Society for the Study of Celiac Disease position statement on gaps and opportunities in celiac disease

M. Ines Pinto-Sanchez1,2,9, Jocelyn A. Silvester3,4,5,9, Benjamin Lebwohl6, Daniel A. Leffler3,5,7, Robert P. Anderson8, Amelie Therrien3,5, Ciaran P. Kelly3,5 and Elena F. Verdu1,2,9

Abstract | Progress has been made in understanding celiac disease, a relatively frequent and underappreciated immune-mediated condition that occurs in genetically predisposed individuals. However, several gaps remain in knowledge related to diagnosis and management. The gluten-free diet, currently the only available management, is not curative or universally effective (some adherent patients have ongoing duodenal injury). Unprecedented numbers of emerging therapies, including some with novel tolerogenic mechanisms, are currently being investigated in clinical trials. In March 2020, the Celiac Disease Foundation and the Society for the Study of Celiac Disease convened a consensus workshop to identify high-yield areas of research that should be prioritized. Workshop participants included leading experts in clinical practice, academia, government and pharmaceutical development, as well as representatives from patient support groups in North America. This Roadmap summarizes key advances in the field of celiac disease and provides information on important discussions from the consensus approach to address gaps and opportunities related to the pathogenesis, diagnosis and management of celiac disease. The morbidity of celiac disease is often underestimated, which has led to an unmet need to improve the management of these patients. Expanded research funding is needed as celiac disease is a potentially curable disease.

Coeliac disease, an immune-mediated enteropathy triggered by gluten, is a relatively common condition affecting ~1% of the world population that can develop across the lifespan.1 The incidence has been increasing rapidly over the past four decades worldwide.2 A diagnosis of coeliac disease is associated with increased overall mortality.3 Currently, the primary management for coeliac disease is a strict gluten-free diet, which is practically challenging and socially difficult to follow.4 Thus, patients often have inadequate symptom control on a gluten-free diet, yet the few alternative therapies available are repurposed medications, such as budesonide, that are not disease specific.

To establish priorities for the support of relevant and high-yield areas of research, the Celiac Disease Foundation (CDF) and the Society for the Study of Celiac Disease (SSCD) convened the first SSCD consensus workshop on ‘Research Opportunities in Celiac Disease’ in March 2020 (REF.6). The consensus workshop was attended by leaders from academia and pharmaceutical companies, patient support group members and scientists from government institutions (NIH) that support research in celiac disease. The consensus workshop was organized under the umbrella of SSCD and CDF. Workshop participants were identified and invited based on their area of expertise. A workshop outline was determined a priori, and each expert was asked to address specific topics. A round-table discussion followed each presentation. After the workshop, participants ranked the initiatives in a formal voting process (25 participants submitted votes for each topic), to determine prioritization. The complete list of attendees of the workshop in addition to the authors is detailed in the Acknowledgments. The authors of this article were selected by the SSCD to report on the discussion and recommendations arising from the workshop.

This Roadmap summarizes the latest advances and controversies in the field (TABLE 1) and provides information on selected milestones and consensus recommendations to address gaps and opportunities in pathogenesis and genetics (TABLE 2), and diagnosis, management and prevention of celiac disease (TABLE 3). Recognized gaps...
Key points

- Coeliac disease is a common and serious medical condition that is under-recognized among the health-care provider community, government and the public.
- This Roadmap summarizes consensus recommendations to address gaps and opportunities in pathogenesis, diagnosis and management of coeliac disease.
- Various animal models are available to translate hypotheses generated from human studies, and progress is being made in the development of physiological coeliac epithelial models based on organoid technology.
- Coeliac-specific serology is highly reliable for the diagnosis of coeliac disease; however, there is disagreement between experts as to the necessity of intestinal biopsy to confirm the diagnosis.
- There is increasing need for development of programmes for proper clinical management of coeliac disease, and the number of potential therapeutic targets and clinical trials has grown exponentially over the past 15 years.
- Increased funding for coeliac disease research is crucial to improve clinical management and facilitate development of therapies for this condition.

Milestones and gaps in pathogenesis

Coeliac disease is triggered by the ingestion of gluten in a subgroup of genetically predisposed individuals. Specifically, coeliac disease confirmed by recall response to gluten challenge is currently limited to individuals positive for HLA-DQ2, HLA-DQ8 or, rarely, HLA-DQ7 (Ref. 2). Gluten-specific CD4+ T cells in coeliac disease are activated by particular peptide fragments derived from gluten proteins and related prolamins present in wheat, barley and rye when they are bound to HLA-DQ2 or HLA-DQ8 (currently no HLA-DQ7 gluten epitopes are defined). Deamidation of wild-type gluten in the lumen propria by tissue transglutaminase 2 (TG2) increases binding efficiency to HLA-DQ2 (Ref. 3) and HLA-DQ8 (Ref. 4), which preferentially accommodate peptides with negatively charged residues at anchor sites. HLA-DQ-gluten peptide complexes activate CD4+ T cells, leading to the release of pro-inflammatory cytokines and chemokines that favour inflammatory cell infiltration and CD8+ T cell cytotoxic activity that contributes to mucosal damage in coeliac disease (Ref. 5). Patients with coeliac disease can develop typical upper gastrointestinal symptoms, such as nausea and abdominal pain and systemic markers of immune activation within hours of oral or intradermal gluten exposure (Ref. 6). It is clear that both gluten and permissive HLA-DQ genotypes are required for disease development; however, other genetic and environmental factors (such as enteric infections and high gluten load) also influence disease risk. As such, coeliac disease represents a model condition in gastroenterology and autoimmunity with exquisite pathophysiological insight.

