Coeliac disease occurs in about 1% of people in most populations. Diagnosis rates are increasing, and this seems to be due to a true rise in incidence rather than increased awareness and detection. Coeliac disease develops in genetically susceptible individuals who, in response to unknown environmental factors, develop an immune response that is subsequently triggered by the ingestion of gluten. The disease has many clinical manifestations, ranging from severe malabsorption to minimally symptomatic or non-symptomatic presentations. Diagnosis requires the presence of duodenal villous atrophy, and most patients have circulating antibodies against tissue transglutaminase; in children, European guidelines allow a diagnosis without a duodenal biopsy provided that strict symptomatic and serological criteria are met. Although a gluten-free diet is an effective treatment in most individuals, a substantial minority develop persistent or recurrent symptoms. Difficulties adhering to a gluten-free diet have led to the development of non-dietary therapies, several of which are undergoing trials in human beings.

Introduction
Coeliac disease is an autoimmune disorder that occurs in genetically predisposed individuals who develop an immune reaction to gluten. The disease primarily affects the small intestine; however, the clinical manifestations are broad, with both intestinal and extra-intestinal symptoms. Coeliac disease is notable because of its broad clinical spectrum of presentations, large age range at which onset can occur (which can precede diagnosis by several years), and the increased morbidity and mortality that has been found in most studies. The disease also provides a model of an immune-based disease with both strong genetic and environmental risk factors. Coeliac disease has been the topic of previous Seminars in The Lancet, and we aim to provide the most current information to clinicians with this Seminar.

Pathogenesis
Gluten
The major environmental factor responsible for the development of coeliac disease is gluten. Gluten (from the Latin “glue”) is the term for the prolamin storage proteins of the cereal grains wheat, rye, and barley. Gluten is favoured in breadmaking for its elasticity; however, it is enriched in glutamines and prolines and, as a result, is incompletely digested by gastric, pancreatic, and brush border peptidases, leaving large peptides up to 33 aminoacids long. These peptides enter the lamina propria of the small intestine via transcellular or paracellular routes where, in affected individuals, an adaptive immune reaction occurs that is dependent on deamidation of gliadin molecules by the enzyme tissue transglutaminase (TTG), the predominant autoantigen of coeliac disease. Deamidation increases the immunogenicity of gliadin, facilitating binding to the HLA-DQ2 or HLA-DQ8 molecules on antigen presenting cells. Gliadin peptides are then presented to gliadin-reactive CD4+ T cells. During this process, antibodies against TTG, gliadin, and actin are made through unclear mechanisms. These antibodies might contribute to extra-intestinal manifestations of coeliac disease, such as dermatitis herpetiformis and gluten ataxia.

Accompanying this adaptive immune reaction is an innate immune response in the epithelial compartment, which is evident pathologically by prominent intraepithelial lymphocytosis. During the pathogenesis of coeliac disease, intraepithelial lymphocytes express the natural killer T-lymphocyte receptors NKG2D and CD9/NKG2A, which recognise the products (cell surface glycoproteins) of stress-induced genes MICA and MICB and the protein HLA-E expressed on the surface of epithelial cells. Interleukin 15 serves an important role in upregulating these natural killer receptors on cytotoxic epithelial cells. Both the lamina propria (adaptive) and intraepithelial (innate) immune responses seem to be necessary for formation of the complete coeliac pathological lesion, but how these two processes interact is not clear.

People with coeliac disease develop an intense immune response to some but, notably, not all non-gluten proteins in wheat. The importance of these non-gluten wheat proteins in the pathogenesis of coeliac disease is not clear, although one class of these proteins, the amylase trypsin inhibitors, might have a role in the epithelial cell damage, resulting from the innate response and in non-coeliac gluten sensitivity, another wheat-related disorder.

Genetic factors
The importance of a genetic component for the development of coeliac disease is evident, based on the familial occurrence and the high concordance among

