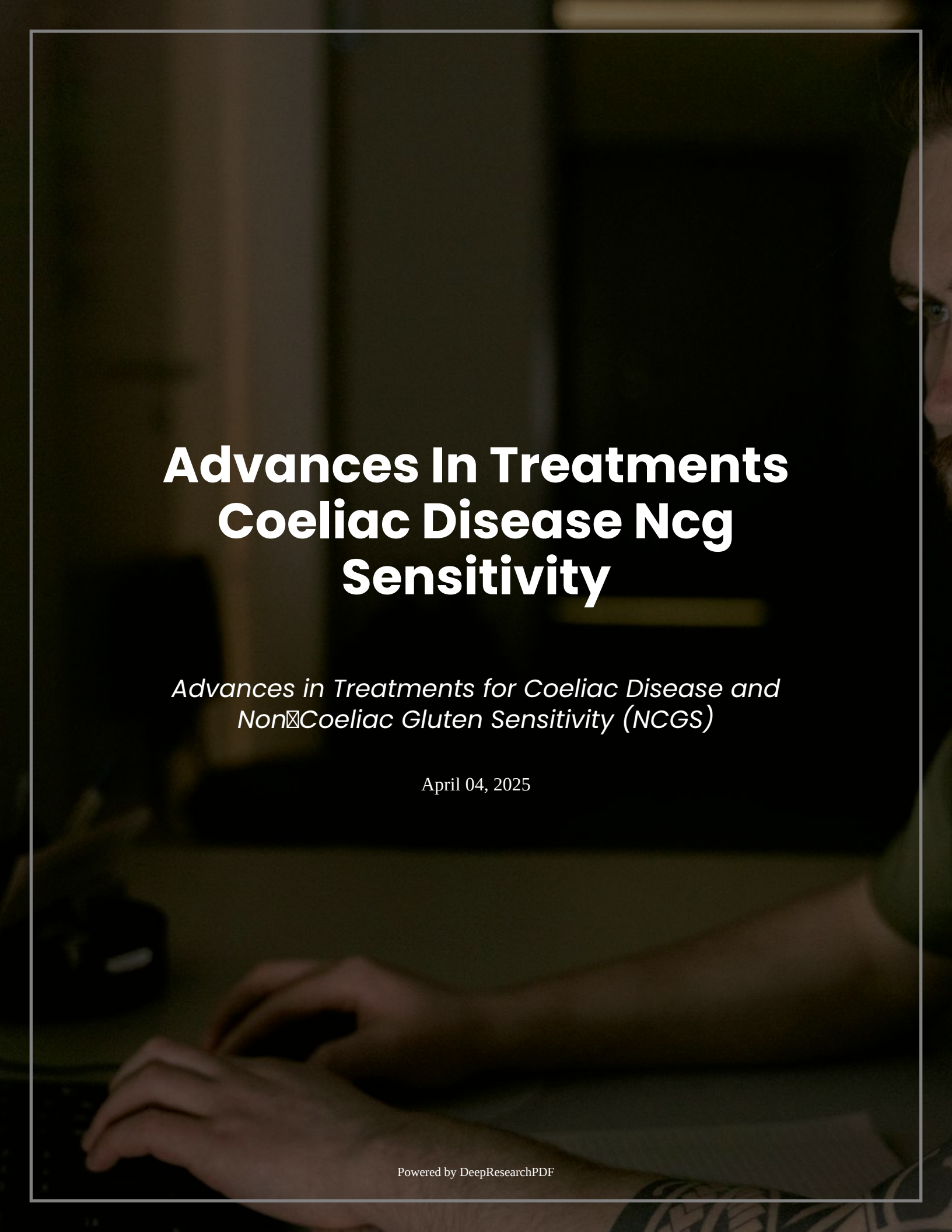

Advances In Treatments Coeliac Disease Ncg Sensitivity

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Introduction and Pathophysiological Differences

Coeliac disease (CD) is an autoimmune condition triggered by gluten (proteins in wheat, barley, and rye) in genetically susceptible individuals. In coeliac patients, specific gluten peptides (gliadins and glutenins) resist complete digestion and become deamidated by the enzyme tissue transglutaminase-2 (TG2) in the gut. These modified peptides bind to HLA-DQ2/DQ8 molecules on antigen-presenting cells, activating T-cells and causing an inflammatory cascade that leads to villous atrophy in the small intestine (New Hope for Celiac Disease: Promising Drug Shows Progress in Clinical Trials | Celiac Disease Foundation). This autoimmune reaction can cause malabsorption and serious complications (e.g. osteoporosis, anaemia, increased cancer risk) if unmanaged (Scientists pursue mRNA vaccines to stop celiac disease) (Scientists pursue mRNA vaccines to stop celiac disease). By contrast, **non-coeliac gluten sensitivity (NCGS)** – sometimes termed non-coeliac wheat sensitivity – is not an autoimmune disease and does not involve the same tissue-damaging immune response. NCGS patients experience gastrointestinal and extra-intestinal symptoms triggered by gluten/wheat ingestion, but without coeliac-characteristic villous damage or anti-transglutaminase antibodies. The mechanisms in NCGS remain partly unclear; gluten may provoke innate immune responses, and other components of wheat (such as FODMAP carbohydrates, amylase-trypsin inhibitor proteins (ATIs), and wheat germ agglutinin) are also implicated (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year

Narrative Review) (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review). ATIs, for example, resist digestion and can activate Toll-like receptor 4, inciting innate inflammation (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review). NCGS thus appears to involve a more **innate immune activation and gut–brain axis dysregulation** rather than the targeted adaptive autoimmunity seen in coeliac disease. Importantly, NCGS does not typically cause intestinal mucosal injury – any increase in intraepithelial lymphocytes or mast cells is mild, with **preservation of villous architecture** (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review).

Current management reflects these differences. **Strict, lifelong gluten-free diet (GFD)** is the only effective treatment for coeliac disease, necessitating complete avoidance of even trace gluten to prevent intestinal damage and complications ([

Beyond the gluten-free diet: Innovations in celiac disease therapeutics - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC11525874/#:~:text=dysregulated%20immune%20response,both%20quantitative%20strategies%20such%20as)). Adhering to a GFD is challenging and burdensome, affecting quality of life. In NCGS, a gluten-free or *low-gluten* diet is also the primary management, which typically alleviates symptoms. However, NCGS patients may not need to be as rigorously strict as coeliac patients, since small amounts of gluten usually do not cause lasting harm (though they can still trigger symptoms) (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review). Notably, some individuals labelled as NCGS might actually be reacting to non-gluten wheat components (e.g. FODMAPs), so dietary guidance may differ (for instance, a low-FODMAP diet might be beneficial in such cases – see later section).

- *Need for New Therapies: **In the past 3–5 years, there has been intensified research into treatments beyond the gluten-free diet for both conditions. For coeliac disease, the goals are to: reduce the immune reaction to inadvertent gluten (as an**

- **adjunct to diet), allow safer dietary freedom, or even induce lasting tolerance to gluten. For NCGS, which currently lacks any pharmaceutical interventions, research is exploring ways to manage symptoms or target possible underlying factors (e.g. microbiome or gut permeability). Below, we outline recent developments across three domains – pharmaceutical treatments, dietary innovations, and alternative/complementary therapies – noting which are aimed at** coeliac disease **versus** NCGS**, and highlighting key advances (especially those in clinical trials or nearing approval).