Although studies performed in biopsy samples and human tissue pioneered important discoveries in coeliac disease and continue to be key in the study of its pathogenesis, the development of animal models in coeliac disease has long been an unmet need, in particular to promote and accelerate development and testing of preclinical therapies. Various animal models have been developed that reveal key relevant pathways amenable to diagnostic and therapeutic modulation, as well as additional risk factors that constitute future targets for primary prevention. Most models are based on MHC class II transgenic mice expressing HLA-DQ2 or HLA-DQ8 (Refs 7,8), as well as transgenic expression of IL-15 (Ref. 9), a key cytokine in cytotoxic transformation of intraepithelial lymphocytes. Animal models have also revealed the role of microbial factors in the metabolism of the main dietary trigger, gluten, as well as other dietary components (such as the essential amino acid tryptophan) that participate in the activation of immune pathways that can affect coeliac disease risk (Ref. 10).

Models that combine genetic susceptibility and transgenic expression of IL-15 have been essential to unravel epithelial-cytotoxicity mechanisms and the role of transient viral infection in the breakdown of oral tolerance to gluten (Ref. 11). Although no single mouse model recapitulates all features of human disease, well-characterized humanized mouse models expressing different key features of coeliac disease pathogenesis and disease stages are now available and represent an invaluable research tool.

In vitro models based on organoid technology have gained attention. As in other intestinal inflammatory disorders, 3D organoids, as well as 2D organoid-derived monolayers from patients with coeliac disease, expressed phenotypic differences compared with those derived from healthy individuals as controls (Ref. 12,13). Advantages of these tools reside on the physiological complexity of the intestinal epithelium compared with classic transformed or primary cell lines. The limitations are common to organoid modelling, including lack of vasculature and immune cells, high cost, technical difficulties and the closed nature of the 3D structure. Chip technology, microfluidics and co-culturing systems could address some of these limitations (Ref. 14). However,

Author addresses

1Farncombe Family Digestive Health Research Institute, Hamilton, Ontario, Canada.
2McMaster University Medical Center, Hamilton, Ontario, Canada.
3Harvard Medical School Celiac Research Program, Boston, MA, USA.
4Boston Children’s Hospital, Boston, MA, USA.
5Celiac Center, Beth Israel Deaconess Medical Center, Boston, MA, USA.
6Celiac Disease Center, Columbia University, New York, NY, USA.
7Takeda Pharmaceuticals, Cambridge Massachusetts, Cambridge, MA, USA.
8Wesley Medical Research, The Wesley Hospital, Auchenflower, Queensland, Australia.
9These authors contributed equally: M. Ines Pinto-Sanchez, Jocelyn A. Silvester.
Table 1 | Selected milestones and gaps in coeliac disease

| Area of interest | Milestones | Challenges | Opportunities | Readiness |
|------------------|------------|------------|---------------|-----------|
| Pathogenesis     | Key pathways revealed by animal models (MHC class II HLA-DQ2 or HLA-DQ8 and transgenic for IL-15) | Limited understanding of pathways of disease tolerance and tissue destruction, as well as different phenotypes of the disease | Current knowledge of mechanisms generates opportunities in translational research | Tools available |
| Diagnosis        | Once thought to afflict primarily children of Irish descent, coeliac disease is a common condition affecting nearly 1% of the worldwide population, and the incidence is increasing | The reason for increasing incidence over time is unclear | Clinical trials on high-risk population using novel approaches such as HLA-DQ-gluten tetramer assays or IL-2 release to measure immune response | Tools available |
| Disease management | Novel tools to improve detection of gluten to improve disease management | GFD is difficult to follow and a great proportion of those with coeliac disease remain symptomatic | Identification of markers of preclinical disease and development of more accurate tools to assess disease activity, which could be tested in preclinical models | Needs development |
| Funding          | Research efforts in coeliac disease have proved highly efficient, leading to a better understanding of the disease | Funding for research is lower than for other less prevalent conditions, such as Crohn’s disease | Increasing funding would catalyse and sustain coeliac disease research centres, supporting patients and generating new knowledge | Insufficient |

GFD, gluten-free diet.

Collectively, the cellular and mouse models developed in the past decade provide a long-awaited milestone that should stimulate translational and preclinical research in coeliac disease.

**Challenges.** Despite the key milestones achieved, there is limited understanding of pathways of disease tolerance and tissue destruction. This gap in knowledge limits the development of preventive agents, pharmaceutical adjuncts to diet or curative therapies for coeliac disease. Furthermore, one consequence of the lack of prescription therapies and alternatives to a gluten-free diet is that patients might not consistently receive follow-up care, so the medical community and, to a lesser extent, the research community, is disengaged from patient needs and the burden of disease. In addition, as suspected by many in the research community, several different coeliac disease phenotypes exist that should be better defined, as differing treatments could be required. In particular, improved quantitative assays that enable clinical and immune phenotype to be accurately defined will play a crucial part in future efforts to develop therapeutics, and might also enable coeliac disease to be redefined and diagnosed on the basis of a recall immune response to gluten.

