**Integrative Medicine Approaches to Gluten Sensitivities**

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**December 19, 2023**

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# **Introduction**

With the rising popularity of gluten-free diets and increasing medical recognition of non-celiac gluten sensitivity (NCGS), research in this field has expanded significantly in recent years, aiming to enhance scientific understanding and improve clinical management for individuals who experience adverse reactions to gluten despite testing negative for celiac disease or wheat allergy (Biesiekierski, 2017). However, the diverse clinical presentations, absence of definitive biomarkers, and reliance on non-standardized gluten challenge protocols continue to pose challenges in diagnosis and treatment, leaving this condition likely underdiagnosed and inadequately managed (Biesiekierski, 2017). Hence, by comprehensively synthesizing insights from immunological, neurological, psych behavioral, nutritional, and patient-outcomes research perspectives through a systematic review of the accumulating evidence base, this analysis clarifies contemporary scientific knowledge related to contributory mechanisms, clinical evaluations, therapy considerations, lingering critical unknowns, and emerging areas ripe for impactful study across the domains of basic science as well as diagnostic and therapeutic innovation (Igbinedion et al., 2017). It aims to propose an integrated future research agenda encompassing both reductionist and holistic investigative paths towards the shared goal of illuminating definitive causal explanations, cost-effective precision diagnostics, evidence-guided lifestyle-based management recommendations, and compassion-driven support resources necessary to alleviate the substantial yet often unaddressed burdens associated with fundamental food intolerance towards enhancing well-being and promoting dignity for all contending with non-celiac gluten sensitivity well into the twenty-first century and beyond.

# **Literature Review**

## **Epidemiology of Gluten Sensitivity**

Non-celiac gluten sensitivity (NCGS) appears to be more prevalent than previously believed. Early research estimated its prevalence at 0.6–6% of the population (Hills et al., 2019), but more recent studies suggest even higher rates, with 3–13% of individuals across various countries reporting gluten-related issues (Hills et al., 2019). Notably, NCGS affects individuals of all ages, making it a widespread concern. Interestingly, women are disproportionately affected, with some studies indicating a ratio as high as five women for every one man diagnosed with gluten sensitivity (Igbinedion et al., 2017). This gender disparity raises intriguing questions about potential underlying mechanisms. Current research suggests that differences in gut microbiota between men and women, as well as hormonal influences—particularly estrogen—may play a role in gluten sensitivity (Borroto-Escuela et al., 2021). However, further studies are needed to fully understand these associations and their clinical implications.

A significant proportion of individuals who adopt a gluten-free diet—ranging from 17% to 30%—do so because they feel better without gluten, despite not having a formal celiac disease diagnosis (Igbinedion et al., 2017; Hills et al., 2019). This suggests that the true prevalence of gluten sensitivity may be much higher than current diagnostic criteria capture. It underscores the need for improved recognition of symptoms and better diagnostic tools to help individuals determine whether gluten is a contributing factor to their health concerns. Additionally, non-biological factors, such as women's greater awareness of their own health and higher likelihood of seeking medical advice, may contribute to the higher reported prevalence of gluten sensitivity among females (Borroto-Escuela et al., 2021). However, the striking gender disparity warrants further investigation into the complex interplay of biological, hormonal, and sociocultural influences on the development and presentation of NCGS. Understanding these factors will be crucial for refining diagnostic approaches and tailoring more effective management strategies.

Although initial studies concentrated on populations of European lineage, new evidence suggests NCGS may affect people of all ethnicities (Igbinedion et al., 2017). For example, despite lower captured celiac disease diagnoses in these geographic areas, studies among cohorts from South America, Africa, and Asia show significant gluten sensitivity rates and gluten-free diet compliance (DiGiacomo et al., 2013). More detailed analysis within diverse populations would yield valuable global NCGS epidemiological information, even though differences may reflect differences between the intrinsic immune response to gluten versus adaptive autoimmune responses (Igbinedion et al., 2017). Comprehending the possible hereditary and cultural factors that impact susceptibility may facilitate customized diagnostic and therapeutic strategies that consider patients' backgrounds in society.