Pharmaceutical Treatments Beyond the Gluten-Free Diet

Research into non-dietary therapies for coeliac disease has produced a broad pipeline of drug candidates. These can be categorised by mechanism: **(1) Gluten-neutralising enzymes**, **(2) Gut barrier modulators**, **(3) Immune modulators and tolerance-inducing therapies**, and **(4) TG2 inhibitors**. Many of these are currently in clinical trials, offering hope that coeliac patients may soon have adjunctive medications to ease the burden of a strict diet (New Treatments for Celiac Disease Gain Traction - BioSpace) (New Treatments for Celiac Disease Gain Traction - BioSpace). It is important to note that **NCGS has no specific drug trials to date** – the pharmaceutical advances mentioned here are largely directed at coeliac disease's autoimmune pathway. However, a few (such as gluten-digesting enzymes) might also have utility for NCGS or other gluten-related disorders. Below we discuss each category and notable recent developments.

Gluten-Degrading Enzyme Therapies

One approach is to **break down gluten in the digestive tract** before it can trigger an immune response. Gluten is rich in proline/glutamine, making it resistant to normal human proteases (Frontiers | Beyond

gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Enzyme supplements ("glutenases") aim to supplement this deficiency.

- **Latiglutenase (ALV003/IMGX003):** Latiglutenase is an orally administered mixture of two recombinant proteases that specifically cleave gluten. It is designed to be taken with meals to digest gluten into smaller, non-immunogenic fragments. In a recent phase II trial (published 2022), latiglutenase showed promising results: during a 6-week gluten challenge in diet-adherent coeliac patients, those receiving latiglutenase had significantly less small-intestinal mucosal damage than those on placebo, as measured by villus height/crypt depth ratios (New Treatments for Celiac Disease Gain Traction - BioSpace). Symptom severity was also reduced. This indicates the enzyme can mitigate gluten-induced injury when small amounts of gluten are ingested (New Treatments for Celiac Disease Gain Traction - BioSpace). As a result, a phase III trial of latiglutenase in coeliac disease is slated to begin (early 2024) (New Treatments for Celiac Disease Gain Traction - BioSpace). If successful, this therapy could become an adjunct to a GFD, protecting against cross-contamination or occasional lapses. It is being positioned specifically for **coeliac disease** (to prevent relapse/injury), but could also potentially aid those with **NCGS** who want to minimise gluten in their diet, by degrading any ingested gluten.

- **AN-PEP (Aspergillus niger prolyl endopeptidase):** AN-PEP is another enzyme that can digest gluten peptides. It has been available as an over-the-counter supplement in some regions and has shown efficacy in **healthy volunteers** by accelerating gluten breakdown in the stomach ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=Another%20treatment%20option%20under%20investigation,symptoms%20or%20soaring%20food%20costs)). Recent controlled trials are investigating AN-PEP in gluten-sensitive individuals to see if it can protect the gut from gluten

exposure ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=Another%20treatment%20option%20under%20investigation,symptoms%20or%20soaring%20food%20costs)). If proven, AN-PEP or similar enzymes might be used by NCGS patients or coeliacs as a preventative measure when eating out, although they are **not a license to consume normal diets**.

- **Other Enzyme Therapies:** Takeda Pharmaceutical is developing an engineered glutenase called **TAK-062 (code name "zamaglutenase" or Kuma062)**. This enzyme was originally derived from a bacterial enzyme (engineered for high gluten activity). Takeda completed a phase II trial of TAK-062 in late 2024 (New Treatments for Celiac Disease Gain Traction - BioSpace). While detailed results are pending, this reflects the pharma industry's investment in enzyme treatments. Another product, **AMY02** (Amyra Biotech), is an enzyme cocktail in development intended to "quickly and comprehensively" degrade gluten during digestion (Future Therapies | Celiac Disease Foundation).

- *Applicability: **Enzyme therapies are primarily being trialled in** coeliac disease **– not to cure the disease but to serve as** adjuncts **to a GFD. The idea is to reduce mucosal damage from accidental gluten (e.g. hidden gluten in foods) and thereby prevent symptoms and long-term complications (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease) (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Notably, earlier large trials of latiglutenase had mixed results on symptoms and no histological benefit when patients were on a strict GFD (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). However, when challenged with moderate gluten intake,**

- **benefits became clear (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease) (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). This suggests enzymes could be useful in controlled gluten challenges or in real-world situations of minor gluten exposure. For** NCGS**, such enzymes could potentially alleviate symptoms by reducing the load of intact gluten reaching the intestine, although formal NCGS trials are lacking. An advantage is that these therapies are gut-restricted and non-absorbed (acting like digestive aids), so they have shown excellent safety so far (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease).

Gut Barrier Modifiers (Tight Junction Regulators)

Another therapeutic strategy is to **reinforce the intestinal barrier**, so that fewer gluten fragments cross into the lamina propria to incite the immune system. In coeliac disease, gluten can increase gut permeability (partly via the protein zonulin), which may exacerbate immune exposure. The prototype drug in this class has been **larazotide acetate**.

- **Larazotide Acetate (AT-1001):** Larazotide is an 8-amino-acid peptide that acts on tight junctions between intestinal cells, reducing paracellular permeability (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). By keeping the gut barrier “closed,” larazotide aims to block gluten from leaking into the tissue and thus dampen the immune trigger (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). In multiple phase II trials (totaling >600 patients), larazotide showed modest benefits: it significantly reduced the frequency of days with **GI symptoms** (like diarrhoea, bloating, abdominal pain) in coeliac patients undergoing gluten challenge,

- compared to placebo (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). However, it did **not prevent mucosal injury** or reduce inflammation markers in a meaningful way (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease) (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Essentially, larazotide helped symptom control but was not a cure. It was envisioned as a maintenance therapy for coeliac patients with persistent symptoms despite a GFD, or as an emergency aid for accidental gluten exposure (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease).

Unfortunately, larazotide's phase III trial (the "CedLara" trial) was **halted in 2022** after interim analysis suggested it was unlikely to meet its endpoints (9 Meters Discontinues Phase 3 Clinical Trial for Potential Celiac Disease Drug Larazotide | Celiac Disease Foundation) (9 Meters Discontinues Phase 3 Clinical Trial for Potential Celiac Disease Drug Larazotide | Celiac Disease Foundation). The company (9 Meters Biopharma) discontinued its development, making larazotide a high-profile setback. As reviewers have noted, larazotide proved unable to sufficiently prevent mucosal damage in coeliac disease, even if it did alleviate some gastrointestinal symptoms (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Nonetheless, its good safety profile and symptom benefits hint that it *could* still be useful as a **complementary therapy**, perhaps for non-autoimmune gluten reactions. For instance, experts have suggested larazotide might aid patients with **NCGS or IBS-like symptoms** who do not have mucosal lesions, since tightening the gut barrier could lessen gut hypersensitivity and symptom generation (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease).

At present, no other tight junction drugs are as far along, though **Immunic Therapeutics' IMU-856** is a novel small molecule that targets

intestinal barrier function and mucosal regeneration. In a 2023 phase Ib trial in coeliac patients, IMU-856 was reported to be safe and showed positive signals across histology, symptoms, and biomarkers (Future Therapies | Celiac Disease Foundation) (Future Therapies | Celiac Disease Foundation). This drug aims to restore barrier integrity *without* broadly suppressing the immune system (Future Therapies | Celiac Disease Foundation). A phase IIb trial is in preparation (Future Therapies | Celiac Disease Foundation). If IMU-856's early promise is confirmed, it could represent a new class of therapy that heals and protects the gut lining in active coeliac disease – potentially useful for refractory cases or to accelerate recovery upon diagnosis. Its effect on NCGS hasn't been studied, but restoring barrier function and normalising the gut wall might also benefit those patients (many NCGS patients are thought to have subtle barrier impairment and dysbiosis) (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review).

- *Applicability: **Gut barrier therapies are focused on** coeliac disease**, particularly to reduce** "leaky gut" phenomena and resulting immune activation**. Larazotide was tested as an add-on for coeliac patients on a GFD (to help those with ongoing symptoms from microscopic contamination or coexisting irritable bowel symptoms). Though larazotide will not reach market soon, the concept remains valid. In** NCGS**, strengthening the gut barrier could, in theory, reduce the passage of poorly digested wheat components that trigger innate immune or nervous system responses. While not yet in trials, such an approach could be part of future NCGS management (e.g. a mild larazotide-like agent to ease sensitivity).