**Opportunities.** In contrast to other T cell-mediated organ-specific immune diseases, many of which are genetically linked or associated with coeliac disease, researchers can undertake patient-based so-called proof-of-concept studies with outcomes broadly relevant to understanding and treating other conditions.

For example, antigen-specific adaptive immunity has a central role in many serious autoimmune diseases, but coeliac disease is the only one for which molecular determinants of cellular and humoral immunity are confidently known, and tissue from the affected organ can be sampled while exposure to the causative antigen is safely manipulated. Blood and tissue biomarkers of humoral immunity including gliadin and autoantigen (TG2)-specific antibodies, B cells and plasma cells can be assessed, and the gluten-specific CD4+ T cell population can be studied in gut tissue, repeatedly in blood for single-cell analyses or in fresh samples for functional assessments. A newly characterized human serum cytokine release profile dominated by pronounced, early elevations in the T cell-associated cytokine IL-2 following acute gluten exposure provides an additional biomarker for coeliac disease research and promises to inform diagnostics and therapeutics development.

Relevant animal models are available to reverse-translate hypotheses generated from human studies, and progress is being made in the development of physiological coeliac epithelial models based on organoid technology to study variations in gene expression, microbiota-host interactions and immune response to gliadin. Altogether in vitro systems and the latest mouse models enable understanding of specific pathogenic mechanisms that are difficult to study clinically and for preclinical drug testing. Thus, researchers have developed a unique toolbox for understanding and developing treatment of antigen-specific cell-mediated human disease by focusing their efforts on coeliac disease. In fact, patients with coeliac disease are often affected by other common...
autoimmune diseases such as type 1 diabetes mellitus\(^7\). Future research implementing mechanistic models, including organoids, to selectively modify gluten immunity is likely to be broadly applicable to antigen-specific immunotherapy of autoimmune disease.

**Milestones and gaps in diagnosis**

By epidemiological standards, coeliac disease is common (affecting nearly 1% of the worldwide population) and has shown increasing incidence over the past several decades\(^7\). On the basis of birth cohort studies in Finland and Colorado, USA, there is evidence that disease penetration is deeper than commonly assumed\(^4\).

**Challenges.** Researchers do not know why disease incidence is increasing, although environmental factors including viral infections during childhood or changes in gut microbiota (composition or metabolite production)\(^3\), which have led to an increase in many autoimmune and allergic conditions, have been implicated. Despite the combination of high prevalence and low diagnosis, major questions have emerged about who to test for coeliac disease and when. Although screening of first-degree relatives might be feasible, there is insufficient data to determine whether there is a benefit to screening asymptomatic individuals, particularly adults\(^3\). The alternative to screening is a case-finding approach.