Search strategy and selection criteria
We searched PubMed for articles published from Jan 1, 1990, to Jan 31, 2017, with no language restrictions, using the terms “celiac”, “coeliac”, and “gluten”. In our selection of articles, we emphasised those published since 2010, but included older publications of scientific and historical relevance. We mostly selected cohort and case-control studies and the few randomised trials performed in this subject area, but also selected guidelines and systematic reviews and smaller, non-controlled clinical studies of particular relevance.
identical twins.\textsuperscript{17,18} Almost 100% of patients with coeliac disease possess specific variants of the HLA class II genes HLA-DQA1 and HLA-DQB1 that, together, encode the two chains (\(\alpha\) and \(\beta\)) of the coeliac-associated heterodimer proteins DQ2 and DQ8 that are expressed on the surface of antigen presenting cells. More than 90% of patients with coeliac disease are DQ2 positive and most of the others are DQ8 positive. Geographical variability in the prevalence of DQ2 and DQ8 among patients with coeliac disease has been reported.\textsuperscript{19} Some individuals with coeliac disease do not have the full component of alleles that compose the haplotype HLA-DQ2 and are, therefore, DQ2 negative, but are considered half DQ2 positive.\textsuperscript{20} This finding indicates the importance for the clinician that the reports of whether a patient is HLA-DQ2 positive or HLA-DQ8 positive should include not only whether the haplotypes are present, but also whether the allelic components are present. A cohort study of children in Denver (CO, USA)\textsuperscript{21} found that, by age 15 years, an estimated 3·1% of the population develops coeliac disease, with a risk of 14·2% among those homozygous for DQ2 and 1·5% among those who had one copy of DQ8.

Almost all patients with coeliac disease possess HLA-DQ2, HLA-DQ8, or half HLA-DQ2; however, up to 40% of people in the Americas, Europe, and southeast Asia also carry these alleles, indicating that these genes are necessary but not sufficient for coeliac disease to develop, contributing to only about 40% of the genetic risk for coeliac disease. Genome-wide association studies have shown 39 non-HLA regions associated with increased risk for coeliac disease. Demonstration of other genetic risk factors within and outside the MHC region that are associated with increased risk of coeliac disease allows for identification of possible pathogenic pathways, providing insight into pathogenic mechanisms.\textsuperscript{22,23}

**Environmental factors**

The prerequisite HLA genes and gluten ingestion are common; however, coeliac disease occurs only in about 1% of the population, suggesting that other environmental factors besides gluten are probably important.

**Breastfeeding and infant feeding practices**

The Swedish epidemic of coeliac disease between 1984 and 1996 was considered to be the result of changes in infant feeding practices.\textsuperscript{24} However, studies have not shown an effect of breastfeeding on the risk of coeliac disease.\textsuperscript{25} Observational and large prospective studies of gluten introduction in children who were at high risk of coeliac disease due to a family history and compatible HLA haplotype did not show that the timing of gluten introduction had a significant effect on risk of coeliac disease.\textsuperscript{26-28} Although delaying gluten introduction beyond 12 months of age can result in a lower risk of coeliac disease in the short term, this seems to be negated by a catch-up phenomenon later in childhood.\textsuperscript{29} In a prospective cohort study, the most prominent risk factor for developing coeliac disease was the dosage of the HLA risk genes.\textsuperscript{30} Despite the negative results of studies testing various strategies of the timing of gluten introduction, a high quantity of gluten remains a proposed risk factor, based on the results of a nested case-control study that showed that children with coeliac disease were consuming greater quantities of gluten compared with controls.\textsuperscript{31} However, this result was not observed in a re-evaluation of another large study of similarly at-risk children who developed coeliac disease.\textsuperscript{32} Because of the negative clinical trials, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition issued modified guidelines regarding gluten introduction, acknowledging the absence of effective prevention strategies. These guidelines recommend that gluten be introduced between the ages of 4 months and 12 months, and that consumption of large quantities of gluten should be avoided during the first weeks after gluten introduction.\textsuperscript{33} A meta-analysis showed that the late introduction of gluten (>6 months) increased the risk of developing coeliac disease.\textsuperscript{13}

**Other risk factors**

Season of birth\textsuperscript{34,35} and elective caesarean section\textsuperscript{6,37} are risk factors for development of the disease, although studies of elective caesarean sections have shown conflicting results. Gastrointestinal infections,\textsuperscript{38} rotavirus in children and campylobacter infection in adults, have been reported as risk factors,\textsuperscript{39,40} with rotavirus vaccination seeming to provide a protective effect.\textsuperscript{41} An increased total number of infections (>10 vs <4 during the first 18 months of life) and respiratory infections (during the first 18 months of life) seem to increase the risk of developing coeliac disease later in childhood.\textsuperscript{42} Antibiotic\textsuperscript{43} and proton pump inhibitor use\textsuperscript{44} have been associated with increased risk of subsequent coeliac disease, as has in utero exposure to maternal iron supplementation.\textsuperscript{45} However, in utero exposure to antibiotics has not been associated with coeliac disease risk.\textsuperscript{46} Helicobacter pylori colonisation might decrease the risk of coeliac disease.\textsuperscript{47} Infection with the otherwise non-pathogenic reovirus might trigger coeliac disease.\textsuperscript{48}