Immune Modulators and Tolerance-Inducing Therapies

Because coeliac disease is fundamentally an immune disorder, several therapies aim to modulate or retrain the immune system's response to gluten. These range from antigen-specific approaches (to induce tolerance) to broader immune suppression of the inflammatory pathways.

NCGS, lacking a single immune trigger or autoimmune pathway, has not been a direct target for these therapies – they are being developed for coeliac (and sometimes for the subset of *refractory coeliac disease* where active inflammation persists despite diet).

- *1. Antigen-Specific Tolerisation (Vaccines and Nanoparticles):** One of the most intriguing avenues is to create a therapy that *induces immune tolerance* to gluten, much like allergy desensitisation.

- **Nexvax2 (ImmusanT):** Nexvax2 was a peptide-based "vaccine" containing immunodominant gluten peptides for HLA-DQ2.5 coeliac patients. The idea was to expose the immune system to controlled doses of the peptides via injection, to induce tolerance (immune hyporesponsiveness). Nexvax2 reached phase II testing, but in 2019 it was **terminated** after it failed to show efficacy (it did not protect patients from gluten reactions in a trial) and had some side effects. Despite this failure, it provided valuable data and proved that targeting T-cells in coeliac disease is challenging.

- **KAN-101 (Anokion):** Rather than a vaccine, KAN-101 uses a novel approach: it attaches gluten peptides to a targeting molecule that directs them to the liver, an organ that can promote immune tolerance. The premise is that by presenting gluten antigens in a tolerogenic environment (liver and its immune cells), the body can learn to treat gluten as "harmless". In 2023–2024, Anokion reported phase I results for KAN-101 showing it was safe and well-tolerated up to high doses, and early signs that it could induce immune changes consistent with tolerance (reduced responses to gluten) (New Treatments for Celiac Disease Gain Traction - BioSpace). A phase II trial ("SynCeD") is actively enrolling to further assess its efficacy in coeliac patients (New Treatments for Celiac Disease Gain Traction - BioSpace). If successful, KAN-101 would be a disease-modifying therapy aiming to *reset the immune response* in coeliac disease.

- **TAK-101 (Cour/Takeda):** Takeda's TAK-101 is an **immune-tolerising nanoparticle** therapy. It consists of gliadin proteins encapsulated in nanoparticles; when infused, these particles

- are thought to be taken up by immune cells in a way that induces tolerance (by promoting regulatory T-cells or anergic T-cells). A phase II trial of TAK-101 is currently underway (New Treatments for Celiac Disease Gain Traction - BioSpace). Early phase Ia data suggested some efficacy in blunting immune responses to gluten. Like KAN-101, TAK-101's goal is to *specifically* make the immune system less reactive to gluten, rather than suppressing immunity globally.

These antigen-specific approaches are unique to **coeliac disease** – they leverage knowledge of gluten peptides and HLA genetics. In theory, a successful tolerising therapy could allow coeliac patients to consume gluten with minimal or no consequences. We are not there yet, but these trials in the past 5 years mark the furthest progress in that direction.

- *2. Monoclonal Antibodies and Other Immune Pathway Modulators:** Another set of therapies involve using biologic drugs or small molecules to interfere with the immune cascades that cause intestinal damage in coeliac disease.

- **Anti-IL-15 (AMG 714, aka PRV-015):** IL-15 is a cytokine that drives the intraepithelial lymphocyte activation in coeliac disease and is especially implicated in refractory coeliac disease (RCD) type II. A monoclonal antibody targeting IL-15 was tested in coeliac patients (a phase II study). It showed some positive results – for example, one trial found a reduction in gluten-induced mucosal injury in patients on the antibody vs placebo – but overall the efficacy was modest and some safety concerns (infections) arose (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). As a result, further development has been uncertain. As of 2024, this therapy did not advance, highlighting the difficulty of immunosuppressive approaches. However, another IL-15 pathway blocker, **Hu-Mik-Beta-1**, which targets the IL-15 receptor, is being investigated for refractory coeliac disease (Future Therapies | Celiac Disease Foundation) (Future Therapies | Celiac Disease Foundation).

- **Anti-**OX40L **(Amlitelimab):** OX40L is a co-stimulatory molecule involved in T-cell activation. Sanofi's antibody *amlitelimab* (SAR445229, previously KY1005) blocks OX40L, thereby dampening T-cell activity. In 2024, Sanofi launched a phase II trial of amlitelimab in coeliac patients who are not responsive to a GFD (New Treatments for Celiac Disease Gain Traction - BioSpace). This trial is noteworthy for its design: it will compare patients on a strict GFD vs those given a controlled gluten challenge, to see if the drug can protect the gut under gluten exposure (New Treatments for Celiac Disease Gain Traction - BioSpace). Amlitelimab is also in trials for other autoimmune diseases (atopic dermatitis, etc.), and if it shows benefit in coeliac disease, it might be one of the first *general immune modulators* approved for the condition. It is intended for **coeliac patients with persistent or severe disease** (including refractory cases). Not applicable to NCGS.

- **JAK Inhibitors:** Small molecules like *ritlecitinib* (a Janus kinase inhibitor) are being repurposed to suppress inflammatory signalling in coeliac disease. Ritlecitinib (already approved for alopecia areata) is currently in a phase II trial (NCT05636293) to see if it can prevent gluten-induced intestinal damage in coeliac patients by broadly inhibiting cytokine signalling (JAK pathways). Similarly, tofacitinib (another JAK inhibitor) has been tried off-label in refractory coeliac with some success. These drugs could help especially in **refractory coeliac disease** where inflammation persists despite diet. They are systemic immunosuppressants, however, so their use would be weighed against infection risks. There is no role for them in NCGS (which doesn't have an ongoing inflammatory lesion to suppress).

- **Other Novel Immune Therapies:** A very recent development is **MTX-101 (Mozart Therapeutics)**, a bi-specific biologic that aims to boost regulatory CD8 T-cells to restore immune balance. It is in phase I trials as of 2025 (Future Therapies | Celiac Disease Foundation). Additionally, companies like **IM Therapeutics** and **Provid** are in early stages of developing small molecules to block HLA-DQ2/DQ8 function (Future Therapies | Celiac Disease Foundation) (Future Therapies | Celiac Disease Foundation), which could theoretically stop the

- autoimmune trigger at its root. These are still preclinical or phase I. Finally, leveraging the success of mRNA vaccine technology, researchers at University of Pennsylvania are exploring **mRNA-based treatments** for coeliac disease – for example, an mRNA vaccine that delivers gluten tolerizing signals or instructs the body to produce protective proteins in the gut (Scientists pursue mRNA vaccines to stop celiac disease) (Scientists pursue mRNA vaccines to stop celiac disease). This work is very early (lab stage), but the adaptability of mRNA platforms could one day allow a tailored therapy that turns off the anti-gluten immune response (Scientists pursue mRNA vaccines to stop celiac disease) (Scientists pursue mRNA vaccines to stop celiac disease).

- *Applicability: **All the immune modulator therapies above are designed for** coeliac disease**. They either target the specific anti-gluten immune response or broadly dampen gut inflammation. None of these would be appropriate for NCGS, since NCGS patients do not have the type of autoimmune pathology these drugs address. However, one could speculate that if NCGS is found to involve certain immune aberrations (e.g. an overactive innate immune sensor or mast cell activation), in the future a targeted therapy could be tested. At present, NCGS management does not include immunosuppressants – it is focused on diet and supportive care.