---

### Table 2 | Selected milestones and current and future research objectives in pathogenesis and genetics

| Mechanism or feature (time frame) | Milestones | Current and future research objectives |
|-----------------------------------|------------|----------------------------------------|
| Cereal protein chemistry and genetics (1900s–) | Osborne\(^6\) characterized cereal grain proteins as ‘prolamins’. Starting with wheat \(\alpha\)-gliadin, protein and gene sequencing provided key information for defining candidate toxic and/or antigenic gluten peptides\(^5\) | Refining understanding of a safe threshold for dietary gluten; improving food testing for gluten; breeding cereals with reduced immunogenicity; defining other cereal components that trigger symptoms; understanding gluten digestion, absorption and systemic handling in health and disease |
| Environmental antigens (1950s–) | Protease-resistant peptides from prolamin in wheat, rye, barley and, possibly, oats\(^1\) drive coeliac disease | More comprehensive molecular characterization of targets for gluten-driven immunity in all genetic subtypes of coeliac disease; triggers for disease onset; microbiome and infections as modifiers of gluten immunity and tissue injury |
| Genetic susceptibility (1970s–) | Starting with HLA associations\(^7\) and defining HLA-DQ2.5 as the primary genetic susceptibility, subsequent genome-wide studies identify multiple non-HLA linkages and genes in common with other HLA-linked autoimmune diseases such as type 1 diabetes mellitus\(^8\) | Precise localization and functional characterization of germline non-MHC genes and any additional MHC genes implicated in coeliac disease and gluten immunity; understanding gene–gene interactions, DNA modification and acquired T cell and B cell receptor mutations facilitating gluten immunity |
| Animal models, ex vivo tissue and in vitro cell culture (1970s–) | Intestinal biopsies, cell lines and clones developed as bioassays for gluten; gluten immunity tested in humanized HLA-transgenic mice from 2000s\(^1\) | Refinement of bioengineering, organoid and microfluidic technologies to develop organ-on-a-chip models to complement humanized mouse models |
| Autoimmunity in coeliac disease (1980s–) | Endomysial antibody later determined to recognize tissue transglutaminase 2, the main autoantigen for gluten-dependent autoantibodies in active coeliac disease\(^9\) | Molecular characterization of targets for autoimmunity accounting for extraintestinal manifestations; more detailed understanding of humoral and cellular autoimmunity, and its relationship to gluten immunity |
| Host receptor-mediated recognition of gluten (1990s–) | The molecular and cellular basis for recognition of gluten was determined by cloning intestinal gluten-specific CD4\(^+\) T cells exclusively from patients with coeliac disease\(^10\), which were complemented by HLA-DQ–peptide binding assays, determining epitope restriction elements and, more recently, structural biology studies\(^10\) | Refining understanding of gluten recognition and contributions of innate and adaptive immunity or other pathways facilitating gluten-mediated intestinal and extraintestinal manifestations of coeliac disease; expanding understanding of antigen-presenting cells including B cells specific for gluten and transglutaminase |
| Immune–intestinal epithelial cell interactions (1990s–) | Identification of crucial innate immune pathways involving IEC–NK cell receptor interactions supported by IL-15 that are conducive to atrophy\(^11\) | Characterization of the role of IEC–NK cell receptor interactions across coeliac disease states and further elucidation of signals leading to licensing of cytotoxicity |
| Extraintestinal immune response to dietary gluten (2000s–) | Gluten ingestion drives expansion of peripheral blood gut-homing gluten-reactive CD4\(^+\) T cells and CD8\(^+\) T cells days later\(^12\). Serum cytokines, especially IL-2, are elevated within hours | Improved characterization of the sources and effects of gluten-stimulated systemic cytokine release; understanding of the cause and effects of intestinal CD8\(^+\) T cell expansion in blood and gut tissue; establishing phenotypic and functional changes in gluten-specific CD4\(^+\) T cells |
| Additional environmental triggers (2010s–) | Resurgence of the microbial hypothesis supported by sequencing technology and longitudinal at-risk cohorts. Used in combination with humanized models, microorganisms could influence key mechanisms in coeliac disease (e.g. gluten metabolism, loss of tolerance, molecular mimicry)\(^13\) | Continued identification of microorganisms and mechanisms that protect or incite breakdown of tolerance to gluten; identify and validate new microbial therapeutics that modulate pathogenic targets in coeliac disease |
| Gluten peptide-specific activation and modulation of gluten immunity (2010s–) | Systemically administered immunogenic gluten peptides cause acute digestive symptoms and immune activation with subsequent tachyphylaxis\(^14\) | Enhanced understanding of natural mechanisms that regulate gluten immunity and disease manifestations; understanding of the basis for potential coeliac disease versus highly symptomatic disease; more complete understanding of molecular events enabling development of neoplasia associated with coeliac disease |

IEC, intestinal epithelial cell; MHC, major histocompatibility complex; NK cell, natural killer cell.
approach, but the optimal set of clinical criteria that should trigger testing has not been established, and there is not a well-defined set of symptoms that increases the probability of a diagnosis of coeliac disease. The primary limitation of case finding, even when well implemented, is that subclinical cases will be missed and, owing to the many protean manifestations of coeliac disease and symptom overlap, diagnosis will be delayed as the condition is overlooked or not considered in the differential diagnosis. The correct balance between the costs and unintended consequences of mass screening and missed opportunities to improve health outcomes by addressing perpetually low coeliac disease diagnosis rates has yet to be found.

There is also disagreement regarding diagnostic standards as to the necessity of intestinal biopsy. A biopsy-free approach for those with markedly elevated serum TG2 IgA levels (>10 times the upper limit of normal of the assay) was delineated by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2020 (Ref. 36), but this approach has not been formally adopted by paediatric counterparts in the USA, and the more rigid non-biopsy pathway outlined in the ESPGHAN 2012 guideline was...
not necessarily implemented, even in central Europe\(^8\). Guidelines for diagnosis of coeliac disease in adults have continued to advocate for intestinal biopsy\(^4\), although a biopsy-avoidant approach was offered by the British Society of Gastroenterology in 2020 in the context of the COVID-19 pandemic\(^\text{[9]}\). There is also debate surrounding best practices for gluten challenge in patients already on a gluten-free diet before testing for coeliac disease, how to evaluate patients whose diagnosis of coeliac disease did not include a small intestinal biopsy for eligibility in clinical trials and how to manage these patients during clinical evaluation of non-responsive coeliac disease\(^5,\text{[10]}\).

**Opportunities.** The uncertainty regarding whether and how to screen for coeliac disease in average-risk and high-risk individuals provides the clinical equipoise necessary to justify a randomized trial. For feasibility, testing screening strategies should first be planned in high-risk groups such as those with a family history of coeliac disease. Although a non-biopsy approach will remain the subject of ongoing debate, it might be rendered moot if a non-invasive diagnostic method is validated to have high-performance characteristics, such as a simple, HLA-DQ-diagnostic blood-based assay identifying gluten-specific T cells or biomarkers released by T cells in response to gluten in vivo or ex vivo\(^\text{[11]}\). These modern assays are less dependent on gluten avoidance and/or exposure and might ultimately prove to obviate a gluten challenge. Such a test could foreshadow redefinition of coeliac disease as an acquired antigen-specific immune disorder diagnosed by the presence of gluten-specific T cells. With improved alignment of international and paediatric and adult coeliac disease diagnostic approaches, resources would be freed to focus on crucial questions related to treatment outcomes.

