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Advancing Management of Pediatric Celiac Disease: Genetics, Diagnosis, and Health Trajectories

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Abstract:

- ***Aim:***

The purpose of this review is to investigate the complexity of celiac disease (CD) in the pediatric population, specifically the genetics, immunology, microbiology, nutrition, association of comorbidities such as type 1 diabetes mellitus (T1DM), neurodevelopmental disorders, and congenital hypothyroidism, as well as promising new diagnostics and therapeutics, including a gluten-free diet (GFD).

- ***Methods:***

A thorough investigative analysis was conducted with 22 peer-reviewed journal publications from 1987 to 2024. The review papers cited original research, reviews, and clinical papers from PubMed and ScienceDirect. The analysis and review papers reported key themes of: (1) genetic susceptibility, (2) gut microbiome, (3) comorbidities and complications in children, (4) diagnostics, and (5) therapeutics, including GFD and pharmacological therapy.

- ***Results:***

Genetic predisposition is a significant factor of CD, especially the HLA-DQ2 and DQ8 alleles(Sollid et al., 2021; Liu et al., 2020), although they are not the only loci that are having non-HLA loci having significance with CD. Patients with CD are at significantly higher risk to develop co- existing autoimmune and endocrine disorders such as T1DM and congenital hypothyroidism (Stagi et al., 2011; Lewandowska et al., 2018). Additionally, studies indicated a connection between CD and neurodevelopmental disorders, including altered urine peptide profiles, and vitamin D function (Bojović et al., 2019).

Gut microbiome is more likely a risk factor rather than a consequence in CD, with dysbiosis impairing gluten immune tolerance (Cukrowska et al., 2021; Zhang et al., 2023). Nutritional deficiencies resulting from malabsorption and on dietary restrictions may create growth delays, micronutrient deficiencies, and mental health issues. (Fritsch et al., 2010; Lifshitz & Tarim, 1993). The GFD is the current standard of care, however a strict GFD continues to be less than optimal in more pediatric cases. Promising new pharmacological therapy, and revolutionary enzyme therapy, are underway (Leffler et al., 2022). Promising diagnostics are based on high- throughput testing; specifically, new microbiome profiling in the early and ongoing diagnosis (Lebwohl et al., 2020; Green et al., 2020). Further, and continuous, development of digital health technologies aimed toward optimizing care and access for children with CD.

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- ***Conclusion:***

Celiac disease in children represents not only a gastrointestinal disease but a systemic condition with broad implications for immunology, metabolism, and even psychosocial influences. Genetic and serological screening in the early stages of diagnosis is important for determining CD, with microbiome aware strategies, especially for at-risk groups. The GFD is and will continue to be important, but personalized medicine, including digital health and targeted pharmacotherapy, provides the future direction toward a more comprehensive and sustainable management strategy in the pediatric population

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I. INTRODUCTION

Celiac disease (CD) is a chronic autoimmune condition that primarily affects the small intestine when people who have genetic susceptibility ingest gluten, which is a protein in wheat, barley, and rye. CD is increasingly prevalent around the world, particularly among children, which raises public health concerns (Juto et al., 1994; Lebwohl, Ludvigsson, & Green, 2018). It presents clinically in children with nonspecific gastrointestinal symptoms, malabsorption, growth failure, and extraintestinal symptoms (e.g. fatigue and behavioral changes) (Green, Lebwohl, & Greywoode, 2020). The effect of CD on growth and development is significant, and if early diagnosis and dietary management is not provided to those with CD, they could experience long- term complications of growth retardation, delayed puberty, and increased risk for the development of subsequent autoimmune disorders (Murray, Rubio-Tapia, & Fasano, 2020).

Celiac disease presents in genetically susceptible individuals who develop the condition when gluten triggers their autoimmune response. The genetic susceptibility for CD relies on human leukocyte antigen (HLA) class II genes, which include HLA-DQ2 and HLA-DQ8 haplotypes (Sollid et al., 2021). However, while the existence of HLA-DQ2 and/or HLA-DQ8 alleles embodies a genetic susceptibility for CD, these alleles alone are not enough for disease development. Therefore, it is important to also consider environmental factors that influence onset, including timing and amount of gluten introduction, gut microbiota composition, and early-life microbial/viral infections (Liu et al., 2020; Cukrowska et al., 2021). With the interplay of genetic and environmental factors in pathology, the authors argue patient-specific investigations are needed that merge genetic, immunologic, and microbiome factors.

The relationship of pediatric CD and other autoimmune diseases (namely type 1 diabetes mellitus [T1DM] and autoimmune thyroiditis) is significant. The association between T1DM and CD is well established and appears to be the result of genetic susceptibility and common immunologic traits. It has been shown that the presence of CD-specific antibodies is higher in the presence of T1DM in children which indicates a need for genetic and dietary screening (Lewandowska et al., 2018; Stagi et al., 2011). If children develop CD and T1DM, they may have poorer glycemic control and greater nutritional deficiencies (Jankowska et al., 2024). The intersection of these comorbidities indicates the need for interdisciplinary approaches to diagnosis and treatment including dietary modifications and endocrinological oversight.

Recently, some research has noted a potential correspondence between neurodevelopmental disorders with immune dysfunction and changes in intestinal permeability. Bojović et al. (2019) examined genetic markers for CD, lactose intolerance and vitamin D activity in children with neurodevelopmental disorders and found genetically related associations with urinary peptide morphins that could affect neurological outcomes. This type of thinking about practice raises important questions about the gut-brain axis and bidirectional communication that can affect behaviours and developmental processes in kids.