TG2 Inhibitors

Tissue transglutaminase-2 (TG2) is the key enzyme that modifies gluten peptides in coeliac disease, converting some glutamine residues to glutamate (deamidation). This increases the peptides' binding affinity to HLA-DQ2/DQ8, essentially turbo-charging their ability to trigger T-cells (New Hope for Celiac Disease: Promising Drug Shows Progress in Clinical Trials | Celiac Disease Foundation). Blocking TG2 activity is therefore an attractive strategy to *reduce the toxicity of gluten* in coeliac patients. In the past few years, a lead compound has emerged:

- **ZED1227 (Zedira/Dr. Falk and Takeda – also known as TAK-227):** ZED1227 is an oral small-molecule inhibitor of TG2. It selectively binds active TG2, preventing it from deamidating gluten peptides (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). By keeping gluten in its native form, the theory is that it will be less immunogenic, resulting in less T-cell activation and intestinal damage. A phase II trial of ZED1227 was conducted in Europe, and the results (published 2021) were very promising: in coeliac patients undergoing a **3g daily gluten challenge for 6 weeks**, those on ZED1227 had significantly **less mucosal injury and maintained better villous/crypt ratios** than placebo (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). The effect was dose-dependent – higher doses (50 mg and 100 mg) offered near-complete protection against villous atrophy and also prevented the rise in intraepithelial lymphocytes that gluten normally provokes (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). The drug was well-tolerated; the main side effect was a mild rash in a few patients at the highest dose (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). These results identify ZED1227 as one of the most **potent and promising candidates** so far (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). It essentially acted like a “chemical gluten lock”, keeping gluten from triggering the disease process.

As of 2024, further development is underway. A new trial is recruiting coeliac patients who still have symptoms despite a GFD, to see if ZED1227 can help those with ongoing low-level exposure or sensitivity (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Takeda has also been involved, referring to ZED1227 as TAK-227 in its pipeline (New

Treatments for Celiac Disease Gain Traction - BioSpace). Notably, even pharma giant GlaxoSmithKline had a TG2 inhibitor (GSK3915393) in early trials, though they discontinued it in 2023 after phase I – possibly to focus efforts on ZED1227 which was more advanced (Future Therapies | Celiac Disease Foundation) (Future Therapies | Celiac Disease Foundation).

If ZED1227 continues to succeed, it could become the **first adjunct drug for coeliac disease**. The vision is that coeliac patients could take a TG2 inhibitor pill before meals (alongside maintaining a GFD as much as possible) to protect against accidental gluten. It would not replace the diet, but it could significantly relieve the constant vigilance and fear of contamination that coeliacs live with.

- *Applicability: **TG2 inhibitors are specific to** coeliac disease** – they target an enzyme central to coeliac pathogenesis. There is no reason to use them in NCGS, because in NCGS there is no abnormal TG2-mediated immune response. (NCGS patients by definition do not mount the anti-TG2 autoantibodies that coeliacs do, and TG2's role in NCGS symptoms is not established.) Thus, ZED1227 and similar drugs will be coeliac-specific tools, likely used *alongside* a GFD to ensure any hidden gluten does minimal harm (New Hope for Celiac Disease: Promising Drug Shows Progress in Clinical Trials | Celiac Disease Foundation) (New Hope for Celiac Disease: Promising Drug Shows Progress in Clinical Trials | Celiac Disease Foundation).

In summary, the pharmaceutical pipeline for coeliac disease is robust and multifaceted. Table 1 provides a comparative overview of key treatment approaches, their mechanisms, stage of development, and which condition(s) they target. Most are in phase II trials, with a few entering phase III or approaching regulatory review. If these trials succeed, the next 3–5 years could see the **first-ever approved medications for coeliac disease**, a paradigm shift in management (New Treatments for Celiac Disease Gain Traction - BioSpace). For NCGS, pharmaceuticals remain speculative; given the heterogeneity of NCGS triggers, it may be that dietary and supportive therapies (see below) continue to be the mainstay, at least in the near term.

Dietary Approaches and Nutritional Innovations

Dietary management is central to both coeliac disease and NCGS, but recent years have seen innovations to improve the quality, safety, and tolerability of diets for these conditions. Here we discuss advances in **gluten-free foods**, development of **low-gluten or altered grains**, and supportive nutritional strategies. We also clarify differences in dietary approach between coeliac and NCGS (since NCGS diets can sometimes be more liberal or differently tailored).

Novel Gluten-Free Products and Diet Quality Improvements

Maintaining a strict GFD can be difficult not only due to hidden gluten risks but also because gluten-free products often have inferior taste, texture, or nutritional profile. Recent efforts aim to close this gap:

- **Improved Baked Goods and Substitutes:** Food technologists have created better formulations for gluten-free bread, pasta, and other staples. Use of alternative grains (rice, corn, buckwheat, sorghum, quinoa, teff, etc.), along with hydrocolloids and starches, has advanced, producing breads with softer texture and pastas with improved firmness. Fermentation techniques (e.g. using sourdough cultures with gluten-hydrolysing bacteria) can enhance flavour and may reduce residual immunoreactivity. Some bakeries use **wheat starch that has had gluten removed** to <20 ppm (Codex quality), allowing baked goods that more closely resemble traditional wheat products while still being officially gluten-free. These products help coeliac patients adhere to the diet by providing enjoyable options, and they likewise benefit NCGS individuals who choose to avoid gluten. The past 5 years have seen a proliferation of such products on supermarket shelves, often fortified with vitamins and minerals that might be lacking in a standard GFD.

- **Nutrient Fortification and Balance:** Researchers have highlighted that long-term GFD followers may have nutritional deficiencies (iron, calcium, vitamin D, B vitamins, fibre) due to both malabsorption (in untreated coeliac) and the poor nutrient content of many GF processed foods. In response, many gluten-free cereals and flours are now fortified (e.g. B-vitamins and iron akin to wheat flour fortification). There's also an emphasis on incorporating naturally nutrient-rich, gluten-free ingredients – such as **legume flours** (for protein and fibre), flax/chia (for omega-3 and fibre), and **psyllium husk** or other fibres to improve bowel health. Supportive nutritional interventions, like **iron and vitamin supplementation**, are routinely recommended for coeliac patients at diagnosis and during healing (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review). Over the last few years, clinical guidelines in many countries (including the EU and UK) have underscored regular monitoring of coeliac patients' micronutrient status and aggressive correction of deficiencies as part of comprehensive care. This isn't so much a novel "treatment" as an enhancement of standard care, but it's worth noting as an advance in how we support patient health.

- **Including (Certified) Oats:** Oats do not contain the same problematic gluten proteins (they have avenin, which most coeliac patients tolerate). However, cross-contamination with wheat often made oats risky. Now, **certified gluten-free oats** are widely available and are accepted in the diets of many coeliac patients. Research in the past 5 years confirms that pure oats are safe for the vast majority of coeliacs and provide a great source of fibre and nutrients. Guidelines suggest moderate intake of oats can enrich the GFD, improving nutrient intake and gut microbiome diversity. A small subset of coeliac patients (perhaps <5%) do react to avenin – so they must individually assess tolerance. For NCGS, oats can be a useful grain alternative as well. The growing availability of GF oats (and derived products like oat bread, granola, etc.) is a positive dietary development.

Overall, these innovations aim to make a gluten-free diet **more nutritious, palatable, and convenient**, which indirectly is a

“treatment” improvement – better adherence leads to better disease control. Both coeliac and NCGS patients stand to benefit, though for coeliac it’s absolutely critical.