**Milestones and gaps in management**

Major advances in coeliac disease management to date have been identification of the role of gluten in perpetuating the disease\(^9\), identification of HLA-DQ2.5 and HLA-DQ8 as the main haplotypes associated with coeliac disease\(^\text{[12]}\), and confirmation of TG2 as an auto-antigen and TG2 IgA antibodies as a biomarker of untreated disease\(^\text{[13]}\). The capacity to identify gluten peptide sequences in foods and the consensus for 20 ppm as the upper threshold of gluten for a foodstuff to be considered gluten free\(^\text{[14]}\) have led to more unified regulations in food processing and labelling worldwide.

**Challenges.** Studies\(^\text{[47,}\text{[48]}\) show that patients are not able to maintain a strict gluten-free diet owing to the great difficulty of adherence, but, as we are all aware, no alternatives exist as yet. In practice, many patients are lost to follow-up, particularly those who do not adopt or who discontinue a gluten-free diet, so the long-term population outcomes are not well characterized\(^\text{[49]}\). Nevertheless, it is known that histological recovery (villi and/or gut healing) is inconsistent, and it seems that younger patients recover better than older patients\(^\text{[50]}\). Researchers acknowledge that the long-term implications of undiagnosed or undertreated coeliac disease are poorly understood\(^\text{[51]}\). There was broad acknowledgement among the workshop attendees that poor understanding of the disease in the medical community and broader population, coupled with misconceptions about indications for a gluten-free diet, has confused many about the seriousness of coeliac disease. On the other hand, the higher cost of gluten-free products, as well as difficulties in accessing an expert coeliac dietitian, are major challenges for the patient community. There was also consensus that the scarcity of coeliac disease academic research centres, particularly in North America (in contrast to the many for inflammatory bowel disease (IBD) and type 1 diabetes mellitus) and the lack of young researchers studying coeliac disease, were major impediments. Initiatives to partner with primary or secondary centres to facilitate the diagnosis and management of patients with coeliac disease, for instance, through more timely and efficient access to endoscopy and dietetic services, would improve diagnosis and clinical management, providing that health-care professionals are educated in the current standards. Quality certification programmes for clinics or health-care professionals involved in the care of patients with coeliac disease, recognized by scientific societies, can help to achieve this milestone (coeliac disease centres). The dearth of pharmaco-economic data\(^\text{[52]}\) has led to an underappreciation of disease burden by employers, insurers and government, and has also severely limited the development of treatments.

**Opportunities.** There is increasing interest and support from industry for development programmes in coeliac disease, and the number of potential therapeutic targets and clinical trials has grown exponentially over the past 15 years\(^\text{[53,}\text{[54]}\). In addition to the much-needed therapies in coeliac disease, there is a need to improve non-pharmacological management of coeliac disease through optimization of the only currently available management — the gluten-free diet. This progress can be achieved by providing financial support to patients; intensifying education efforts in the patient and medical community and the food industry; improving access to a coeliac dietitian, which requires training programmes and patient access through coverage of these services; implementation of new monitoring tools in food, urine and stool gluten immunogenic peptide detection tests in standard of care. New biomarkers (such as IL-2 and circulating gluten-specific T cells\(^\text{[11,}\text{[29,}\text{[41]}\) could both simplify the diagnosis, especially when the individual is already on a gluten-free diet, and reduce the burden of study procedures in drug trials in coeliac disease.

**Milestones and gaps in funding**

Research in coeliac disease has long been a case of accomplishing much with little. Consistent with the authors’ anecdotal experience, systematic review of NIH funding has shown that coeliac disease receives proportionally less funding than a range of comparable conditions (US$3 million annually compared with US$16 million for Crohn’s disease, US$13 million for Barrett oesophagus and US$7 million for nonalcoholic fatty liver disease (NAFLD)\(^\text{[55]}\), a situation that likely is the cause rather than the effect of a relatively small pool
of dedicated investigators. Research efforts in coeliac disease have proved highly efficient, leading to better understanding of its pathophysiology than that of many better-funded gastrointestinal conditions, such as IBD and Barrett oesophagus. Understanding of the key steps in pathophysiology has led to excellent diagnostic tests, which have in turn enabled large and highly accurate epidemiology studies that have uncovered very large populations of coeliac disease outside Europe and North America, which has previously not been recognized, as well as new insights into age and risk factors for coeliac disease onset. With some high-profile exceptions\(^{6,57}\), many of these studies were funded by sources outside the USA. The 2020 federal budget passed by the United States Congress explicitly encourages the NIH to devote sufficient, focused research to the study of coeliac disease; this new milestone might mark an inflexion point in the dedication of public funds to support coeliac disease research in the USA. We are unaware of similar mandates outside the USA.