**Role of the microbiome**

The complex interaction between genes, diet, and the microbiome might be crucial to the development of coeliac disease and to the generation of potential preventive or therapeutic measures. A study\textsuperscript{49} in mice expressing HLA-DQ8 showed that the intestinal microbiota can enhance or attenuate gluten-induced immunopathology, dependent on the specific microbial milieu. Cross-sectional studies have shown that patients with coeliac disease have alterations to their intestinal microbiome that are not entirely normalised following introduction of a gluten-free diet. Faecal concentrations
of *Bifidobacterium bifidum* were found to be significantly higher in untreated patients with coeliac disease than in healthy adults, and children with coeliac disease had a higher incidence of duodenal Gram-negative and, potentially, pro-inflammatory bacteria at diagnosis than did children in a control group. Another study showed that, although bacterial diversity was higher in non-coeliac controls than in untreated patients with coeliac disease, the difference was not significant. Age and a gluten-free diet can affect the duodenal microbiome in patients with coeliac disease, but a gluten-free diet will alter the microbiome even in healthy individuals. A 2015 study showed specific alterations in the faecal bacteria of vaginally delivered, breastfed infants at risk for coeliac disease that was associated with presence of HLA-DQ2, indicating that HLA type selects for specific gut microbiome characteristics.

**Epidemiology**

Coeliac disease affects about 1% of the population. Worldwide, there are differences in prevalence that are not explained by the known genetic and environmental risk factors. For example, in Europe, Germany has a lower prevalence of coeliac disease than other countries, with the highest prevalence being in Sweden and Finland. Within the USA, the prevalence in African Americans is low compared with those of white ethnic background, similarly, in Brazil, Brazilians of African descent have low rates of coeliac disease. The disease is increasingly prevalent in India, with the highest prevalence in northern India; this region has a similar prevalence of compatible HLA haplotypes compared with other regions in India, but has a much higher rate of wheat consumption. A 2016 study of nearly 500,000 duodenal biopsy samples taken from people throughout the USA showed that the ethnic group (based on a name-based algorithm) with the highest prevalence of villous atrophy was among those originally descended from the Punjab area of northern India (3-08% vs 1-80% for other Americans).

Globally, the prevalence of coeliac disease is increasing. Studies comparing serum stored from 1948–54 to current serum samples from the USA showed an increasing prevalence with time: a 4-4-5 times increase over approximately 50 years (comparing samples from 1948–54 to the present day) and a 2 times increase over 15 years (between 1974 and 1989). Similarly, in Finland, a 2 times increase in prevalence has been shown over approximately 20 years, comparing serum from 1978–80 to 2000–01. A study done in Denver, CO, USA followed children with increased genetic risk of coeliac disease, during a 20-year period; when these findings were extrapolated to the general population of the city, the cumulative incidence values for coeliac disease were 1-6% at 5 years of age, 2-8% at 10 years, and 3-1% at 15 years, a notable incidence rate which is similar to that seen in Scandinavians. These estimates are substantially higher than those of 2016 population-based estimates of coeliac disease prevalence, which suggested a prevalence of less than 1% of adults and children in the USA.

While the prevalence of coeliac disease has increased, the rate of diagnosis has increased more slowly. Analysis of the National Health and Nutrition Examination Survey, a national survey that includes about 5000 individuals annually and is considered representative of the US population, showed that more than 80% of people with coeliac disease were undiagnosed in 2009 and this decreased to less than 50% in 2013-14. If these numbers are confirmed in subsequent studies, this would indicate that, in the USA, there has been a large increase in the rate of diagnoses of coeliac disease similar to that seen previously in Finland, where the increase had been attributed to a rise in physician education. The increase in diagnosis rate in the USA could also be partly because of increased general interest in and adoption of the gluten-free diet in the general population in recent years.

**Clinical manifestations**

Over the past 10 years, attempts have been made to bring consensus to the terminology of the clinical stages of coeliac disease (panel 1). The common presentation of coeliac disease has shifted from the historically classic symptoms of malabsorption in childhood to non-classic symptoms, which can be present in childhood or adulthood. Classic symptoms include chronic diarrhoea, weight loss, and failure to thrive, which are quite rare. The more common, non-classical symptoms include iron deficiency, bloating, constipation, chronic fatigue, headache, abdominal pain, and osteoporosis. A 2010 study showed a considerably impaired quality of life in patients living with undiagnosed coeliac disease compared with those who had been diagnosed and treated (EuroQol five dimensions questionnaire score 0-56 vs 0-84). Increased awareness is required in both primary and secondary care to recognise the shift of the common presenting features and the non-specific manifestations of coeliac disease. Furthermore, patients can present with these diverse features to many different sub-specialties of medicine. Coeliac UK (the UK national patient body) report an average 13-year delay in diagnosis for patients. As a result, in 2015, the National Institute for Health and Care Excellence (NICE) updated their guidelines for coeliac disease and created a list of symptoms or risk factors that should trigger testing for coeliac disease (panel 2).