Low-Gluten and Modified Wheat Strains

Another fascinating line of research is developing forms of wheat (and related grains) that have reduced immunogenicity. This could allow consumption of wheat with minimal harm – essentially creating “coeliac-safe” or “low-gluten” wheat. There are a few approaches:

- **Ancient Wheat Varieties:** Studies have looked at older wheat species such as *Triticum monococcum* (einkorn) or certain heritage strains, which have different gluten protein compositions. Some in vitro experiments showed that gluten from these ancient grains may be **less toxic to coeliac intestinal cells** ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=The%20use%20of%20ancient%20diploid,which%20are%20highly%20resistant%20to)). One Italian study by Gianfrani et al. demonstrated that after digestion, einkorn’s gliadin peptides triggered lower immune responses in coeliac patient samples compared to modern wheat ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=The%20use%20of%20ancient%20diploid,which%20are%20highly%20resistant%20to)). Moreover, older wheat types tend to have lower levels of ATIs (the innate immunity-activating proteins) than modern wheat ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=gastrointestinal%20digestion,be%20a%20major%20step%20in)). Modern wheat breeding inadvertently selected for higher ATI content (which contribute to pest resistance), but those ATIs may aggravate NCGS and even coeliac inflammation. Thus, using **older wheat lines or landraces** could benefit

people with NCGS who might tolerate small amounts of these grains without symptoms. A few small-scale human studies have indeed suggested some NCGS individuals tolerate ancient grain breads better. However, these grains **still contain gluten**, so **coeliac patients cannot safely consume them** even if they might be marginally "less immunogenic". This is an area of ongoing research, not a clinical recommendation yet.

- **Selective Breeding and CRISPR Gene Editing:** More high-tech, scientists are attempting to create wheat that either *lacks* certain gliadin components or has them engineered to be non-toxic. Using CRISPR/Cas9 gene editing, researchers have managed to knock out large portions of the gliadin gene family in wheat. For example, a 2020 study targeted the γ-gliadin and ω-gliadin genes, significantly reducing the content of those immunogenic proteins (CRISPR/Cas9-mediated multiplex gene editing of gamma and ...) (CRISPR-based editing of the ω- and γ-gliadin gene clusters ...). The resulting wheat had much lower reactivity with coeliac patient antibodies. Complete removal of all harmful epitopes is challenging (wheat has dozens of gluten genes), but incremental progress is being made toward **"gluten-attenuated" wheat**. The goal would be a wheat variety that could be eaten by coeliac patients without triggering the disease. We are not there yet, but within the next decade it's conceivable that extremely low-gluten (or gluten-safe) wheat lines will emerge. Regulatory and safety testing would be needed, and coeliac advocacy groups are watching this space closely.

- **Barley and Rye:** Similar efforts exist in barley – for instance, the development of **"Kebari" barley in Australia**, which is a barley variety so low in hordein (barley gluten) that it meets gluten-free standards. This has already been used to brew a truly gluten-free barley-based beer (giving celiac consumers a beer with the authentic barley taste). This product came to market around 2016, but refinements and more such products have appeared in the last 5 years, expanding options for coeliac individuals.

For **NCGS**, low-gluten or modified grains might expand what they can eat if gluten (or ATIs) are indeed the symptom triggers. Someone with NCGS might, for example, tolerate a bread made from gene-edited wheat with 90% less gliadin, whereas regular bread makes them ill – this remains to be tested, but is plausible. For **coeliac disease**, these grains are a more distant promise; complete safety would need to be assured. Still, the very notion of a “gluten-safe wheat” was once science fiction and is now an active research reality.

Supportive Nutritional Interventions

Both coeliac disease and NCGS can be accompanied by other gastrointestinal or nutritional issues that merit supportive therapy. Key approaches from the past few years include:

- **Proactive Correction of Deficiencies:** As noted, newly diagnosed coeliac patients often have deficiencies (iron, folate, B12, vitamin D, calcium, magnesium, etc.). In NCGS, severe deficiencies are less common, but some NCGS patients (especially if misdiagnosed or on unnecessary restrictive diets) may have imbalanced nutrition. Recent guidelines emphasise routine monitoring and supplementation. For example, treating iron-deficiency anaemia with iron supplements, ensuring adequate calcium and vitamin D to protect bone health (especially since coeliac disease can cause bone density loss), and supplementing fibre to compensate for the low fibre content of many gluten-free foods. A 2020 meta-analysis highlighted that treated coeliac patients following a GFD for >12 months still often had low fiber and high fat intake; thus dietitians now work with patients to incorporate naturally GF high-fibre foods (fruits, veg, legumes, nuts) and potentially a fibre supplement if needed. This kind of **dietary optimisation** improves gastrointestinal function and overall well-being.

- **Addressing Lactose Intolerance and FODMAPs:** Coeliac disease can cause secondary lactose intolerance (due to loss of lactase enzyme in damaged villi). In the short term after diagnosis, lactose restriction or use of lactase enzyme supplements can help symptoms until the gut

- heals. Additionally, there is recognition that some coeliac or NCGS patients have overlapping **irritable bowel syndrome (IBS)**. For those individuals, simply removing gluten might not fully resolve symptoms because fermentable carbohydrates (FODMAPs) in the diet could be contributing to bloating and pain. A low-FODMAP diet trial can be considered in patients who continue to have IBS-like symptoms despite a GFD. For **NCGS in particular**, some studies have suggested a proportion of patients improve on a low-FODMAP diet even more than on a standard GFD, implying their issue might be fermentable wheat components rather than gluten per se. In practice, a carefully supervised low-FODMAP diet (which incidentally eliminates most gluten-containing foods as well) might be used for NCGS symptom control, then liberalised to identify specific triggers.

- **Holistic Lifestyle Factors:** Nutrition research increasingly overlaps with lifestyle. For coeliac patients, maintaining a healthy weight and metabolic profile is important – interestingly, a significant subset of coeliacs gain excess weight after going gluten-free due to the high glycaemic index of many GF foods. The past few years have seen more attention on *healthy* gluten-free diets (emphasising whole foods and limiting sugary, starchy GF processed snacks). Regular exercise is encouraged, both for general health and bone density improvements. In NCGS, there is some discussion that stress and the gut-brain axis can exacerbate symptoms ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=Mayer%20and%20Tillisch%20highlighted%20the,which%20thus%20suggest)), so lifestyle interventions like stress reduction, yoga, or mindfulness-based therapies could indirectly help by reducing visceral hypersensitivity.

In summary, while a gluten-free diet remains the cornerstone therapy for both conditions, refinements in dietary approach over recent years are making management more effective and personalised. **Coeliac disease diet** therapy now goes beyond just “avoid gluten” – it means ensure nutritional adequacy, consider lactose/FODMAP issues, and use

high-quality GF products to improve adherence and health. **NCGS diet** therapy involves gluten avoidance to the level needed for symptom relief (which may vary by individual), and sometimes experimenting with eliminating other components (like ATIs or FODMAPs) to see if symptoms improve.

Alternative and Complementary Therapies

Beyond pharmaceuticals and diet, various **alternative or complementary therapies** have been explored for managing coeliac disease and NCGS. These include probiotics, microbiome-targeted treatments, and even immunological tricks like helminth (worm) therapy. The appeal of these approaches is that they might modulate the disease in gentler or more holistic ways. However, evidence for most is still emerging. We will examine a few notable examples from the last 3–5 years and clarify their status.

Probiotics and Microbiome Modulation

The gut microbiome plays a significant role in gastrointestinal health and immune regulation. Dysbiosis (an imbalanced microbiota) has been noted in coeliac disease – for instance, higher levels of certain pro-inflammatory bacteria and lower levels of beneficial species. Likewise, some NCGS patients may have IBS-like dysbiosis. Thus, probiotics have been studied as a therapy:

- **Bifidobacterium longum CECT 7347:** A Spanish trial tested this single-strain probiotic in coeliac patients who were already on a GFD but had only partial symptom improvement. Over 3 months, **B. longum** treatment led to reductions in pro-inflammatory immune markers (a decrease in peripheral CD3 T-cells and a trend towards lower TNF-α) and modifications of the microbiota (e.g. reduced Bacteroides fragilis counts, increased fecal IgA) compared to placebo (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease) (Frontiers | Beyond

- gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Clinically, some patients reported feeling better, although histology was not changed. This suggests certain probiotic strains can exert an **anti-inflammatory effect in coeliac patients** on a GFD, potentially helping those with persistent microscopic inflammation or dysbiosis.