**Challenges.** The coeliac disease research and dedicated clinical community is barely at replacement levels. There is a desperate need in many areas for new expert coeliac disease centres, and in some areas coeliac groups have disappeared with the retirement or move of a single dedicated clinician or researcher. Along with providing high-quality care for patients with coeliac disease, which is currently not routine in non-specialized practices, these clinics are synergistic with local research efforts providing access to patients and patient materials for research. New and increased funding would catalyse and sustain a new generation of coeliac disease centres, supporting and sustaining patients and research in the coming years. Efforts should be made to improve training of community physicians and other health-care providers through symposia, webinars and development of clinical guidelines, as well as increasing opportunities for research funding coming from industry or government (TABLE 4).

**Opportunities.** As with many areas of research today, laboratories and clinical groups working individually will only be able to make incremental gains. Larger problems will only be able to be solved by larger teams. For both clinical and basic research, multinational networks, as exist for other conditions such as type 1 diabetes mellitus and IBD will be needed to address some of the most fundamental questions in coeliac disease. Relevant examples include TrialNet (in the diabetes research community) and ImproveCareNow for IBD, both of which have accelerated research in their respective fields. Researchers, physicians and stakeholders are working collaboratively with the community to accelerate innovation, discovery and the application of new knowledge to disease management, such as adoption of novel tools to detect gluten excretion in urine and stool in clinical practice\(^{6,59}\). Such networks will enable efficient clinical trials providing sufficient numbers of heterogeneous patients to ensure that findings are generalizable and reproducible. In addition, networks of laboratories will enable distribution of the cost and expertise needed to implement the latest technologies, including immune cell phenotyping, microbiome characterization, genome sequencing and reverse translation into improved animal models. In turn, this network would serve as an incubator for new clinicians and researchers, thereby forming a virtuous cycle. As discussed in the next section, creation of an international coeliac disease consortium should be considered a key priority for the next decade. A summary of the milestones and gaps identified in coeliac disease is provided in FIG. 1, and a timeline of milestones in pathophysiology, diagnosis, treatment and management of coeliac disease is provided in TABLE 1. These discoveries include examples of how coeliac disease researchers have made substantial contributions through partnership with type 1 diabetes mellitus researchers to include secondary aims related to coeliac disease in multi-site multinational collaboratives (for example, the TEDDY study\(^{60}\)) and of how new therapeutic concepts in the autoimmunity field have been applied to coeliac disease\(^{61}\).

**Final comments and reflections**
Over the past decades, the field of coeliac disease has had many research accomplishments to celebrate. We have gained tremendous understanding of the

### Table 4 | Models for innovation and potential application in coeliac disease

| Model                                 | Examples outside coeliac disease                                                                 | Dividends                                                                                       | Potential applications in coeliac disease                                                                 |
|---------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Clinical trials consortium            | Children’s Oncology Group; TrialNet (type 1 diabetes); FARE (Food Allergy Research Education)  | Successful multicentre treatment and prevention trials in difficult-to-recruit populations (e.g. double-blind placebo with oral peanut challenge in anaphylaxis); overall survival for childhood cancer >80%; patients outside major academic centres participate in research | More rapid evaluation of increasing number of emerging therapies; increased generalizability of findings and increased rate of discovery and innovation; more efficient use of existing resources; identification of well-defined patients |
| Inception cohort study                | Epic-IBD                                                                                         | Identification of prognostic features                                                          | Risk stratification at diagnosis; personalized dietary prescription                                     |
| Screening study                       | Colorectal cancer screening trials                                                              | Justification for population-based cancer screening                                            | Evidence-based strategies regarding who to screen and why                                              |
| Collaborative care network            | Cystic Fibrosis Foundation Accredited Care Centers; ImproveCareNow (IBD)                      | Improved quality of care and life expectancy of patients with cystic fibrosis; increase in number of children with IBD in remission off steroids | Personalized treatment for different disease phenotypes; improved understanding of natural history of treated coeliac disease |

*IBD, inflammatory bowel disease.*

**Figure 1** | Natural history of treated coeliac disease
physiopathology of the disease, which is one of very few autoimmune diseases for which the inciting antigen can be administered safely, with the ability to track antigen-specific T cell responses. Thus, coeliac disease is a very attractive model for antigen-specific immune tolerance and other therapies. There are great opportunities for major research in coeliac disease with a potential for high returns on investment. However, as described already, the most important challenges and opportunities require the coordination of efforts in the laboratory and in the clinic and systematic data collection that exceeds the abilities of research groups working in isolation. As coeliac disease is common and heterogeneous with both individual and regional variations, a multinational consortium will be essential to solving the current gaps in diagnosis and management. At the same time, the strong current foundation of knowledge regarding coeliac disease pathophysiology and clinical impact, along with the advanced assortment of powerful clinically available tests such as highly accurate serology and laboratory technologies including isolation of circulating gluten-specific T cells, suggests that with targeted investment, there is the opportunity to make substantial progress in coeliac disease that would benefit autoimmune disorders broadly.

Specifically, this multidisciplinary working group makes the following recommendations for coeliac disease.

- Increase government funding, as philanthropic and industry funding is insufficient to achieve common goals. This approach would require lobbying government to establish priority to allocate research funding in coeliac disease. Focusing on early detection and improvement in treatment and management of coeliac disease would reduce health-care costs, which will ultimately benefit the community.