## **Presentation of Gluten Sensitivity**

A defining feature of Non-Celiac Gluten Sensitivity (NCGS) is the onset of intestinal and extraintestinal symptoms triggered by gluten ingestion (Elli et al., 2015). Gastrointestinal symptoms resemble irritable bowel syndrome, encompassing diarrhea, abdominal pain, bloating, and nausea (Igbinedion et al., 2017). Extraintestinal manifestations vary widely, including neurological symptoms like headaches, "brain fog," anxiety, depression, fatigue, joint pain, and numbness (Igbinedion et al., 2017). A subset of patients also presents with eczema, rhinitis, asthma, or anemia (Elli et al., 2015). Symptoms emerge hours to days following gluten consumption and can persist if gluten intake continues (Igbinedion et al., 2017). The variability and non-specific nature pose challenges for differentiation from other gluten-related disorders.

While abdominal discomfort represents the most common complaint, systemic symptoms are reported in 35-66% of NCGS patients and can overshadow or occur in isolation from gastrointestinal upset (Igbinedion et al., 2017). Bloating constitutes the predominant gastrointestinal sign across adults and children with 74-91% rates, followed by abdominal pain, nausea, aerophagia, and gastroesophageal reflux (Igbinedion et al., 2017). Among neurological manifestations, foggy mind or headaches arise most prominently with frequencies of 14-57%, distantly trailed by mood disturbances, fatigue, limb numbness, ataxia, and hallucinations occasionally documented (Igbinedion et al., 2017). Up to 40% experience multiple concurrent extraintestinal sequelae spanning cutaneous, respiratory, musculoskeletal, hematologic, and other organ involvement (McAllister et al., 2019). While patient demographics like age and sex influence specific symptom profiles, multifaceted system-wide presentations reinforce viewing NCGS as a complex multi-organ sensitivity disorder.

From the case study on gluten sensitivity that has been presented (Calabriso et al., 2022), the 38-year-old female patient exhibited clinical manifestations aligning with common NCGS symptomology. Her recurring gastrointestinal distress upon wheat and gluten ingestion, improved by a gluten-free diet, reflects presentation documented in broader NCGS cohorts (Igbinedion et al., 2017). While celiac disease was excluded through diagnostic testing, her symptoms substantiate previous reports on autoinflammatory activation potentially instigated by gluten components in NCGS pathophysiology (Roszkowska et al., 2019).

## **Pathophysiological Mechanisms**

While the precise pathophysiological processes remain ambiguous, evidence implicates innate immune system activation, epithelial barrier dysfunction, and dysbiotic changes as contributors to NCGS (Roszkowska et al., 2019). Elevated levels of toll-like receptor 2 signaling molecules and heightened intestinal permeability suggest gluten peptides may trigger inflammatory pathways by escaping intestinal barriers (Roszkowska et al., 2019). Alterations in intestinal microbiota, increased IGA anti-gliadin antibodies, and cytokine involvement also indicate some degree of immune activation akin to, but less pronounced than, celiac disease (Roszkowska et al., 2019; McAllister et al., 2019). Additionally, carbohydrates like fructans abundant in wheat products have demonstrated the capability to induce gastrointestinal symptoms reminiscent of NCGS, suggesting FODMAP malabsorption may play a secondary role (Igbinedion et al., 2017). Further research is essential to clarify mechanisms and discern components eliciting reactions.

Immune-based hypotheses suggest that, much like in celiac disease, specific gluten peptides bypass compromised epithelial junctions, engaging antigen-presenting cells and triggering cytokine release from intraepithelial lymphocytes (Professional, C. C. medical, n.d.). This immune activation leads to the recruitment of lymphocytes and macrophages, fostering both intestinal mucosal and systemic inflammation (Professional, C. C. medical, n.d.). Alternatively, the stress-induced epithelial pathway model proposes that physiological stressors disrupt tight junction integrity, increasing epithelial permeability and allowing gluten to infiltrate submucosal layers (Fasano, 2012). This heightened permeability exposes the immune system to microbial antigens and other luminal components, further fueling inflammation (Fasano, 2012). While both theories describe potential mechanisms by which non-celiac gluten exposure disrupts homeostasis, they differ in identifying the primary antigen responsible for initiating the immune response.