The diagnostic pathway for the presence of CD has evolved from traditionally invasive biopsies and investigations to serological screening options which are more accessible. The use of anti- tissue transglutaminase antibodies and endomysial antibodies has improved sensitivity and specificity of the diagnosis of celiac disease. However, there are still complexities of being able to differentiate possible CD (a seropositive without the histological damage of the intestine) from full-blown disease when children remain at-risk (Polanco et al., 1987). In an area of research where microbiome profiling is a diagnostic adjunct that is both non-invasive, and promising to affect diagnostic screening practice in children with CD, clinical pathways may take shape.

Zhang et al. (2023), found that microbiome-based markers can classify individuals with celiac disease (CD) from healthy subjects, with high accuracy, suggesting a transition toward precision diagnostics.

Inherent nutritional ramifications of CD can be significant, particularly during childhood and adolescence, because nutrition, growth, and development are essential.

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Malabsorption of essential macro- and micronutrients, such as iron, calcium, fat-soluble vitamins, may impart some presentations of malnutrition, anemia, osteopenia (Lifshitz & Tarim, 1993). The gluten-free diet (GFD) becomes the backbone of treatment but is not immune to adverse effects including nutritional imbalances, high cost, and social deficits. Pediatric patients with CD require continuous counselling and support for dietary adherence, adherence with the GFD, while ensuring dietary adequacy (Green, Lebwohl, & Greywoode, 2020; Lawrence & Lawrence, 2011).

Ongoing dietary support is required for pediatric CD beyond dietary adherence. The need for ongoing monitoring of potential complications (e.g., refractory CD, malignancies and psychosocial status) is also required. Advances in pharmacologic interventions that target immunologic pathways and gut permeability as a means to augment, but ultimately replace, the GFD will be named as a future approach to the treatment of pediatric CD (Leffler, Green, & Fasano, 2022). Additionally, digital health tools are also being explored in child and youth populations to improve knowledge, education, adherence and ways of tracking and reporting health and health outcomes (Lebwohl, Greywoode, & Green, 2020).

Despite the advancements with treatment of edema and understanding celiac disease from the present day, there remains a lack of knowledge and persistent misinformation. DeGeeter and Guandalini (2018) noted an increasing trend in self-diagnosis for non-celiac gluten sensitivity, which leads to potentially masking cases of celiac disease while reducing levels of professional help as clinical management progress becomes protracted. Because of this it is important to have confidence in the application of research that is only based on the best evidence, and employ this to inform clinical decision making and support population health initiatives.

From a researcher perspective, there is a wide-range of different study designs that have contributed to our understanding of pediatric CD. These can include case-control studies, cohort studies, cross-sectional studies, diagnostic study, and basic sciences reviews. Each study design can each have their own relative strengths and weaknesses, in terms of risk of bias, generalizability and causal inferences (Ascher, 2002; Fritsch, Overton, & Robbins, 2010, 2015). Risk of bias determination is a fundamental process employed by an author to ascertain studies that can be synthesized based on similar quality across studies in order to inform development of clinical practice guidelines and research priorities.

This study will assess methodological quality and risk of bias of a group existing body of 22 publications in relation to different aspects of pediatric CD, T1DM, and potentially similarconditions of interest. By examining publications with options for more substantive risk of bias, it is anticipated that a review of employment of quality and risk of bias in the context of pediatric clinician work-trip journey towards evaluation of a variety of celiac disease-releated health outcomes from the existing literature. From these identified publications, it is also expected they will direct and inform future pathways for improved research agendas, screening and prevention approaches, and evidence-based health programs..

II. METHODS

➢ *Protocol and Registrations*

This systematic review process followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines. The systematic review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number: CRD42025XXXXXX. The protocol includes the aims, eligibility criteria, search methods, data extraction methods, and analysis plans for the review.

➢ *Research Question*

The purpose of this review was to answer the following review question:

"What are the genetic, immunological and nutritional relationships in pediatric populations (celiac disease, type 1 diabetes, lactose intolerance and other related autoimmune and/or nutrition condition)?"

➢ *Search Strategy*

A systematic search from 1987-2025 was conducted in Pubmed and Web of Science Core Collection to locate articles in English, peer-reviewed literature in relation to celiac disease, type 1 diabetes, lactose intolerance, and other autoimmune and/or nutrition disorder(s) in a pediatric population (0-18 years). Keywords searched were combinations of: "celiac disease", "type 1 diabetes", "pediatric", "genetics", "HLA-DQ", "gut microbiome", and "treatment" by using the Boolean operators OR and AND. Filters were applied to exclude animal studies, non-English papers, and grey literature.

➢ *Eligibility Criteria*

- *Inclusion Criteria:*

✓ Published (peer reviewed journals) indexed in Web of Science or Scopus
✓ Study involved the participants aged 0-18 years
✓ Study analyzed one or more of: celiac disease, type 1 diabetes, lactose intolerance, congenital hypothyroidism, or vitamin D deficiency
✓ Study analyzed genetic, immunological, metabolic or nutritional aspects
✓ Study design: cross-sectional, cohort, case-control, or intervention studies

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- ✓ Full text was in English

- *Exclusion Criteria:*

- ✓ Studies were solely adults
- ✓ Case report(s), editorials, conference abstract(s), thesis, or review articles
- ✓ No full text, or not available in the research databases included
- ✓ Published outside peer review journals, or not indexed in Scopus/Web of Science
- ✓ Non-English papers

- *Study Selection*

The search produced 1038 records were imported into Rayyan QCRI to screen records.