- **Multi-strain Probiotics (VSL#3):** In contrast, another study used VSL#3 (a high-potency mix of 8 probiotic strains) in coeliac patients with ongoing symptoms. After 3 months, they found **no significant differences** in outcomes versus placebo (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease) (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). This indicates that not all probiotics are equal – some strains might help, while others do little. It underlines the need for strain-specific research.

- **Gluten-Degrading Bacteria:** A novel concept is to use bacteria (probiotics or their enzymes) specifically to break down gluten in the gut. In 2024, a groundbreaking randomized trial in healthy adults tested a combination of probiotics that produce gluten-digesting enzymes (including certain *Lactobacillus* and *Bacillus* species, along with microbial proteases). Volunteers were given increasing doses of gluten (up to 10 g) while taking either the probiotic mix or placebo. The results showed that those on the probiotics had **much lower levels of gluten detected in their stool**, implying the gluten was broken down more completely in their intestines ([

Novel probiotic preparation with in vivo gluten-degrading activity and potential modulatory effects on the gut microbiota - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC11218521/#:~:text=blind%20placebo,Probiotics)) ([

Novel probiotic preparation with in vivo gluten-degrading activity and potential modulatory effects on the gut microbiota - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC11218521/#:~:text=The%20untapped%20potential%20of%20gluten,Our%20study)). Additionally, the probiotic improved markers of gut health (like short-chain fatty acid production) ([

Novel probiotic preparation with in vivo gluten-degrading activity and potential modulatory effects on the gut microbiota - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC11218521/#:~:text=amounts%20of%20gluten%20,chain%20fatty%20acids)) ([

Novel probiotic preparation with in vivo gluten-degrading activity and potential modulatory effects on the gut microbiota - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC11218521/#:~:text=The%20untapped%20potential%20of%20gluten,Our%20study)). This research is still in healthy subjects, but it paves the way for using such probiotics in coeliac or NCGS patients. A product that can be taken with meals to **neutralise gluten in vivo** and concurrently support a healthy microbiome would be doubly beneficial. It's essentially a probiotic analog of the enzyme therapies discussed earlier.

- **Fecal Microbiota Transplant (FMT):** Although not yet widely studied for coeliac disease, there has been interest in whether FMT (transferring gut flora from a healthy donor) could restore tolerance or alleviate symptoms. One case series a few years back suggested some refractory coeliac patients had symptomatic improvement after FMT, but robust trials are absent. In NCGS or IBS, FMT research is ongoing, but no clear application for gluten sensitivity has emerged.

For **NCGS** specifically, a recent trial (2018) investigated probiotics: patients with NCGS underwent a gluten challenge (two slices of bread per day for 1 week) while receiving either *Bifidobacterium longum* ES1 or placebo. The hypothesis was that the probiotic might mitigate symptoms by correcting dysbiosis and dampening inflammation ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=methods%20for%20NCGS%20besides%20the,has%20long%20been%20a%20source)) ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=introduction%20of%20gluten%20in%20a,exact%20role%20as%20far%20as)). Results from that study indicated a trend toward improved gastrointestinal symptom scores in the probiotic group, though larger studies are needed. Probiotics are generally safe, so many NCGS patients try them as a complementary measure, despite limited evidence.

- *Bottom line: **Probiotics and related microbiome therapies represent a gentle approach to managing gluten-related disorders.** Coeliac disease** is unlikely to be *treated* by probiotics alone (they cannot prevent autoimmune damage if gluten is present), but certain strains might become recommended adjuncts – for example, to help normalize the gut milieu on a GFD, potentially aiding symptom resolution and nutrient absorption. **NCGS** patients, especially those with IBS-like features, might experience symptom relief from specific probiotics that reduce bloating or inflammation. However, not all commercial probiotics will have these effects – the field is moving toward targeted strains with proven benefits (as seen with B. longum CECT 7347). Future “symbiotic” therapies that combine probiotics with gluten-digesting enzymes are particularly promising for both conditions.

Helminth Therapy (Immunomodulation via Hookworms)

One of the most unconventional experimental therapies for autoimmune diseases is intentional infection with helminths (parasitic worms). The rationale stems from the hygiene hypothesis – worms have co-evolved with humans and can secrete substances that calm the immune system to avoid being expelled. This immune modulation might counteract autoimmune reactions. In coeliac disease, researchers speculated that

hookworm infection could induce tolerance to gluten.

A notable trial was conducted in Australia/New Zealand (results published 2020) with the human hookworm *Necator americanus*. **Fifty-four coeliac patients** were randomly given either microscopic hookworm larvae (applied to the skin to establish a low-level infection) or placebo (Can hookworms cure coeliac disease - Coeliac Australia) (Can hookworms cure coeliac disease - Coeliac Australia). After the worms had time to colonise, the patients underwent escalating gluten challenges: starting with a very low dose (equivalent to a couple of spaghetti strands of wheat per day) and gradually increasing to a high dose (60 spaghetti strands per day) over several months (Can hookworms cure coeliac disease - Coeliac Australia). The hope was that hookworm-carriers would adapt and tolerate the gluten without intestinal damage, thanks to the worms' immunoregulatory effects.

- *Findings: **The final results were mixed. Unfortunately, in the high-dose gluten phase,** both worm-infected and placebo groups experienced relapse** – about half in each group could not tolerate the sustained gluten consumption, meaning the hookworms did *not* provide a magic cure (Can hookworms cure coeliac disease - Coeliac Australia). There was no significant difference in villous atrophy or antibody levels between the groups at the end – so in terms of preventing mucosal damage, hookworm therapy failed in the larger trial (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). However, there were some intriguing positives: the worm-infected group seemed to have **fewer symptoms at lower gluten doses** and reported better quality of life during the gluten challenges than the placebo group (Can hookworms cure coeliac disease - Coeliac Australia) (Can hookworms cure coeliac disease - Coeliac Australia). These trends echoed earlier, smaller trials where hookworms appeared to increase gluten tolerance up to a point (Can hookworms cure coeliac disease - Coeliac Australia). Additionally, the infection at the levels given was quite safe – no serious adverse events occurred apart from the expected mild skin rash at entry site and some transient gut discomfort.

This research suggests that while hookworms are not a viable standalone treatment to allow a normal diet, they do reveal mechanisms of immune suppression that could be beneficial. Ongoing analyses of samples from the trial are examining how worm infection altered immune responses, gut bacteria, and inflammation mediators (Can hookworms cure coeliac disease - Coeliac Australia) (Can hookworms cure coeliac disease - Coeliac Australia). Such insights might guide development of new drugs that mimic the worms' immunomodulatory molecules *without* requiring actual infection.

For **coeliac patients**, helminth therapy is very much experimental and not something to pursue outside of clinical studies. For **NCGS**, helminths have not been specifically studied, and given NCGS's less severe pathology, the risks likely outweigh any hypothetical benefit. That said, this line of inquiry underscores the principle that *dialling down immune reactivity* in the gut can increase gluten tolerance – a principle also being targeted by pharmaceutical immunomodulators (like the IL-2/15 blockers and immune tolerance therapies discussed earlier).