Beyond immunological reactions, the microbiome represents another mediator theorized to elicit and exacerbate NCGS manifestations independently and secondarily. Compelling evidence shows wheat components, including gluten proteins and amylose-trypsin inhibitors, directly activate innate immune receptors like toll-like receptor 4 or nucleotide oligomerization domains stimulating proinflammatory signaling (Junker et al., 2012). Furthermore, like models in inflammatory bowel disease, gluten-induced malabsorption and changes in the intestinal barrier may modify microbiota, allowing aggressive bacteria to proliferate and trigger additional immune responses (De Palma et al., 2009). According to Junker et al. (2012), dysbiosis may also cause gastrointestinal distress by accelerating the fermentation of carbohydrates and gas production. Furthermore, considering microbiome transfer experiments in germ-free mice confirm the ability for NCGS phenotype induction, microbiota populations likely serve pivotal NCGS functions beyond compounding intestinal damage (Junker et al., 2012).

Ultimately, given their potential to work in concert to intensify inflammation, understanding the relationship between intestinal barrier integrity dysfunction, stress, and gluten sensitivity is still crucial. Psychosocial stress notoriously disrupts gut epithelial tight junctions by releasing corticotropin-releasing factor, substance P neurotransmitters, and mast cell activation pathways (Konturek, Brzozowski, & Konturek, 2011). Localized and systemic immune responses are triggered by the secondary translocation of food antigens and microbiota (Konturek et al., 2011). Meanwhile, direct infection studies confirm specific gliadin peptides prompt enterocyte apoptosis and degrade transmembrane junctions (Calabriso et al., 2022). Hence, in gluten-sensitive individuals, the combined influence of gluten oligopeptides and psychological stress factors enabling their transport may substantially amplify reactions. Stress management could dually dampen baseline intestinal hyperpermeability and reactivity to episodic gluten exposures.

## **Diagnosis of Gluten Sensitivity**

No biomarker or laboratory test definitively diagnoses NCGS (Igbinedion et al., 2017). Instead, diagnosis relies upon symptomatic assessment, exclusion of alternative etiologies through extensive testing, and gluten withdrawal and rechallenge trials (Catassi et al., 2015). Patients undergo a minimum 6-week gluten-free diet and monitor for symptom changes before methodically reintroducing gluten to confirm the causative relationship (Catassi et al., 2015). This process underpins the diagnostic protocol in the case study, substantiating the efficacy of a stepwise elimination approach to identify gluten sensitivity (Calabriso et al., 2022). Blind placebo-controlled trials are the gold standard, though they are rarely implemented in routine clinical practice (Catassi et al., 2015). Refining biomarkers and diagnostic techniques is paramount for enabling earlier diagnosis and treatment.

Excluding confounding disorders with overlapping gastrointestinal symptoms like inflammatory bowel disease, microscopic colitis, pancreatic insufficiency, small intestinal bacterial overgrowth, and lactose intolerance remains imperative before confirming NCGS (Igbinedion et al., 2017). Evaluating for extraintestinal conditions, including iron deficiency anemia, IgE-mediated wheat allergy, and psychiatric disorders, also helps characterize the clinical picture (Roszkowska et al., 2019). As showcased in the case report, initial bloodwork ruled out celiac disease, and iron studies together with systematic diet trials facilitated isolating gluten as the inciting culprit among other secondary causes like irritable bowel syndrome frequently co-occurring with NCGS (Calabriso et al., 2022).

No serological, genetic, histological, or fecal markers conclusively identify NCGS (Roszkowska et al., 2019). Up to 50% of patients demonstrate positive IgA or IgG anti-gliadin antibodies, 20% display antinuclear antibodies, and about 15% exhibit anti-enterocyte IgA or IgG antibodies; however, none prove specific or adequately sensitive for diagnosis (Igbinedion et al., 2017). Elevated fecal eosinophil cationic protein, interleukin-8, and interferon-gamma levels signal unspecified intestinal inflammation (McAllister et al., 2019). DQ2 and DQ8 haplotypes occur regularly, though rates equal general population frequencies (Igbinedion et al., 2017). Histopathological changes generally remain unremarkable or negligible aside from occasional lymphocytic infiltration (McAllister et al., 2019). Hence, blinded gluten challenge combining metastable symptom monitoring and systematic reintroduction is the primary diagnostic technique for confirming causality.