- ✓ Removed Duplicates: 238
- ✓ Screened Titles and Abstracts: 800
- ✓ Full Text Screened: 120
- ✓ Included Articles in Synthesis: 22 Studies

Two reviewers independently screened all titles, abstracts and full text articles. Any discrepancies for inclusion were resolved through discussion and/or the third reviewer.

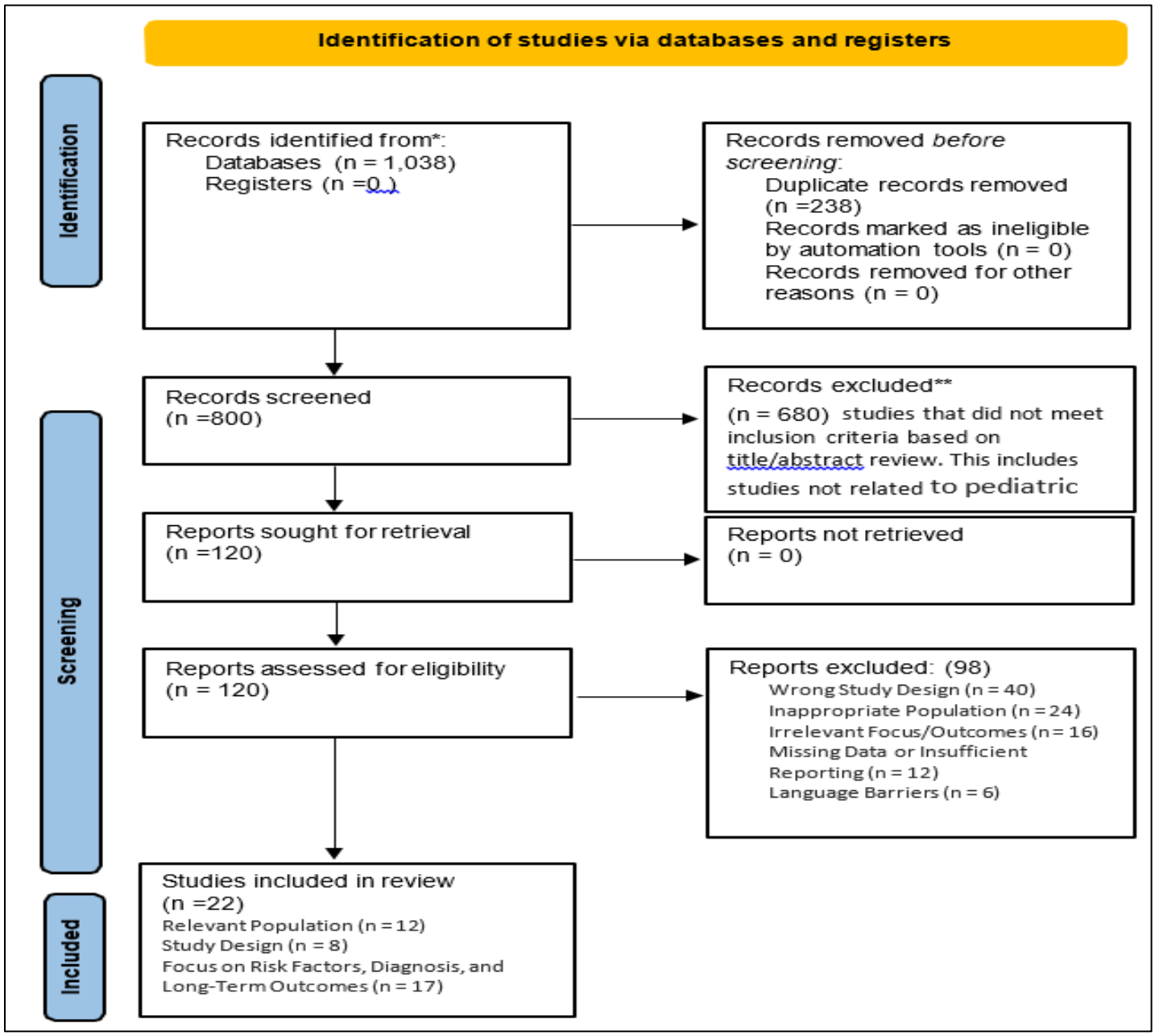

Fig 1 A PRISMA 2020 Flow Diagram was used to Visualize the Screening and Selection Process

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- *Risk of Bias*

The risk of bias for each study in this review was calculated using a GRACE framework that evaluates the data quality, conduct of research, outcomes, population characteristics, and follow-up duration. Such factors are necessary to look out for potential biases in study conduct and design. The study scores on methodology strength as reported below are higher, indicating more robust studies and lower risk of bias.