- Improve understanding of coeliac disease as a serious medical condition among the health-care provider community, government and the public.

- Develop the infrastructure to support an international consortium that links clinical, microbiome, genetic and immunological data, alongside adult and paediatric patient data, into one accessible community resource that can promote mechanistic study of human disease, evidence-based management approaches and clinical trials.

- Innovative models that have been successful in managing other conditions could potentially be implemented in coeliac disease. For instance, successful multicentre trials for treatment and prevention in
populations with known difficulties in recruitment have been implemented by various groups, such as paediatric oncology\textsuperscript{6} and food allergy\textsuperscript{7}. Moreover, population databases to establish risk factors as well as screening programmes have been implemented for IBD\textsuperscript{8} and cancer (such as the SEER database, which is supported by the Surveillance Research Program in the NCI’s Division of Cancer Control and Population Sciences. Collaborative multidisciplinary networks have improved the quality of care of patients with cystic fibrosis\textsuperscript{9} and IBD (such as the Promoting Access and Care through Centres of Excellence (PACE) network in Canada). More detailed explanation of various models for innovation that can be applied in coeliac disease are shown in Table 4.

Conclusions
Overall, we remain confident that research breakthroughs in the near term have the potential to greatly improve clinical care in coeliac disease and facilitate innovations across autoimmunity. However, if funding opportunities do not increase for coeliac disease in the coming years, then the breakthroughs needed to continue to advance and possibly cure this morbid condition will be delayed or lost. We hope that this Roadmap will provide guidance to private organizations and governmental agencies justifying and prioritizing funding for coeliac disease, a common and serious yet understudied condition.

Published online 15 September 2021
56. Liu, E. et al. Risk of pediatric celiac disease according to HLA haplotype and country. *N. Engl. J. Med.* 371, 42–49 (2014).
57. Rubio-Tapia, A., Ludvigsson, J. F., Brantner, T. L., Murray, J. A. & Everhart, J. E. The prevalence of celiac disease in the United States. *Am. J. Gastroenterol.* 107, 1538–1544 (2012).
58. Comino, I. et al. Monitoring of gluten-free diet compliance in celiac patients by assessment of gliadin 33-mer equivalent epitopes in feces. *Am. J. Clin. Nutr.* 95, 670–677 (2012).
59. Silvester, J. A. et al. Exposure sources, amounts and time course of gluten ingestion and excretion in patients with celiac disease on a gluten-free diet. *Aliment. Pharmacol. Ther.* 52, 1469–1479 (2020).
60. TEDDY Study Group. The environmental determinants of diabetes in the young (TEDDY) study: study design. *Pediatr. Diabetes* 8, 286–298 (2007).
61. Getts, D. R., Shea, L. D., Miller, S. D. & King, N. J. C. Harnessing nanoparticles for immune modulation. *Trends Immunol.* 36, 419–427 (2015).
62. O’Leary, M., Kralio, M., Anderson, J. R. & Reaman, G. H. Progress in childhood cancer: 50 years of research collaboration, a report from the Children’s Oncology Group. *Semin. Oncol.* 35, 484–493 (2008).
63. PALISADE Group of Clinical Investigators. AR101 oral immunotherapy for peanut allergy. *N. Engl. J. Med.* 379, 1991–2001 (2018).
64. Egberg, M. D., Kappelman, M. D. & Gullati, A. S. Improving care in pediatric inflammatory bowel disease. *Gastroenr. Clin. North. Am.* 35, 419–427 (1996).
65. Mogayed, P. J., Dunitz, J., Marrow, L. C. & Hazle, L. A. Improving chronic care delivery and outcomes: the impact of the cystic fibrosis Care Center Network. *BMJ Qual. Saf.* 23, 3–8 (2014).
66. Osborne, T. B. Our present knowledge of plant proteins. *Science* 287, 417–427 (1980).
67. Rej, A., Aziz, I. & Sanders, D. S. Breaking bread! *Proc. Nutr. Soc.* 78, 118–125 (2019).
68. Atri, N., Rostami-Nejad, M., Anderson, R. P. & Rostami, K. The gluten gene: unlocking the understanding of gluten sensitivity and intolerance. *Appl. Clin. Genet.* 14, 57–50 (2021).
69. Hardy, M. Y. et al. Ingestion of oats and barley in patients with celiac disease mobilizes cross-reactive T cells activated by avenin peptides and immunodominant hordein peptides. *J. Autoimmun.* 56, 56–65 (2015).
70. Selheim, B. G. et al. HLA antigens in dermatitis herpetiformis and celiac disease. *Tissue Antigens* 7, 57–59 (1976).
71. Sailese, M., Lopetuso, L. R., Ethymakas, K. & Neri, M. Beyond the HLA genes in gluten-related disorders. *Front. Nutr.* 7, 1–7 (2020).
72. Ju, J. M., Marietta, E. V. & Murray, J. A. Generating transgenic mouse models for studying celiac disease. *Methods Mol. Biol.* 1326, 23–35 (2015).
73. Lundin, K. E. et al. Gliadin-specific, HLA-DQ(alpha) 1*0501/ beta 1*0201 restricted T cells isolated from the small intestinal mucosa of celiac disease patients. *J. Exp. Med.* 178, 187–196 (1993).
74. Chisari, F. V. and the Gastrohep group for antigen recognition by transglutaminase 2-specific autoreactive T cells in celiac disease. *J. Biol. Chem.* 290, 21365–21375 (2015).
75. Mayassa, T. & Jabri, B. Human intraepithelial lymphocytes. *Microsc. Immunol.* 11, 1281–1289 (2018).
76. Tye-Din, J. A. et al. Elevated serum interleukin-2 after gluten correlates with symptoms and is a potential diagnostic biomarker for celiac disease. *Aliment. Pharmacol. Ther.* 50, 901–910 (2019).
77. Caminero, A. & Versil, E. F. Celiac disease: should we care about microbes? *Am. J. Physiol. Gastrointest. Liver Physiol.* 317, G161–G170 (2019).
78. Shiner, M. Duodenal biopsy. *Lancet* 270, 17–19 (1956).
79. Cichowitz, A. B. et al. Diagnosis and treatment patterns in celiac disease. *Dig. Dis. Sci.* 64, 2095–2106 (2019).
80. Anderson, C. M. Histological changes in the duodenal mucosa in celiac disease. Reversibility during treatment with a wheat gluten-free diet. *Arch. Dis. Child.* 35, 419–427 (1960).
81. Silvester, J. A. et al. Tests for serum transglutaminase and endomysial antibodies do not detect most patients with celiac disease and persistent villous atrophy on gluten-free diets: a meta-analysis. *Gastroenterology* 153, 689–701 e1 (2017).
82. Lahdeaho, M. L. et al. Safety and efficacy of AMG 714 in adults with celiac disease exposed to gluten challenge: a phase 2a, randomised, double-blind, placebo-controlled study. *Lancet Gastroenterol.* 4, 948–959 (2019).
83. Daveson, A. J. M. et al. Baseline quantitative histology in therapeutics trials reveals villus atrophy in most patients with celiac disease who appear well controlled on gluten-free diet. *Gastrology* 2, 22–30 (2020).
84. Montir, B. et al. Toward the assessment of food toxicity for celiac patients: characterization of monoclonal antibodies to a main immunogenic gluten peptide. *PloS ONE* 3, e2294 (2008).
85. Shahmar et al. Effect of addition of short course of prednisolone to gluten-free diet on mucosal epithelial cell regeneration and apoptosis in celiac disease: a pilot randomized controlled trial. *Dig. Dis. Sci.* 57, 3116–3125 (2012).
86. Lionetti, E. et al. Introduction of gluten, HLA status, and the risk of celiac disease in children. *N. Engl. J. Med.* 371, 1295–1305 (2014).
87. Gottlieb, K., Dawson, J., Hussain, F. & Murray, J. A. Development of drugs for celiac disease: review of endpoints for phase II and III trials. *Gastroenr. Rep.* 3, 91–102 (2015).
88. Leffer, D. et al. Development of celiac disease therapeutics: report of the third gastroenterology therapeutics workshop. *Gastroenterology* 151, 407–411 (2016).
89. Vriezea, S. L. et al. Randomized feeding intervention in infants at high risk for celiac disease. *N. Engl. J. Med.* 371, 1304–1315 (2014).