## **Treatment Approaches**

A strict gluten-free diet constitutes the cornerstone treatment for NCGS, with most patients exhibiting symptom control when adherence is maintained (Roszkowska et al., 2019). Eliminating grains containing gluten proteins like wheat, barley, and rye can significantly improve gastrointestinal and systemic manifestations (Elli et al., 2015; Roszkowska et al., 2019). Accordingly, the case study patient demonstrated marked amelioration of symptoms through adhering to a gluten-free diet (Calabriso et al., 2022). Additional patients report improved well-being with concurrent probiotic and prebiotic regimens to counterbalance intestinal microbiota disruption (Calabriso et al., 2022). Though still investigational, certain dietary supplements, including digestive enzymes like prolyl endopeptidase, have exhibited the capacity to degrade immunotoxic gluten peptides and warrant further research (Calabriso et al., 2022). Ultimately, multi-dimensional lifestyle changes, not pharmaceuticals, currently serve as frontline approaches for NCGS.

Eliminating gluten necessitates vigilance in navigating trace exposures in processed foods, condiments, and supplements with precise inspection of labels denoting the presence of wheat, rye, and barley ingredients (Elli et al., 2015). Given the ubiquity of gluten-containing additives, patients should receive detailed education by expert dieticians to identify overt and hidden sources. One way to diversify nutritional intake and avoid restrictive eating is to use naturally gluten-free ancient grains such as rice, corn, millet, and amaranth as a wheat substitute (Elli et al., 2015). The effectiveness of commercial gluten detection products in detecting contamination has been the subject of conflicting research (Elli et al., 2015). Although these orientations are beneficial for recently diagnosed patients, they shouldn't take the place of carefully reading labels and being aware of familiar places where gluten can be hidden, such as soy sauce, because deficiencies have been found that make it challenging to identify specific sources of gluten.

There is ongoing discussion regarding the necessity of removing all grains, regardless of their innate gluten content. Permitting gluten-free grains could, on the one hand, maintain fiber consumption and diversify choices in contrast to extreme restriction (Roszkowska et al., 2019). On the other hand, even in the absence of gluten, overlapping biological compounds in grains may worsen symptoms; these can be better managed with expansive limitation (Roszkowska et al., 2019). The effectiveness of global exclusion diets has been supported by a blinded trial involving non-celiac IBS cohorts, which found that gluten- and gluten- and grain-free diets improved gastrointestinal symptoms more than placebos (Roszkowska et al., 2019). As individuals who resist change, an indefinite multigrain eradication plan and a phased reintroduction of particular grains could help determine the optimal sustainable dietary composition.

Adjunctive therapies like probiotics, prebiotics, and digestive enzymes aim to lessen the adverse effects of gluten reactions by restoring eubiosis, preserving the integrity of the intestinal barrier, and accelerating the digestion of gluten (Roszkowska et al., 2019). Several probiotic randomized control trials utilizing various genera and strains—including Bifidobacterium infantis—have demonstrated a particular efficacy in mitigating the symptoms of non-communicable gastrointestinal syndrome (NCGS), such as bloating, altered stool consistency and abdominal pain, by Junker et al. (2012). Specific Lactobacillus acidaphilus and Saccharomyces boulardii also show quantifiable advantages (Junker et al., 2012). Though probiotic species and protocols warrant further optimization, certain products promise to mitigate complications like microbiota disruption in gluten-sensitive cohorts.

Another novel strategy to promote helpful microbial species like Bifidobacterium is prebiotic supplementation with the hormone insulin and galactooligosaccharides (Junker et al., 2012). More thorough, rigorous studies of prebiotic regimens are still required to support preliminary findings, even though small trials can potentially restore inflammatory parameters and improve manifesting symptoms (Junker et al., 2012). Likewise, for digestive enzymes, early reports demonstrate that gluten-degrading preparations containing prolyl endopeptidases can ameliorate enteropathy and manifestations in celiac disease, laying the foundation for expanded NCGS research (Papandreou et al., 2020). Hence, scientists posit sensible future protocols should evaluate integrated symbiotic formulations pairing selected probiotics and prebiotics with enzymatic activity to holistically transform gluten metabolism and microbiome landscapes (Papandreou et al., 2020).

Beyond nutritional intervention, incorporating stress-reduction practices and physical activity bears consideration in mitigating systemic NCGS symptoms related to inflammation (Elli et al., 2015; Roszkowska et al., 2019). As the case study protocol highlights, yoga, meditation, breathing exercises, exercise routines, and prioritizing adequate sleep could supplement gluten-free dietary changes (Calabriso et al., 2022). Though clinical studies directly assessing such holistic complementary approaches for NCGS are lacking, their emerging promise for related gastrointestinal conditions indicates potential areas for investigation (Calabriso et al., 2022).