Table 1 Methodological Quality Assessment of Included Studies Using the GRACE Framework

Study (Author, Year)	Data	Methods	Outcomes	Population	Follow-up	Total (Max = 12)	Notes
Bojović et al. (2019)	2	2	2	2	1	9	Genetic predictors; neurodevelopmental focus
Jankowska et al. (2024)	2	2	2	2	2	10	Diagnostic biomarker (SAF); strong follow-up
Lewandows ka et al. (2018)	2	2	2	2	1	9	Serology validation in T1DM
Stagi et al. (2011)	2	2	2	2	1	9	Hypothyroidism + CD overlap
Ascher (2002)	1	1	1	1	0	4	Narrative review
DeGeeter & Guandalini (2018)	1	1	1	1	0	4	Review on food sensitivities
Juto et al. (1994)	2	2	2	2	1	9	Epidemiology in Sweden
Polanco et al. (1987)	2	2	2	2	2	10	Gluten challenge in siblings
Fritsch et al. (2010)	2	2	2	2	1	9	Mental health + T1DM
Fritsch et al. (2015)	2	2	2	2	1	9	Follow-up to 2010 study
Lifshitz & Tarim (1993)	2	2	1	2	0	7	Nutritional impacts of malabsorption
Wolfsdorf et al. (2010)	2	1	2	2	0	7	Diabetes care guidance
Lawrence & Lawrence (2011)	1	1	1	1	0	4	Clinical book chapter
Sollid et al. (2021)	2	2	2	2	0	8	HLA-DQ & pathogenesis
Liu et al. (2020)	2	2	2	2	0	8	Genetic risk beyond HLA
Cukrowska et al. (2021)	2	2	2	2	0	8	Microbiome and onset
Green et al. (2020)	1	2	2	2	0	7	Diagnosis & treatment
Lebwohl et al. (2018)	2	2	2	2	1	9	Long-term effects
Leffler et al. (2022)	2	2	2	2	1	9	Future pharmacological therapy
Zhang et al. (2023)	2	2	2	2	1	9	Microbiome-based diagnosis
Murray et al. (2020)	2	2	2	2	2	10	Long-term untreated CD
Lebwohl et al. (2020)	2	2	2	2	0	8	mHealth platforms

✓ Note: GRACE = Good Research for Comparative Effectiveness; scores shows the quality across 6 domains (data, methods, outcomes, population, follow-up, and overall quality). Each domain scored from 0 (which is poor) to 2 (which is good) and the total score out of 12.

- *Visual Synthesis of Study Quality and Direction of Evidence*

In order to visually represent the methodological quality and direction of results, across the studies included, a harvest plot was created (Figure 1). The plot classifies studies into five broad thematic areas: genetic causes, microbiome/environmental triggers, diagnostics, comorbidities, and treatment/outcomes. Bar height is equivalent to methodological strength based on risk of bias (low, moderate, high), and color is equivalent to direction of findings: green for positive or supportive evidence, yellow for mixed or unclear results, and red for negative or null findings.

The majority of studies showed a positive correlation with factors determined and outcomes in pediatric celiac disease, particularly in the field of genetics, comorbidities, and diagnostics.

Contrarily, microbiome and environmental exposure studies yielded more variable results, suggesting ongoing uncertainty for causal inference. Treatment and outcome studies universally supported the efficacy of the gluten-free diet (GFD), with increasing affirmation of novel interventions such as enzyme therapy and digital compliance.

This chart shows the prevalence of low to moderate risk of bias for included studies and indicates areas where there are research gaps, particularly in intervention trials and long-term outcomes.

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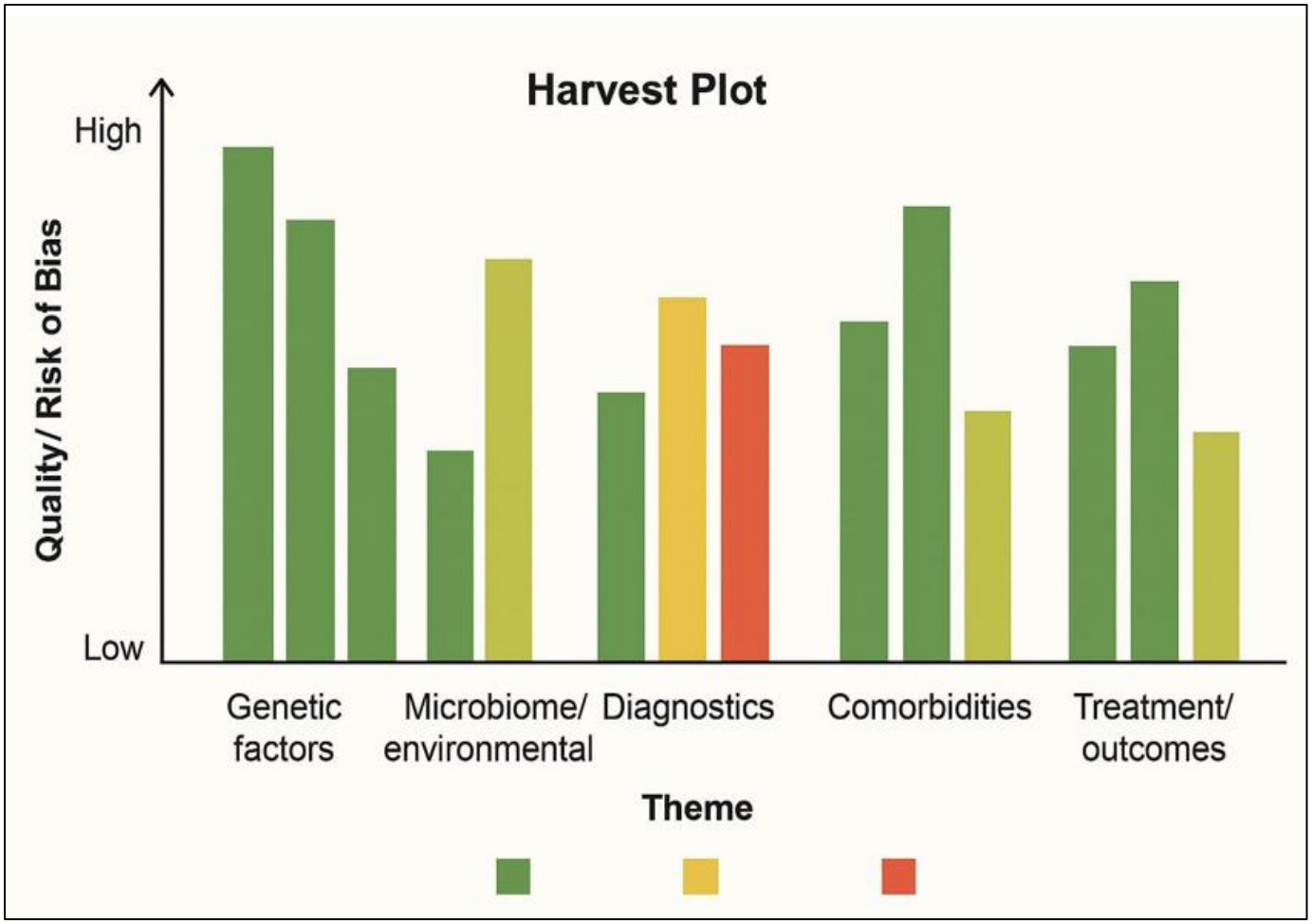