Other Complementary Approaches

A few additional approaches have been considered or tried by patients, although robust evidence is limited:

- **Herbal and Nutraceutical Supplements:** Various herbs (such as aloe vera, turmeric (curcumin), ginger, etc.) with anti-inflammatory or gut-soothing properties have been suggested to help coeliac or NCGS symptoms. For instance, curcumin is known for anti-inflammatory effects and has been tested in other inflammatory gut conditions; in coeliac disease there is no clinical trial yet, but some patients take it hoping to reduce gut inflammation. Similarly, supplements like zinc or l-glutamine, which support intestinal mucosal healing, are sometimes used in refractory cases (recognising that coeliac disease involves a healing process once gluten is removed). While these may support general gut health, none are proven to prevent the coeliac immune reaction. One herbal compound that has entered formal testing is

- **Nigella sativa (black seed)** extract – known for immunomodulatory effects – which anecdotally might help autoimmune conditions, but again, data in coeliac disease are lacking or of low quality.

- **Acupuncture and Mind-Body Therapies:** Some patients with NCGS or coeliac disease report using acupuncture or stress-reduction techniques to manage symptoms like pain or "brain fog." Given the overlap of NCGS with IBS, and IBS's responsiveness to therapies like gut-directed hypnotherapy or cognitive-behavioural therapy (CBT), it is plausible these could help NCGS patients as well. For coeliac disease, such therapies do not address the cause (gluten autoimmunity) but could help with secondary issues (stress, anxiety around food, functional gut symptoms). There is no harm in these approaches, but they remain adjunctive to diet.

- **Vagus Nerve Stimulation:** This is a very novel idea mentioned in recent literature as a hypothetical treatment for NCGS and IBS. The vagus nerve helps regulate inflammation via the "cholinoceptive anti-inflammatory pathway." Some researchers have speculated that **vagal nerve stimulation** (in use for epilepsy and depression) might also reduce gastrointestinal inflammation or hypersensitivity, thus potentially benefiting conditions like NCGS where a gut–brain dysregulation is suspected ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=Mayer%20and%20Tillisch%20highlighted%20the,which%20thus%20suggest)) ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=be%20viewed%20as%20a%20dysregulation,which%20thus%20suggest)). As of now, this is theoretical – no trials specifically in NCGS have been done, but it represents out-of-the-box thinking on how to normalize gut–nervous system communication in functional GI disorders.

In conclusion, complementary therapies form a supportive backdrop to the main treatments. **Probiotics** have the most scientific traction recently,

especially those that can degrade gluten or modulate immunity. **Helminth therapy** provided important scientific insights even if it’s not a practical treatment. General wellness approaches (dietary supplements, stress management) can improve quality of life, which is an important part of managing chronic conditions like coeliac and NCGS. Patients often combine these supportive measures with their primary treatment (GFD, and in the future possibly medication). It’s crucial that patients discuss any alternative therapies with their healthcare providers to ensure they’re safe and don’t interfere with essential treatment (for example, a coeliac patient should never use alternative medicine *instead of* a GFD – only in addition to it).

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The landscape of treatments for coeliac disease is rapidly evolving. Table 1 below summarises many of the key emerging therapies and approaches discussed, comparing their type, mechanism, development stage, and the condition(s) they target. This highlights how far the field has progressed beyond the days when “just diet” was the only option. For coeliac disease, a number of pharmacological therapies are in late-stage trials, bringing hope that patients will soon have additional protection or even partial freedom from their restrictive diet. For NCGS, the advances are more about understanding triggers and supportive care, since by definition removing gluten/wheat is the primary solution. Distinguishing the two conditions remains important: coeliac disease demands lifelong strict avoidance of gluten and may soon have medications to assist with that, whereas NCGS management is a bit more flexible and still focused on symptom relief and dietary adjustments.

- *Table 1: Comparative Summary of Emerging Treatments for Coeliac Disease vs NCGS (2019–2025)**

| **Treatment (Type)** | **Mechanism** | **Stage of Development** | **Target Condition** |

|---|---|---|---|

| **Latiglutenase (Glutenase enzyme)** | Oral protease mixture that digests gluten into smaller, non-immunogenic fragments before it can trigger an immune response (New Treatments for Celiac Disease Gain Traction - BioSpace). | Phase II completed (showed reduced mucosal damage in gluten challenge (New Treatments for Celiac Disease Gain Traction - BioSpace)); Phase III planned. | Coeliac disease (adjunct to diet for protection). Potential off-label use for NCGS to mitigate symptoms. |

| **AN-PEP (prolyl endopeptidase enzyme)** | Fungal enzyme taken with food to break down gluten in the stomach, reducing gluten reaching the intestine ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=Another%20treatment%20option%20under%20investigation,symptoms%20or%20soaring%20food%20costs)). | Available as supplement; small trials in NCGS/gluten-sensitive individuals ongoing ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=Another%20treatment%20option%20under%20investigation,symptoms%20or%20soaring%20food%20costs)). | NCGS (used for symptom relief); coeliac (not a cure, but may help with cross-contamination – still experimental). |

| **ZED1227 (TG2 inhibitor)** | Small-molecule inhibitor of tissue transglutaminase, preventing gluten peptide deamidation and thus reducing T-cell activation (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). | Phase II trial successful (dose-dependent mucosal protection during gluten exposure (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease)); entering Phase II/III. | Coeliac disease (to prevent autoimmune damage from inadvertent gluten (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease)). *Not applicable to NCGS.* |

| **Larazotide (Tight junction modulator)** | Peptide that tightens intestinal barrier, blocking paracellular passage of gluten peptides into tissue (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). | Phase II trials showed reduced GI symptoms but no histology benefit (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Phase III (2022) discontinued for lack of efficacy (9 Meters Discontinues Phase 3 Clinical Trial for Potential Celiac Disease Drug Larazotide | Celiac Disease Foundation). | Coeliac disease (adjunct for symptom control (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease)). *Possibly NCGS/IBS* in future for reducing gut permeability (research interest (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease)). |

| **KAN-101 (Immune tolerogen)** | Engineered gluten peptides targeted to the liver to induce immune tolerance (promote non-reactivity to gluten). | Phase I completed (safe, signs of tolerance) (New Treatments for Celiac Disease Gain Traction - BioSpace); Phase II ongoing. | Coeliac disease (aiming to reprogram immune response). *Not for NCGS.* |

| **TAK-101 (Immune nanoparticle)** | Nanoparticles loaded with gliadin – induce regulatory immune response to gluten by presenting antigen in tolerogenic fashion. | Phase II ongoing (New Treatments for Celiac Disease Gain Traction - BioSpace) (earlier data showed attenuation of gluten-driven inflammation). | Coeliac disease (disease-modifying immunotherapy). *Not for NCGS.* |

| **Amlitelimab (Anti-OX40L mAb)** | Monoclonal antibody blocking OX40L, which down-regulates T-cell activation and inflammatory response. | Phase II trial in coeliac started 2024 (New Treatments for Celiac Disease Gain Traction - BioSpace). Also in trials for other autoimmune diseases. | Coeliac disease (especially those not responding to diet (New Treatments for Celiac Disease Gain Traction - BioSpace); could be used in refractory cases). *Not applicable to NCGS.* |

| **IMU-856 (Intestinal repair modulator)** | Oral small molecule that modulates a protein controlling gut barrier function and mucosal healing (without suppressing immunity) (Future Therapies | Celiac Disease Foundation) (Future Therapies | Celiac Disease Foundation). | Phase Ib (2023) in coeliac showed safety and positive signals in histology, symptoms, biomarkers (Future Therapies | Celiac Disease Foundation); Phase IIb planned. | Coeliac disease (to restore gut integrity and improve nutrient absorption (Future Therapies | Celiac Disease Foundation) (Future Therapies | Celiac Disease Foundation)). *Potential in NCGS not studied (theoretically could help gut barrier).* |

| **PRV-015 (Anti-IL-15 mAb)** | Monoclonal antibody that neutralises interleukin-15, reducing intraepithelial lymphocyte-driven inflammation. | Phase II (completed ~2019) – modest symptom benefit but overall limited efficacy (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Further development uncertain. | Coeliac disease (especially investigated in refractory CD where IL-15 is high). *No role in NCGS.* |