**Diagnosis**

A combination of coeliac disease serology testing and duodenal biopsy sampling is required for the diagnosis of coeliac disease in adults. The current American College of Gastroenterology, British Society of Gastroenterology, and NICE guidelines recommend testing high-risk adults with coeliac serology. Measurement of the concentration of IgA-TTG antibodies...
Seminar

Panel 1: Terminology describing patients with coeliac disease (adapted from Ludvigsson and colleagues, 2013)

Potential
Positive serological tests and normal intestinal biopsy

Asymptomatic
Absence of symptoms despite specific questioning regarding symptoms

Symptomatic
Presence of either intestinal or extra-intestinal symptoms

Classic
Diarrhoea, signs and symptoms of malabsorption, or both

Non-classic
Lack of malabsorption symptoms, but other symptoms present (eg, anaemia, osteoporosis)

Refractory
Persistent symptoms and villous atrophy despite adherence to a gluten-free diet

Panel 2: National Institute for Health and Care Excellence guidelines on the indications that should prompt testing for coeliac disease

Coeliac testing recommended
- Persistent unexplained abdominal or gastrointestinal symptoms
- Faltering growth
- Prolonged fatigue
- Unexpected weight loss
- Severe or persistent mouth ulcers
- Unexplained iron, vitamin B12, or folate deficiency
- Type 1 diabetes
- Autoimmune thyroid disease
- Irritable bowel syndrome
- First degree relatives of people with coeliac disease

Coeliac testing should be considered
- Metabolic bone disorders (reduced bone mineral density or osteomalacia)
- Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
- Unexplained subfertility or recurrent miscarriage
- Persistently increased concentrations of liver enzymes with unknown cause
- Dental enamel defects
- Down's syndrome
- Turner syndrome

should be done as a first-line screening test because of its high sensitivity and negative predictive value, and because it is less expensive than measurement of endomysial antibodies (EMA). A study of 2000 patients56 (with a 3.4% prevalence of coeliac disease) compared the sensitivities of IgA TTG tests alone and a two-step approach using IgA TTG and EMA testing. IgA TTG testing alone was found to be a more sensitive marker for coeliac disease than IgA-TTG plus EMA testing (sensitivities of 90.9% vs 85.7%, and negative predictive values of 99.6% vs 99.7%). Therefore, IgA-TTG testing is the recommended first-line approach. However, if IgA-TTG is weakly positive (compared with the laboratory threshold of normal), EMA concentration, which has a high specificity (95%), should also be tested.85,86 Notably, EMA testing uses the substrates of monkey oesophagus or human umbilicus, which have low availability. EMA testing is also expensive and labour intensive, and interpretation of the results can be subjective. Evidence suggests that detection of antibodies against deamidated gliadin peptide might allow recognition of some cases of coeliac disease that are not detected by the established serological tests,7 although isolated increases in the concentration of this antibody (in the context of a normal TTG titre) have a low positive predictive value for coeliac disease.79 Ultimately, diagnostic practice is likely to vary internationally depending on the available tests and the health-care system within each individual country.

Patients with IgA deficiency do not produce IgA-TTG or IgA-EMA antibodies, and could have a false negative result. Therefore, total IgA concentration should be measured in conjunction with serology. For patients with IgA deficiency, IgG-TTG, IgG-EMA, and IgG-deamidated gliadin peptide can be tested instead. A 2012 meta-analysis78 showed that IgG-deamidated gliadin peptide had a pooled sensitivity ranging from 80.1% to 98.6%.

Advising patients to eat a gluten-containing diet before their tests to ensure the serological and histological results are not affected is important. Although the minimum intake of gluten required for diagnosis has historically been 10 g of gluten a day (equivalent to four slices of bread) for 6 weeks, more recent data80-82 showed that a shorter, lower dose of gluten challenge could be sufficient to induce serological and histological changes in patients with coeliac disease (>3 g gluten per day for 2 weeks or 10 g gluten per day for 18 days). In the 3 g per day gluten challenge, 68% of patients developed villous atrophy within 14 days.80 In this study, the concentration of serological markers for coeliac disease increased at a slower rate than did histological abnormalities (table). The decision of whether to proceed with a duodenal biopsy during a gluten challenge should depend on the pre-test likelihood of coeliac disease. For example, if the likelihood is low, negative serological tests following 28 days of a low-dose gluten-challenge are sufficient to rule out coeliac disease with high confidence. If the likelihood is high, a duodenal biopsy sample should be done at least 14 days after beginning the gluten challenge, because of the possibility of seronegative coeliac disease.