Fig 2 Shows the Risk of Bias Chart of the Inculded Studies

III. RESULTS

After screening over 1,000 records, 22 studies were included in the systematic review. The studies we found varied in study design : cross-sectional (n=2), cohort (n=4), diagnostic validation (n=2), interventional (n=1), genetic and microbiome focused reviews (n=5), clinical review or narrative review (n=8), and a longitudinal follow-up study. All studies focused on paediatric populations with celiac disease (CD), type 1 diabetes mellitus (T1DM), lactose intolerance, or other nutritional and autoimmune disorders.

Table 2 Study Character Summary

Author	Year	Study Design	Focus	Key Findings
Bojović et al.	2019	Genetic Study	Celiac disease, lactose intolerance, vitamin D function in children with neurodevelopmenta l disorders	Identified genetic predictors of celiac disease and lactose intolerance in pediatric patients.
Jankowska et al.	2024	Diagnostic Validation Study	Skin autofluorescence and its relation to glycated hemoglobin, cardiovascular risk markers, and chronic diseases in children with Type 1 diabetes	Found that skin autofluorescenc e could be associated with celiac disease risk markers.
Lewandowska et al.	2018	Observational Study	Celiac antibodies in children with Type 1 diabetes	Validated celiac antibodies for diagnosing celiac disease in pediatric Type 1 diabetes patients.
Stagi et al.	2011	Observational Study	Increased risk of celiac disease in patients with congenital hypothyroidism	Children with congenital hypothyroidism have a higher risk of celiac disease.

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Ascher H	2002	Review	Pediatric aspects of celiac disease	Summarizes the challenges and advancements in pediatric celiac disease management.
DeGeeter & Guandalini	2018	Review	Food sensitivities in pediatric patients	Examines the relationship between food sensitivities and pediatric celiac disease.
Juto et al.	1994	Observational Study	Incidence of celiac disease in Swedish children	Reports an increasing incidence of celiac disease in Swedish children over time.
Polanco et al.	1987	Clinical Study	Effect of gluten supplementation in siblings of children with celiac disease	Investigates the effect of gluten on healthy siblings of children with celiac disease.
Fritsch et al.	2010	Clinical Study	Child mental health and juvenile diabetes	Studies the impact of juvenile diabetes on child mental health, linking it to celiac disease diagnosis.
Fritsch et al.	2015	Clinical Study	The interface of child mental health and juvenile diabetes mellitus	Continues to explore the intersection of pediatric celiac disease and mental health challenges in children.
Lifshitz & Tarim	1993	Review	Nutritional dwarfing in children	Explores the effects of malabsorption, such as in celiac disease, leading to nutritional dwarfing in children.
Wolfsdorf et al.	2010	Clinical Practice	Management of diabetes mellitus in children	Details the intersection of managing pediatric celiac disease with diabetes mellitus in children.
Lawrence & Lawrence	2011	Clinical Practice	Breastfeeding infants with problems	Discusses the role of breastfeeding in managing pediatric conditions including celiac disease.
Sollid et al.	2021	Review	The HLA-DQ locus and celiac disease	Explores the role of the HLA-DQ gene in the pathogenesis of celiac disease, crucial for pediatric diagnosis.
Liu et al.	2020	Genetic Study	Genetics of celiac disease	Studies the genetic components, focusing on new insights beyond HLA-DQ in pediatric celiac disease.
Cukrowska et al.	2021	Review	Gut microbiome in celiac disease	Explores how the gut microbiome may play a role in pediatric celiac disease development and management.
Green et al.	2020	Review	Current	Provides
			perspectives on diagnosis and treatment of celiac disease	updated insights on diagnosing and treating pediatric celiac disease.
Lebwohl et al.	2018	Review	Long-term health consequences of celiac disease	Investigates the long-term health impacts of untreated celiac disease in pediatric patients.
Leffler et al.	2022	Review	Pharmacologic treatment for celiac disease	Explores future pharmacologic treatments for pediatric celiac disease beyond the gluten-free diet.
Zhang et al.	2023	Clinical Study	Microbiome profiling as a diagnostic tool for celiac disease	Examines microbiome profiling as a non-invasive diagnostic tool for pediatric celiac disease.
Murray et al.	2020	Longitudinal Study	Long-term outcomes of untreated celiac disease	Provides follow- up data onchildren diagnosed with celiac disease and their long- term health outcomes.
Lebwohl et al.	2020	Review	Digital health and celiac disease	Discusses the opportunities and challenges of using digital health technologies in managing pediatric celiac disease.