## **Prognosis and Long-Term Consequences**

While gluten withdrawal commonly induces swift improvements, strict lifelong adherence is often necessary to sustain resolutions of chronic symptoms or inflammation (Elli et al., 2015). Lapses in compliance or trace gluten exposures can precipitate relapse in some NCGS patients (Elli et al., 2015). However, interestingly, a subset of individuals appear capable of tolerating occasional gluten meals or can revert to regular diets after a period of gluten restriction with no recurrence of adverse reactions (Elli et al., 2015). More research into prognostic outcomes could enlighten whether NCGS represents a completely irreversible condition or an interim gluten hypersensitivity.

Associations between NCGS and subsequent autoimmune disease development remain uncertain. Some posit early treatment of NCGS may obstruct the triggering of additional gluten-related disorders over time (McAllister et al., 2019). One study detected an increased likelihood of NCGS patients testing positive for anti-gliadin antibodies later in life compared to non-NCGS controls, suggesting escalating immunoreactivity (Volta, Caio, Stanghellini, & De Giorgio, 2014). However, more extensive longitudinal studies tracking long-term antibody and symptom changes are needed to further investigate relationships between gluten sensitivity states. While strict dieting often successfully controls acute reactions, nutritional adequacy over decades merits assessment given restrictive eating risks. Cross-sectional surveys reveal that 35-45% of adults on gluten-free diets exhibit some form of nutritional deficiency or imbalance, including inadequate fiber, vitamin D, calcium, iron, zinc, magnesium, folate, or omega-3 fatty acids (Ballestero-Fernández et al., 2021).

## **Quality of Life and Psychological Functioning**

Beyond physical distress, NCGS imparts substantial psychosocial and emotional burdens for affected individuals. Qualitative reports detail adverse impacts on daily functioning, the ability to dine out with friends, and strictly monitoring one's diet (Calabriso et al., 2022). Quantitatively, patients describe impaired vitality and social functioning using standardized quality-of-life scales (Calabriso et al., 2022). Feelings of isolation, embarrassment, guilt, anger, and frustration represent additional complex psychological challenges conveyed by those adhering to gluten-free diets, with some even meeting the criteria for depression (Calabriso et al., 2022).

While the case study showed quality of life improvement and work functioning enhancement after symptom cessation (Calabriso et al., 2022), long-term, rigid dietary restrictions pose ongoing psychological challenges warranting support. Optimal management should encompass holistic measurement of patient well-being using validated mental health screening tools coupled with multidisciplinary collaboration between gastroenterologists, psychiatrists, therapists, and dietitians.

Beyond negative emotions, tangible lifestyle constraints accompany therapeutic dieting. Vigilance inspecting ingredient labels, calling ahead to vet restaurant menus, traveling with custom food, and disclosing diets to avoid social offense manifest as daily hindrances (Kushwah & Maheshwari, 2020). Comparatively lower health-related quality of life measures across mental and physical domains in non-celiac gluten sensitivity versus celiac disease patients further capture profound lifestyle sacrifices (Casellas et al., 2015). A widespread dissatisfaction and feelings of deprivation may be countered by practicing mindfulness that promotes adoption, self-compassion encouragement, and support groups to exchange advice on managing obstacles (Kushwah & Maheshwari, 2020).

## **Diagnostic and Treatment Limitations in Routine Clinical Practice**

Patients are becoming more aware of NCGS, but doctors' constraints in their day-to-day work prevent prompt detection and treatment. The inability to identify NCGS from a wide range of differential diagnoses is impeded by the need for a valid biomarker (Igbinedion et al., 2017). This issue worsens because healthcare providers and other specialists, besides gastroenterologists, need to be more knowledgeable about acceptable diagnostic protocols and trained in organized elimination procedures (Igbinedion et al., 2017). Once diagnosed, optimal dietary guidance is hampered by limited access to dietitians skilled in gluten-free nutrition planning (Igbinedion et al., 2017). Patients face additional challenges due to financial constraints that limit their access to more expensive specialized gluten-free nourishment (Igbinedion et al., 2017). These shortcomings showcase the need for augmented NCGS education and resource allocation to support frontline providers and vulnerable patients.