| **Hookworm therapy (Helminthic)** | Deliberate infection with *Necator americanus* worms; worms release immunomodulatory factors that may increase gluten tolerance (Can hookworms cure coeliac disease - Coeliac Australia) (Can hookworms cure coeliac disease - Coeliac Australia). | Tested in Phase I/II trials. Small trial showed preserved mucosa on low-dose gluten (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease); larger trial showed no benefit on high gluten dose, but did improve some symptom/QoL measures (Can hookworms cure coeliac disease - Coeliac Australia) (Can hookworms cure coeliac disease - Coeliac Australia). Not pursued for approval (experimental only). | Coeliac disease (attempt to induce tolerance). *Not used in NCGS.* |

| **Bifidobacterium longum CECT 7347 (Probiotic)** | A probiotic strain that modulates gut flora and immune markers; aims to reduce dysbiosis and inflammatory tone in the intestine. | Phase II trial in coeliac on GFD showed reduced pro-inflammatory cells and trends to symptom improvement (Frontiers | Beyond gluten-free diet: a critical perspective on

phase 2 trials on non-dietary pharmacological therapies for coeliac disease). Probiotics with gluten-digesting ability also tested in volunteers ([

Novel probiotic preparation with in vivo gluten-degrading activity and potential modulatory effects on the gut microbiota - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC11218521/#:~:text=blind%20placebo,Probiotics)) ([

Novel probiotic preparation with in vivo gluten-degrading activity and potential modulatory effects on the gut microbiota - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC11218521/#:~:text=The%20untapped%20potential%20of%20gluten,Our%20study)). | Coeliac (adjunct to improve gut health on GFD) (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease); NCGS (being studied for symptom relief during gluten exposure ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=methods%20for%20NCGS%20besides%20the,has%20long%20been%20a%20source))). Generally complementary therapy. |

| **Low-FODMAP Diet (Dietary intervention)** | Dietary approach limiting fermentable carbs (fructans, etc.) in wheat and other foods, thereby reducing gut bloating and IBS-like symptoms. | Supported by clinical studies in IBS. In NCGS, trials indicate some patients respond to low-FODMAP diet, sometimes instead of gluten avoidance (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review). Not a formal drug development – a dietary management option. | NCGS (for those whose symptoms might be driven by FODMAP components of wheat rather than gluten per se). Also used in coeliac patients with IBS overlap (post-GFD) to manage residual symptoms. |

| **Ancient/Modified Wheat (Einkorn, CRISPR-edited)** | Use of wheat varieties with lower immunogenic gluten or reduced ATI content; or gene-edited wheat with knocked-out gliadin genes, to minimise toxic

epitopes ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=The%20use%20of%20ancient%20diploid,which%20are%20highly%20resistant%20to)) ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=gastrointestinal%20digestion,be%20a%20major%20step%20in)). | Research stage. In vitro and ex vivo studies show reduced immune reactivity ([

Non-celiac gluten sensitivity: All wheat attack is not celiac - PMC

](https://pmc.ncbi.nlm.nih.gov/articles/PMC5677194/#:~:text=The%20use%20of%20ancient%20diploid,which%20are%20highly%20resistant%20to)). CRISPR-edited wheat lines are being developed (not yet in commercial use) (Scientists announce breakthrough discovery of safer gluten protein) (CRISPR-based editing of the ω- and γ-gliadin gene clusters ...). | Primarily aimed at coeliac disease (ultimate goal to create safe wheat). In nearer term, ancient grains could be used cautiously by some NCGS sufferers (not safe for coeliacs yet). |

| **Gluten-Free Oats and Enhanced GF Foods** | Inclusion of oats (which contain avenin, a benign protein for most coeliacs) to improve diet variety and fiber; development of GF foods with better nutritional composition (fortified, high-fiber, high-protein). | Implemented in practice. Certified GF oats widely available; recent guidelines endorse moderate oats intake in coeliac diet (if tolerated). Ongoing product development in food industry for nutrient-enriched GF products. | Coeliac (to improve diet quality and long-term health on GFD); NCGS (oats provide more options in diet since only wheat/rye/barley need avoidance). |

- Table Notes:* “Phase” indicates the highest clinical trial phase reached as of 2025. GFD = gluten-free diet; NCGS = non-coeliac gluten sensitivity; ATI = amylase-trypsin inhibitors; IBS = irritable bowel syndrome. Target condition refers to where the therapy is primarily

- aimed – many coeliac therapies are not relevant to NCGS due to different pathophysiology. NCGS-focused approaches are mostly dietary or probiotic, since no drug has a defined target in NCGS yet.

Conclusion

In the past 3–5 years, treatment research for gluten-related disorders has advanced remarkably. For **coeliac disease**, a number of pharmaceutical therapies are on the horizon – including enzyme supplements to safeguard against hidden gluten (New Treatments for Celiac Disease Gain Traction - BioSpace), a TG2 inhibitor that has demonstrated real protection of the gut (Frontiers | Beyond gluten-free diet: a critical perspective on phase 2 trials on non-dietary pharmacological therapies for coeliac disease), and immune-based treatments that aim to retrain or calm the immune system (some already in phase II trials). These therapies, used alongside the gluten-free diet, could significantly improve quality of life by reducing fear of accidental gluten and perhaps eventually allowing a degree of dietary freedom. It's conceivable that within the next few years, coeliac patients might pop a pill before a meal – such as a glutenase or a TG2 blocker – and suffer far less consequence from any gluten contamination. This would be a game-changer in coeliac management, which for decades has relied solely on dietary discipline.

For **non-coeliac gluten sensitivity**, the focus remains on diet and supportive care, but our understanding has sharpened. We now appreciate that NCGS may involve reactions not just to gluten but to other components of wheat (like FODMAPs and ATIs) (Non-Celiac Gluten/Wheat Sensitivity—State of the Art: A Five-Year Narrative Review), which has led to more personalised dietary strategies (e.g. combining gluten avoidance with low-FODMAP approaches when needed). While no drug "cure" is on the immediate horizon for NCGS, sufferers can take some comfort in the expanding availability of high-quality gluten-free foods and perhaps in emerging adjuncts like probiotics that might alleviate symptoms. Moreover, ongoing research into the gut-brain axis and innate immunity in NCGS could eventually yield targeted therapies (for instance, if a specific

inflammatory pathway is identified, a drug could be repurposed to block it in NCGS patients).

It's also important to clearly delineate which therapies are for coeliac disease and which for NCGS. Coeliac disease's autoimmune nature means that **immune-targeted therapies (vaccines, biologics, TG2 inhibitors)** are relevant to coeliac only – these aim to prevent intestinal damage and long-term complications. NCGS, being a diagnosis of exclusion with primarily symptomatic effects, will be managed with a combination of **dietary modification, symptom-based treatments, and possibly microbiome or neurological modulators** (should they prove effective in the future). Both groups, however, benefit from the general improvements in gluten-free product quality and nutritional care.

In summary, the treatment landscape is expanding. Coeliac disease patients can be optimistic as multiple clinical trials approach readouts, and the first adjunct treatments (like enzymes or perhaps ZED1227) inch closer to regulatory approval. NCGS patients, while not the focus of pharmaceutical pipelines, are gaining from research that clarifies their triggers and from a wider choice of gluten-free or modified-grain foods. The hope is that continuing research – including cutting-edge areas like mRNA therapy (Scientists pursue mRNA vaccines to stop celiac disease) and tolerogenic immune techniques – will eventually make life substantially better for those with gluten-related disorders. Until then, strict adherence to a gluten-free diet remains the foundation for coeliac disease management, and careful personalised diets are key for NCGS, with these new therapies serving to **support and enhance patients' ability to live healthy, symptom-free lives**.

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