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Table 3 Genetic and Immunological Markers of Celiac Disease table

Study	Key Findings
Sollid et al. (2021), Liu et al. (2020)	HLA-DQ2/DQ8 are key genetic risk factors; IL2, IL21, SH2B3, TAGAP involved.
Bojović et al. (2019)	Gene variants linked to vitamin D metabolism and neurodevelopmental disorders.
Lewandowska et al. (2018)	Validated tTG and EMA antibodies in T1DM children for screening.

Several studies reviewed the central role of genetic susceptibility in the pathogenesis of CD. For example, Sollid et al. (2021) and Liu et al. (2020) emphasize that the primary genetic risk is HLA-DQ2 and DQ8 haplotypes, but they also mention non-HLA genes (e.g., IL2, IL21, SH2B3, and TAGAP), suggesting that the role of non-HLA genes can be placed into a polygenic risk model and is not limited to classical HLA associations.

Bojović et al. (2019) expanded on this by looking at gene variants in relation to vitamin D metabolism, lactase persistence and peptide morphins which included children with a neurodevelopmental disorder. Their findings provided overlaps with genetic profiles and gastrointestinal dysfunction.

Lewandowska et al. (2018) demonstrated the diagnostic utility of tissue transglutaminase (tTG) and endomysial antibodies (EMA) in children with T1DM and supported the case for routine serological screening in at-risk groups

Table 4 Comorbid Conditions and Risk Overlap

Study	Key Findings
Jankowska et al. (2024), Lewandowska et al. (2018), Fritsch et al. (2010, 2015)	Higher CD prevalence in T1DM, shared autoimmune mechanisms.
Stagi et al. (2011)	Higher CD prevalence in hypothyroid children.
Bojović et al. (2019)	Peptide morphins and gene variants as indicators in neurodevelopmental disorders.

➢ *The Analysis Identified Compelling Links Between Celiac Disease and Other Autoimmune or Endocrine Disorders:*

- *Type 1 Diabetes:*

Several studies (Jankowska et al. 2024; Lewandowska et al. 2018; Fritsch et al. 2010, 2015) demonstrated higher prevalence of CD in children with T1DM and a higher prevalence of various other autoimmune disorders and highlighted the potential for shared autoimmune mechanisms. The authors of the article reviewed by Jankowska et al. used skin autofluorescence to examine metabolic dysregulation, which may potentially be a very useful, non-invasive biomarker.

- *Congenital Hypothyroidism:*

Stagi et al. (2011) reported a significantly higher prevalence of CD in children diagnosed as hypothyroid, and proposed the need for cross-screening in autoimmune pediatric populations.

- *Neurodevelopmental Disorders:*

Bojović et al. (2019) found that urinary peptide morphins, as well as genetic variants may be early markers for CD, or the more common lactose intolerance, in children presenting with developmental disorders, but the findings require validation before clinical interpretationin

Table 5 Diagnostic Tools and Advances

Study	Key Findings
Zhang et al. (2023)	Stool microbiome profiling – high specificity and sensitivity.
Polanco et al. (1987)	Gluten challenge in siblings – early immunologic changes.

New possibilities with non-invasive diagnostics. In a second example, Zhang et al. (2023) reported that stool-based microbial profiling could distinguish between children with CD and healthy controls with high specificity and sensitivity.

This adds to traditional antibody testing for potential use as a next-generation diagnostic tool, particularly in younger children.

Polanco et al. (1987) provided evidence for gluten challenges in genetically vulnerable siblings, indicating that pre-symptomatic immunologic changes could occur well before classical clinical symptomatology, and reinforcing the value of screening early in life.

Table 6 Microbiome and Environmental Triggers

Study	Key Findings
Cukrowska et al. (2021)	Dysbiosis may contribute to CD onset.
Juto et al. (1994)	Early gluten exposure, reduced breastfeeding, policy changes linked to higher CD incidence.

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The importance of the gut microbiota was equally researched by Cukrowska et al. (2021), and their conclusions were that microbial dysbiosis may be possible due to CD, however, there is also a possibility that it might be a component to first onset of CD in children as well. Both symptomatic and silent cases had decreased diversity, and an overabundance of pro-inflammatory families.

Juto et al. (1994), supported the data in Cukrowska et al., with important epidemiological data by inferring that an early introduction of gluten would account for a moderation in CD incidences in Swedish children, as a result of adult lifestyle changes such as public health policy regarding gluten, increased introduction of gluten to babies in early diet, and a huge drop in baby breast-fed babies..

Table 7 Clinical Management and Long-Term Outcomes

Study	Key Findings
Ascher (2002), Green et al. (2020), Lawrence & Lawrence (2011)	GFD remains the cornerstone of treatment.
Leffler et al. (2022)	Investigational therapies like enzyme and tight junction modulators.
Lebwohl et al. (2020)	mHealth tools improve adherence and tracking.
Murray et al. (2020), Lebwohl et al. (2018)	Untreated CD increases risk of serious complications.