Acknowledgements
M.P.S received an Innovation Grant from CCC Medicine Internal Career Research Award. Division of Gastroenterology AFP grant, and Farncombe Family Digestive Health Research Institute Award. J.A.S is supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH under award number K25DK119584. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Canadian Institutes of Health Research. E.F.V is funded by a CIHR grant, and Farncombe Family Digestive Health Research Institute Award. Only participants of the workshop included as authors were involved in the writing of this Roadmap Review.

Author contributions
All authors participated in the conception, writing and editing of the article.

Competing interests
B.L. has consulted for Takeda and Anokian. D.A.L receives salary support from Takeda Pharmaceutica unrelated to this manuscript. M.P.S has consulted for Takeda and Lupin unrelated to this manuscript. J.A.S has consulted for Takeda Pharmaceauticals and received grant funding from Glutenostics, Milky Way Life Sciences, the Celiac Disease Foundation and BEYOND Celiac. E.F.V received grant funding from Biocodex Foundation and Gilead unrelated to this manuscript. R.P.A has served as consultant for Takeda, GSK, Anokion, Allero Therapeutics, TregTherapeutics and EVOQ Therapeutics. R.P.A is founder and shareholder of Novoviah Pharmaceutica and is the inventor of patents relating to the diagnosis and treatment of celiac disease. The remaining authors declare no competing interests.

Peer review information
Nature Reviews Gastroenterology & Hepatology thanks Stefano Guandalini, Knut Lundin, David Sanders and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher’s note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

RELATED LINKS
Celiac Disease Foundation: https://celiac.org/
Coeliac disease centres: https://celiac.org/collectivecentersandprograms/
ImproveCareNow: https://www.improvecarenow.org/
SEER database: https://seer.cancer.gov/
Surveillance Research Program: https://surveillance.cancer.gov/
Society for the Study of Celiac Disease: https://www.coeliac.org/
TrialNet: https://www.trialnet.org/