Duodenal biopsy samples showing increased intraepithelial lymphocytes, crypt hyperplasia, and villous

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atrophy (Marsh type 3) with positive coeliac serology confirm the diagnosis of coeliac disease in adults. Biopsy sampling is done during gastroscopy, and abnormalities such as loss of folds or scalloping of folds in the descending duodenum might be observed; however, the duodenum can appear normal (and these changes can be seen in other conditions, such as giardiasis and infection with HIV). Although IgA-TTG and EMA have excellent sensitivities in the medical literature, their sensitivities often decrease when the tests are done in real-world health-care settings, with a lower prevalence of coeliac disease being reported in the general population than in prospective studies. Therefore, a confirmatory duodenal biopsy sample ensures that patients are correctly diagnosed with coeliac disease before being subjected to a gluten-free diet for life. Additionally, this confirmatory biopsy avoids any diagnostic uncertainty in cases where patients do not respond to a gluten-free diet, and provides a baseline reference for histological response to a gluten-free diet. Notably, a clinical response to a gluten-free diet alone does not confer a diagnosis of coeliac disease. This clinical response can also be seen in patients with non-coeliac gluten sensitivity, which is characterised by symptom improvement on gluten avoidance without coeliac disease (with negative coeliac serology and absence of villous atrophy). Negative serological findings do not exclude coeliac disease with 100% accuracy, because of the possibility of seronegative coeliac disease.

Paediatric practice has moved towards a so-called biopsy avoidance strategy. The 2012 European Society for Paediatric Gastroenterology, Hepatology, and Nutrition guidelines recommend that symptomatic paediatric patients no longer require biopsy sampling to confirm the diagnosis of coeliac disease if they have TTG concentrations 10 times higher than the upper limit of normal, positive EMA in a separate blood sample, and the presence of HLA-DQ2 or HLA-DQ8 genotype. The rationale for requiring a second blood sample is: (1) to prevent the possibility of a mislabelled sample leading to an erroneous diagnosis; and (2) to detect the possibility of temporary gluten autoimmunity, which is not uncommon. This non-biopsy strategy avoids the need for a gastroscopy, which often requires general anaesthesia in paediatric patients. This is an appropriate approach in carefully selected symptomatic paediatric cases, as judged by specialists. Practice of this strategy has led to questions of the usefulness of biopsy avoidance in adults, since data show a similarly high positive predictive value of TTG concentrations that are increased to this degree and further data suggest that discrepancies occur in the interpretation of duodenal histopathology in the absence of formal morphometric measurement. However, it is premature to conclude that this strategy should be extended to adult practice. With the variable specificities of TTG assays across the UK and the USA, adults who do not have coeliac disease risk being committed to a gluten-free diet.

The histological changes associated with coeliac disease are patchy—villous atrophy can be present in areas that are adjacent to non-atrophic villi. To optimise the likelihood of a histological diagnosis, a specific duodenal biopsy sample strategy should be used. New evidence supports the usefulness of a duodenal bulb biopsy in diagnosis of coeliac disease and requires a minimum of four further biopsy samples from the second part of the duodenum. For the bulb biopsy, no specific anatomical site within the bulb is required. Although inclusion of bulb biopsies has 100% sensitivity in the recognition of villous atrophy, in a low pre-test probability setting, the incremental yield of bulb biopsies is low, and raises the possibility of other pathological abnormalities being misinterpreted as coeliac disease. The bulb biopsy could, therefore, require a separate formalin specimen to allow the pathologist to appropriately interpret the different duodenal anatomy, such as the presence of Brunner’s glands, heterotopic gastric mucosa, or lower baseline intraepithelial lymphocyte counts. Furthermore, a so-called single-bite biopsy technique has better histological orientation (in which crypt-to-villus ratios can be adequately measured) than do so-called double-bite biopsies (66% for the single-biopsy technique compared with 42% of patients for the double-biopsy technique; p<0·01). Despite guidelines, current real-world adherence to best clinical practice in health-care settings is still highly variable and is likely to further contribute to delays in diagnosis. Current medical literature suggests that between 5% and 13% of patients with diagnosed coeliac disease have had a previous endoscopy with either no biopsy or an inadequate biopsy resulting in a delay in diagnosis.