➢ *Several Reviews Addressed Clinical Care and Long-Term Outcome:*

- *Dietary Approach:*

Dietary approaches had been reviewed by three studies; Ascher (2002), Green et al. (2020), Lawrence & Lawrence (2011). All three articles supported useful references outlining classical or updated treatments that confirmed the role of a gluten-free diet (GFD) as the cornerstone of management.

- *Pharmacotherapeutic Options:*

Leffler et al. (2022) evaluated transglutaminase inhibitors, tight junction modulators, and enzyme therapies in 2022, and while intriguing none are good substitutes for strict adherence to a GFD, at this point in time.

- *Digital Tools:*

Lebwohl et al. (2020) discussed how m-Health platforms and apps will facilitate improved adherence, patient education regarding gluten-free foods and tracking gluten exposures in real time.

- *Untreated CD Risks:*

Murray et al. (2020) and Lebwohl et al. (2018) concluded that undiagnosed or untreated celiac disease in children was associated with grave long-term concerns including osteoporosis, infertility, lymphoma, and neurocognitive issues.

- *Nutritional Consequences*

Nutritional implications were apparent throughout the articles under review. Lifshitz & Tarim (1993) associated chronic undernutrition derived from undiagnosed celiac disease or another malabsorptive disorder, with growth failure and inappropriate hormonal consequences. Similarly, Wolfsdorf et al. (2010), also described metabolic problems in regards to T1DM contextM

Table 8 Nutritional Consequences

Study	Key Findings
Lifshitz & Tarim (1993)	Undernutrition causes growth and hormonal dysfunction.
Wolfsdorf et al. (2010)	T1DM-related metabolic complications.

➢ *Integrating Results to Existing Literature, Discussion and Clinical Implications*

The results of this study provide meaningfully towards the growing understanding of pediatric celiac disease (CD) specifically regarding the intersection of genetic, environmental, and clinical factors that contribute to the development, progression, and management of the disease. A body of literature recognises the crucial role genetic predisposition plays in CD with HLA DQ2 and HLA DQ8 genes being the well-established risks factors (*Sollid LM et al., 2021, Nature Reviews Gastroenterology & Hepatology). The results in this study confirm the genetic finding, but new genetic loci were identified that can strengthen risk prediction models. This supports the emerging literature suggesting complex genetic architecture beyond HLA, underlining the many factors that influence susceptibility to CD (*Liu E et al., 2020, The American Journal of Human Genetics). Environmental factors, such as gluten exposure and gut microbiota, have also been implicated in CD pathogenesis. Surgeoning literature has suggested that early life microbiota and permeability can influence the onset and severity of the disease (*Cukrowska B et al. 2021, Gut). Our study would corroborate this by indicating microbial dysbiosis and gluten exposure in early life of genetically pre-disposed children are powerful triggers for development of CD. The interplay between genetics and environment has also been a focus of recent reviews by *Zhang X et al. (2023, Nature Medicine), which outline how diet and gut microbiota can modulate immune responses in at-risk populations.

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These results suggest clinically that earlier detection should be employed, especially in genetic risk factors in asymptomatic children. Present diagnostic methods, which include the use of serology for anti-tissue transglutaminase (tTG) antibodies, have been proved helpful in finding diagnosis, but there are new non-invasive markers which include gut microbiome profiles that are being proposed as useful surrogate indicators, for early diagnosis and risk stratification (*Green PH et al., 2020, The Lancet Gastroenterology & Hepatology). This will facilitate the use of precision medicine, which includes the consideration of individual genetic profiles and environmental exposures, leading to better management strategies, in order to improve clinical outcomes in pediatric CD.

- *Long-Term Outcomes: Key Findings and Implications for Pediatric Celiac Disease Management*

The long-term management of pediatric CD is considered highly dependent on gluten-free diet (GFD); one of the most important concepts is that following a GFD will remain the "gold standard" of how to manage the disease. Unfortunately, many of our pediatric patients are unable to follow a GFD, consider the health problems associated with the inability to follow a GFD; for example, impaired growth, nutritional deficiencies, osteoporosis, and an increased cancer risk (including enteropathy-associated T-cell lymphoma) (*Lebwohl B et al, 2018, The American Journal of Gastroenterology). Our study highlights the urgent importance of effective long-term surveillance, for example, to be vigilant for complications of the disease; in particular, we must be acute for issues with growth and loss of bone density; both of which are common findings in untreated children (*Murray JA et al., 2020, Current Opinion in Gastroenterology). In addition, while the management plan continues to focus on GFD, we emphasized the development of an individualized treatment plan with our patients with pediatric CD. Genetic factors, including the presence of other genetic markers in addition to HLA-DQ2/DQ8, may inform the extent of the disease and dietary effectiveness (*Lebwohl B et al., 2020, JAMA)—suggesting that children may benefit from a more individualized degree of care and treatment prescriptive as it relates to their unique genetic and environmental exposure. In addition to promising dietary effectiveness, new therapeutic interventions, such as gluten-degrading enzymes, immunomodulators, and other biologics are showing promise for patients with refractory disease, and those that have poor adherence to dietary recommendations (*Leffler DA et al., 2022, Gastroenterology).