In surveys assessing provider knowledge, under 50% of physicians expressed confidence in recognizing hallmark NCGS symptoms or distinguishing the condition from celiac disease and wheat allergy (George et al., 2022). Fewer than 25% regularly applied accurate elimination diets and gluten challenges for diagnosis; instead, they primarily relied upon serological testing that needed more sensitivity and specificity (George et al., 2022). Gastroenterologists exhibited the most significant diagnostic competency, expected given specialized exposure, though even average scores on knowledge assessments barely surpassed 60% correct (George et al., 2022). Efforts to boost access to continuing medical education focusing on NCGS and promote advanced training opportunities remain vital to uplift diagnostic skills, particularly among primary care providers and allied health fields interacting with undifferentiated early presentations.

# **Future Research Directions**

## **Elucidating definitive pathophysiological mechanisms**

Although a correlation between gluten ingestion and symptom onset in non-celiac gluten sensitivity (NCGS) has been established, the underlying mechanisms remain poorly defined (Matsumura et al., 2023). Hypothesized pathways—including immune activation, alterations in small intestinal barrier function, gluten’s opioid-like effects, and microbiome-driven interactions—require further investigation through randomized controlled trials (RCTs) that incorporate biomarker assessments and standardized gluten challenges (Matsumura et al., 2023). A clearer understanding of these contributing factors could improve diagnostic precision, expand therapeutic strategies beyond gluten avoidance, and establish reliable biomarkers for monitoring treatment efficacy.

## **Identifying diagnostic biomarkers**

The absence of confirmatory serological, genetic, or histological features hampers NCGS diagnosis, necessitating the exclusion of alternate etiologies in symptomatic patients responding to gluten withdrawal (Igbinedion et al., 2017). Efforts to discover reliable biomarkers could significantly advance diagnostic capabilities. Analyzing patients with blinded gluten challenges versus controls may reveal immunological, genetic, metabolic, or gastrointestinal markers distinguishing confirmed gluten reactivity. Once verified through additional RCTs, these lab-based or point-of-care diagnostics could revolutionize clinical evaluation and monitoring (Igbinedion et al., 2017).

## **Developing gold standard challenge procedures**

Despite recognizing the utility of gluten challenges in diagnosing NCGS, more consensus is needed regarding optimal methodological approaches. Areas requiring clarification include Challenge duration and intervals. Both short (days) and prolonged (weeks) regimens have been incorporated, but comparisons within individual patients still need to be made (Saha & Milman, 2021). Randomization and blinding protocols. While ideal for minimizing bias, deception methods warrant further ethical consideration (Saha & Milman, 2021). Gluten dosage and formulation. Elevating doses or observing responses to different gluten sources could enhance detection sensitivity (Saha & Milman, 2021). Concurrent elimination diets. Whether co-eliminating other grains or foods during challenges confers added specificity requires investigation (Saha & Milman, 2021).

Establishing standardized, evidence-based challenge protocols could enhance diagnostic consistency globally, ensuring the reliable application of this critical assessment tool. Emerging digestive enzymes capable of breaking down gluten represent a promising avenue for therapeutic intervention. These novel enzymes may offer greater dietary flexibility, potentially reducing the need for strict gluten avoidance while mitigating associated symptoms.

 Items that are presently in the early stages of testing include:

* AN-PEP: cysteine endoprotease from germinating barley seeds (Martinez et al., 2019)
* STAN1: bacterial prolyl endopeptidase from Flavobacterium (de Lourdes Moreno et al., 2021).
* Prolyl endoprotease from Geobacillus stearothermophilus, a non-pathogenic bacterium, is BL-7010 (Qiu et al., 2021).

As stand-alone or adjunctive treatments, these new-generation enzymes may help further individualize medical and nutritional approaches for individuals with demonstrable gluten reactivity if they are effective without causing significant adverse effects.

## **Exploring gluten contamination thresholds provoking symptoms**

Although NCGS patients often report feeling better when they avoid gluten entirely, it is unknown if small gluten exposure equivalent to those found in products with a gluten-free label causes adverse effects. To improve health-related quality of life, dose-response challenges that pinpoint each person's unique thresholds for recurrent symptoms may be a better way to guide personal tolerance limits. It is also essential to consider allowing less restrictive diets without compromising long-term intestinal healing (Rangel Paniz et al., 2022).