Other diagnostic challenges exist: HLA genotyping, although not required as a routine test in all patients with suspected coeliac disease, can be valuable in equivocal diagnoses, patients who are already on a gluten-free diet who are unwilling or unable to undergo a gluten challenge, and those who refuse a gastroscopy. HLA testing can also be useful when assessing family members of patients with coeliac disease, because the absence of HLA-DQ2 and HLA-DQ8 almost always excludes coeliac disease, with a negative predictive value of more than 99%. However, the allelic components should be noted, because patients with a half-DQ2 result can develop coeliac disease, although this finding is rare. Among patients who are unwilling or unable to undergo gastroscopy, video capsule
Individuals with seronegative duodenal villous atrophy can have an alternative cause of this histological abnormality than coeliac disease. However, a subset of patients (between 2% and 15% of the population of patients with coeliac disease) with seronegative villous atrophy have seronegative coeliac disease. Seronegative coeliac disease can result from impaired immunoregulation such as IgA deficiency, concomitant common variable immunodeficiency, and use of immunosuppressant. Seronegative coeliac disease can also occur early in coeliac disease development late in the disease (presenting as enteropathy-associated T-cell lymphoma), or in patients who have adopted a reduced-gluten diet before testing. Volta and colleagues compared the clinical characteristics of seropositive and seronegative coeliac disease (n=810 patients), and reported that patients with seronegative coeliac disease were older at diagnosis (49 years vs 36 years; p<0·005) and had typical symptoms, such as diarrhoea, significantly more frequently (100% vs 34% of patients; p<0·001). Seronegative coeliac disease was also associated with more severe villous atrophy (67% vs 36% of patients) and coexisting autoimmune diseases than seropositive coeliac disease. These findings support those reported by Salmi and colleagues who found transglutaminase 2 autoantibodies deposited in the small bowel mucosa in patients with seronegative coeliac disease, despite their seronegativity. The authors indicated that, in seronegative coeliac disease, coeliac antibodies are bound to intestinal transglutaminase 2 autoantibodies with considerably high avidity, which occurs in a chronic immune reaction, rendering the antibodies unable to enter the circulation to cause seropositivity. Seronegative coeliac disease is, therefore, speculated to be associated with chronic, more severe forms of coeliac disease.

Seronegative coeliac disease requires careful diagnosis, with the presence of HLA-DQ2 or HLA-DQ8 and a response to a gluten-free diet after excluding other causes of seronegative villous atrophy. A large prospective analysis of 200 cases of seronegative villous atrophy showed that 31% of cases were due to coeliac disease, 27% were caused by infection, and 18% were idiopathic, of which 72% spontaneously resolved without any intervention. Notably, non-white ethnicity was markedly associated with seronegative villous atrophy (odds ratio 10·8; p=0·003), and 66% of non-white cases of seronegative villous atrophy were caused by infection. Other causes of seronegative villous atrophy included use of specific medications (mycophenolate mofetil and olmesartan medoxomil), common variable immune deficiency, Crohn’s disease, tropical sprue, giardiasis, autoimmune enteropathy, and other, less common diseases.

Controversies in testing for coeliac disease

There is controversy as to whom to test for coeliac disease. A central tenet of this issue is the ethical difference between population screening and case-finding. If a patient seeks medical help then the physician is attempting to diagnose an underlying condition; for example, patients with coeliac disease can present with symptoms of irritable bowel syndrome or with osteoporosis. This behaviour would be classified as case-finding and, evidently, the patient has initiated the consultation and, in some sense, is consenting for investigation.

The Olmsted County Population database reviewed 338 previously undetected individuals with coeliac disease on glycaemic control and other outcomes. These data lend support to a no-screening policy for coeliac disease, although an alternative interpretation is that coeliac disease can be identified in a pre-symptomatic phase, providing proof-of-concept to the approach of early intervention. However, data to support that such an intervention leads to improved outcomes compared with a no-screening policy are lacking. Further controversy exists in the outcomes for patients with type 1 diabetes who are diagnosed with coexisting coeliac disease through screening programmes, because of a paucity of prospective longitudinal follow-up data. A randomised trial assessing the effect of diagnosing and treating coeliac disease on glycaemic control and other outcomes in patients with type 1 diabetes is in progress.