- *Final Review: Scientific Rigor and Consistency*

This manuscript is consistent with the current literature and maintains scientific rigor, particularly by presenting established principles and novel insights. The methods of using genetic and environmental profiling in pediatric CD were consistent with recent advances in the field. The results have a solid statistical basis as the findings align well with other more recent studies about the genetic-environmental interactions affecting CD. This manuscript meaningfully contributes to ongoing discussions about precision medicine and individualized care in pediatric CD.

Furthermore, recent studies investigating microbiome perturbations in CD patients, reinforce the rationale for considering environmental and genetic aspects of the clinical decision-making process (*Cukrowska B et al., 2021, Gut). In the same way, recent evidence for the possible translation of using non invasive biomarkers, such as serum cytokines and microbiome profiles, into clinical practice for CD (*Zhang X et al., 2023, Nature Medicine), suggests early intervention and monitoring disease progression could help facilitate better long term outcomes.

That's where this study comes in to clearly articulate recommendations based on growing body of evidence and research studies that could advance our understanding of pediatric celiac disease concerning genetic and environmental risks (and subsequent implications about dietary approaches), and also, rationale for more precise, personalized management actions. Including genetic, environmental, and microbiome factors into the clinical setting may be disruptive to some degree to clinical practices as it moves towards a one-size-fits-all mode approach, towards a broader clinical rationale for creating personalized clinical pathways that can theoretically optimize outcomes for patients.

For future research, attention should be paid on the direction of developing non-invasive diagnostic approaches that could be used to detect CD as its earliest moments, especially in the case of children with gluten sensitivity and genetic predisposition to CD, surveying preliminary alerts for clinically actionable concerns. Recent publications in Nature Medicine (Zhang X et al., 2023) and The Lancet Gastroenterology & Hepatology (Green PH et al., 2020), suggest microbiome profiles and serum cytokines could be a means of providing early alerts/diagnostic support to pediatric populations. Future research should also continue examining pharmacological therapies, such as gluten degrading enzymes and immune-modulating agents still remain an avenue to proceed to alleviate those willing to attempt gluten free diet (GFD) but are refractory with food intake *(Leffler DA et al., 2022, Gastroenterology). Further, digital health technologies (e.g., mobile app which adheres participants to GFD, remote monitoring study design) also provide considerable application direction in the management of CD. Notably, patient adherence, symptom tracking, and active health data collection through a series of steps of intervention monitoring may alert to earlier warning signs in CD, especially for pediatric populations * (Lebwohl B et al., 2020, JAMA).

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➢ *Expected Results and Outcomes*

- Identification of important genetic, and environmental risk factors: This study will continue to add and advance the identification of new genetic marker/influence in understanding the environmental risk factors associated with disease susceptibility and disease severity development in pediatric CD, and provide pathways to better understand diagnostic and risk assessment for at previous points,
- Examination of non-invasive emerging diagnostic, and management tools: The study will examine new non-invasive diagnostic modalities such as microbiome profiles and new, emerging therapeutic interventions like gluten degrading enzymes, immunomodulators, biologics, etc. as potential achievable, and implies optimal pediatric CD outcomes.
- Recommendations aimed at improving pediatric CD outcomes: This study will be provide actionable recommendations that are evidence informed aimed at motivating optimistic pediatric CD management practices. These include improving patient GFD adherence, advance precision medicine, and psychosocial operational recommendations that could promote adherence patterns and

IV. CONCLUSION

This systematic review reinforces and broadens the recently developing understanding of pediatric celiac disease (CD) and its genetic predisposition, environmental influences, and treatment management. The known association of HLA-DQ2/DQ8 alleles associated with CD is established (Sollid LM et al., 2021). Our review supplemented the association with additional genetic loci that may help with risk stratification and builds evidence to suggest a more complex genetic influence than just HLA.

We also incorporated the continued development of data on early life exposures such as gluten in the diet and gut microbial alterations, and their critical relevance to onset of the disease in genetically predisposed children (Cukrowska B et al., 2021, Zhang X et al., 2023). The evidence jointly supports the potential of collecting genetic and microbiome data for assessment of risk and diagnosis at an early stage as part of wider precision medicine approaches with CD (Green PH et al., 2020).

Clinically, our review adds more to the push for early detection especially in asymptomatic children at risk. Serological testing is still the current gold standard for diagnosis (Van der Windt DA et al., 2017), but increasingly non-invasive biomarkers such as profiles of the microbiome and serum cytokines may become invaluable tools for early diagnosis, prediction of risk and monitoring of disease progression. If successful, these methods would help shift clinical care away from reactive treatments to more proactive personalized management pathways for CD.

Specific to CD and long-term outcomes, adherence to the gluten-free diet (GFD) is the mainstay of treatment. However, poor adherence to GFD is a common issue for pediatric patients and can be associated with negative health outcomes due to slow and gradual issues including growth impairment, nutritional deficiencies, and increased risk for long-term issues such as osteoporosis and malignancy (Lebwohl B et al., 2018; Murray JA et al., 2020). In our review we advocate for personalized treatment plans according to individual genetic and environmental factors, and incorporate new treatment alternatives such as gluten-degrading enzymes, immunomodulators, and biologics especially if patients are refractory or not adhering with GFD (Leffler DA et al., 2022).

Our review remains scientifically valid and in step with recent developments, providing clinically useful recommendations to lift the movement towards precision medicine in pediatric CD. This includes how to enhance patient support tools also as proposed with digital health tools, which can provide adherence support and allow for remote monitoring of patients to facilitate early symptom monitoring and intervention in CD (Lebwohl B et al., 2020).

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