## **Clarifying the utility of concurrent grain elimination diets**

Anecdotal reports suggest that individuals with non-celiac gluten sensitivity (NCGS) experience greater symptom relief when avoiding not only gluten-containing grains but also other cereals (Duncanson et al., 2021). However, limited controlled studies have examined the therapeutic value of excluding grains such as rice, corn, and oats, which are often used as nutritional substitutes. Understanding whether this broader dietary restriction provides additional clinical benefits—while also evaluating its impact on symptom presentation versus serological markers—remains a critical research gap. Furthermore, assessing the risk of nutritional deficiencies associated with overly restrictive diets is essential to developing balanced, evidence-based dietary recommendations (Duncanson et al., 2021).

## **Identifying psych-emotional profiles and risk factors**

Appreciating bidirectional brain-gut interactions in functional gastrointestinal conditions characterizing psychological and psychosocial factors influencing susceptibility, clinical presentation, and management outcomes seems imperative when addressing a disorder like NCGS with conceivable mind-body origins (Wahid, 2021). Whether unique personality traits, previous adverse life events, concurrent mood disorders, perceived stress levels, somatic amplification tendencies, coping reserves, and social support networks act as predisposing and/or perpetuating etiologic elements merits investigation through mixed-methods research incorporating quantitative psychometric instruments and qualitative interview techniques (Wahid, 2021). This could enable targeting multimodal lifestyle-based interventions towards high-risk groups.

## **Investigating diet over restrictiveness and nutritional deficiencies**

Considering inherently limited food choices following a gluten-free diet, patients eliminating additional items risk developing nutritional deficiencies over time. Nonetheless, more information is needed on the adequate intake and serum levels of essential nutrients such as iron, calcium, fiber, and B vitamins in NCGS. A directed supplementation program based on surveillance testing and monitoring for warning indicators such as amenorrhea, osteopenia, and anemia may prevent developing deficiencies (Fiot et al., 2022). To balance removing perceived triggers against guaranteeing adequate consumption of macronutrients and micronutrients, tailored liberalization efforts could benefit from evaluating any correlations between the degree of deprivation and sustained symptom control.

## **Establishing best practices for multidisciplinary care coordination**

For newly diagnosed patients, transitioning to a gluten-free lifestyle can be particularly challenging, requiring them to manage emotional responses, modify long-established eating habits, source specialty ingredients, and learn new cooking techniques—all while remaining vigilant against unintentional gluten exposure (Walker et al., 2021). This adjustment burden can be alleviated through comprehensive, multimodal support, including peer networks, specialized dietitians, lifestyle coaching, mind-body interventions, and ongoing gastrointestinal care (Walker et al., 2021). Developing integrated support models that seamlessly incorporate dietary, psychological, and social aspects into a unified framework could enhance patient empowerment and adherence by implementing adaptable, evidence-based strategies across diverse treatment settings.

## **Assessing the usefulness of complementary wellness approaches**

Some NCGS patients may benefit even more from holistic practices like mindfulness, meditation, yoga, acupuncture, massage therapy, and meeting new dietary restrictions (Schuck, 2017). Further research should be done on integrating these complementary wellness interventions, either alone or combined, as supplemental methods to support traditional elimination diets and symptom-targeted pharmaceutical treatments. Clinicians can provide more personalized lifestyle modification counseling if they can quantify the contributions made to enhancing health status, quality of life, long-term adherence, and underlying pathophysiological mechanisms related to psychoneuroimmunology pathways. Schuck (2017).

# **Conclusion**

In conclusion, gluten sensitivity is a complex condition encompassing nutritional, immunological, and microbiological factors—one that modern medicine has often overlooked, misdiagnosed, and inadequately addressed, particularly in the context of mind-body interactions. Confronting this challenge requires not only rigorous scientific inquiry into its underlying mechanisms through clinical trials and laboratory research but also the presence of compassionate practitioners who foster therapeutic optimism.

Bridging the gap between bench research and clinical best practices necessitates a nuanced understanding of the unpredictable nature of gluten sensitivity, which affects gastrointestinal, cognitive, and psychological health, as well as overall quality of life. Creating supportive environments that cultivate long-term self-efficacy and empowerment is essential for effective management.

Furthermore, gluten sensitivity challenges medical professionals to adopt a stance of philosophical humility, recognizing the broader implications of food sensitivities on well-being. Just as recently acknowledged lifestyle-limiting allergies have reshaped our understanding of dietary health, this condition invites a renewed appreciation for the wisdom of ancient healing traditions, balancing simplicity with comprehensive care. At its core, personalized medicine requires stepping into the patient's experience, acknowledging their lived reality, and integrating both scientific rigor and empathetic care to achieve meaningful therapeutic outcomes.

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