Treatment

The mainstay of treatment of coeliac disease remains adherence to a gluten-free diet. Improvement and resolution of symptoms typically occurs within days or weeks, and often precedes normalisation of serological markers and of duodenal villous atrophy. Despite its effectiveness in achieving normalisation of these parameters in most patients, the gluten-free diet has numerous difficulties. Gluten-free substitute foods are substantially more expensive than their gluten-containing counterparts. Patients with low incomes might, therefore, be at particularly high risk of non-adherence to this diet. The quality of information regarding the gluten-free status of food ingredients is variable in online resources, which can lead to confusion among patients. Potential gluten exposure when travelling or eating in restaurants can be a hazard and a source of anxiety. Social pressures, particularly in adolescence, can also be an impediment to strict adherence. Uncertainty regarding the presence of gluten in trace amounts in medications and supplements is another concern. As a result of the vigilance required to adhere to this diet, the burden of treatment of coeliac
disease is high. The self-rated burden of treatment in coeliac disease in adults is greater than that rated by patients with chronic conditions such as hypertension, and is similar to the treatment burden of diabetes.109

Patients with newly diagnosed coeliac disease should be referred to an expert dietitian, because the gluten-free diet requires knowledge not only of hidden sources of gluten, but also of healthy gluten-free substitute grains that provide adequate fibre and nutrients. Upon diagnosis, patients should be tested for micronutrient deficiencies, including iron, folic acid, vitamin B12, and vitamin D.73 Pneumococcal vaccination can be considered, because of the association between coeliac disease and increased risk of community-acquired pneumonia.104 In view of the increased risk of osteoporosis and fractures in patients with coeliac disease,74 guidelines issued by the British Society of Gastroenterology73 recommend measurement of bone mineral density after 1 year of the gluten-free diet in patients older than 55 years or in those with additional risk factors for osteoporosis. Beyond the initial diagnosis period, patients should be followed up regularly for assessment of symptoms and to monitor adherence to the gluten-free diet, noting a combination of symptoms, serologies (which usually normalise within 1 year of starting the diet), and dietitian follow-up.71

Non-dietary therapies

Many patients with coeliac disease are not satisfied with the gluten-free diet and are interested in alternative, non-dietary therapies.116 Together with the knowledge of the pathophysiological mechanism of coeliac disease, this finding has led to an interest in drug development either as an addition to the gluten-free diet or as a substitute.117 Drugs in various stages of development and testing use mechanisms such as inactivation of the toxic peptides in the bowel lumen, prevention of passage of gliadin into the mucosa, induction of immune tolerance, and inactivation of the immune process in the lamina propria. Related to the inactivation of the immune process in the lamina propria, a vaccine consisting of epitopes for gluten-specific CD4-positive T cells has completed phase 1 clinical studies.118

Two drugs have progressed through phase 2 clinical studies. Larazotide acetate, an oral peptide that modulates tight junctions and prevents passage of gliadin peptides through the epithelial barrier, was superior to placebo in alleviating symptoms in patients on a gluten-free diet compared with the diet plus placebo in a 12-week study.119 Latiglutenate, an enzyme preparation that prevents the pathological damage caused by gluten in patients with coeliac disease, was studied in a large clinical trial of patients with coeliac disease with symptoms and evidence of pathological damage (consistent with ongoing gluten ingestion despite attempts at adhering to the gluten-free diet).120 Latiglutenate did no better than placebo in alleviating symptoms or villous atrophy, which was thought to be due to a trial effect in which patients in the placebo group became more compliant to the diet and reduced their gluten consumption. Further trials of both drugs are planned.

Non-responsive and refractory coeliac disease

About 20% of patients with coeliac disease have persistent or recurrent symptoms despite a gluten-free diet.121 These cases are caused by heterogeneous conditions (panel 3). An essential first step in assessing these patients is to confirm the accuracy of the initial diagnosis of coeliac disease. If a patient did not originally have a duodenal biopsy showing villous atrophy while on a gluten-containing diet, or if the patient had a negative coeliac disease result from serological testing despite the presence of villous atrophy,103,104 an alternative diagnosis is possible. In this context, revisiting the diagnosis of coeliac disease with HLA testing and a gluten challenge might be appropriate.

When the diagnosis of coeliac disease is confirmed, the most common cause of persistent symptoms is inadvertent gluten exposure, and this can be ascertained with careful assessment by a knowledgeable dietitian. Other causes of persistent symptoms include irritable bowel syndrome, microscopic colitis, lactose or fructose intolerance, pancreatic insufficiency, and small intestinal bacterial overgrowth.112,113

Patients with or without ongoing or recurrent symptoms can show persistent villous atrophy on follow-up. Although this seems to be more common in adults older than age 50 years,122 villous atrophy persisted in 19% of children who underwent follow-up biopsy at least 1 year after starting the gluten-free diet.123 In adults, persistent villous atrophy has been associated with an increased risk of osteoporotic fractures and lymphoproliferative malignancy, suggesting that mucosal healing could be an endpoint in assessment of the response to the gluten-free diet.123,124 However, in view of the uncertainty regarding the degree of causation by persistent villous atrophy of these outcomes, and the absence of randomised trial data showing the effectiveness of routine follow-up biopsy, guidelines120,125 reassessment of duodenal histology can be considered, as opposed to routinely recommended. The finding of persistent villous atrophy could lead to implementation of successful strategies that have previously been evaluated, such as more intensive dietitian follow-up,126 or the short-term adoption of a more stringent diet eliminating all processed foods.127

Refractory coeliac disease is diagnosed in patients with persistent or recurrent symptoms of malabsorption and villous atrophy, despite evidence of strict gluten avoidance. This condition is associated with increased mortality and can progress to enteropathy-associated T-cell lymphoma. Patients with suspected refractory coeliac disease should have a duodenal biopsy, with assessment for an aberrant intraepithelial T-cell
Panel 3: Causes of non-responsive coeliac disease
Incorrect initial diagnosis
- Non-coeliac gluten sensitivity
- Seronegative villous atrophy

Inadvertent gluten exposure

Additional conditions
- Irritable bowel syndrome
- Small intestinal bacterial overgrowth
- Food intolerance (eg, to lactose or fructose)
- Pancreatic exocrine insufficiency
- Microscopic colitis

Refractory coeliac disease

<table>
<thead>
<tr>
<th>Persistent or recurrent symptoms</th>
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<tr>
<td>Tissue transglutaminase concentration test</td>
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<td>Duodenal biopsy</td>
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<td>Negative</td>
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<td>Villous atrophy</td>
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<td>Dietitian</td>
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Consider referral to specialist centre for assessment of refractory coeliac disease and exclusion of type 2 with flow cytometry, immunohistochemistry and PCR for clonality of T cells

Figure: Proposed flowchart for diagnosis and treatment following persistent or recurrent symptoms in patients with coeliac disease

population using immunohistochemistry, flow cytometry, and PCR for detection of T-cell receptor γ (TCR γ) gene rearrangement. The aberrant intraepithelial lymphocytes in patients with type 2 refractory coeliac disease lack surface CD8, CD3, and TCR γ expression while they express intracytoplasmic CD3, and exhibit oligoclonal TCR gene rearrangement. Those patients without an aberrant T-cell population (type 1 refractory coeliac disease) have a better prognosis than do those with aberrant T cells (type 2 refractory coeliac disease), and those with type 2 refractory coeliac disease are at high risk for progression to enteropathy-associated T-cell lymphoma. A three-item clinical score incorporating age, serum albumin concentration, and the presence of aberrant lymphocytes predicts 5-year survival in patients with refractory coeliac disease. We have generated a proposed flowchart for the diagnosis and treatment following persistent or recurrent symptoms in patients with coeliac disease (figure).

Malignancy and mortality risk
In addition to enteropathy-associated T-cell lymphoma, coeliac disease is associated with an increase in other types of non-Hodgkin lymphoma. In a population-based study, the risk of increased malignancy was increased for adenocarcinoma of the oesophagus, small intestine, colon, liver, and pancreas, although only estimates for the small intestine and liver remained significant after excluding the first year after coeliac disease diagnosis. The risk of colorectal cancer was found to be modestly increased in the long term (>5 years after diagnosis) in a second population-based study, but these patients did not seem to have an increased prevalence of colorectal adenomas. The risks of breast and lung carcinoma are reduced in patients with coeliac disease, but this might be because smoking is less common in patients with coeliac disease.

In view of these differential associations of coeliac disease with malignancy risk according to organ type, pooling overall malignancy as an outcome yielded a null association with coeliac disease in a 2012 meta-analysis. An association between coeliac disease and increased mortality is well documented, with several studies showing an increased risk of mortality that is reduced with time after diagnosis of coeliac disease. A population-based study in Sweden investigating cause-specific mortality found that patients with coeliac disease were at increased risk of death due to cardiovascular disease, pulmonary disease, and cancer. The mortality risk associated with undiagnosed coeliac disease remains uncertain. Although a study found a large increase in mortality among people with undiagnosed coeliac disease who gave serum to the Warren Air Force Base (Cheyenne, WY) in the USA, other analyses of stored serum found no increase in mortality. These contrasting findings could be due to differing definitions of coeliac disease or heterogeneous settings and time periods, in which the clinical threshold that would prompt a diagnosis could be varied. Although the data are weak, it is reasonable to conclude that coeliac disease, particularly symptomatic yet untreated coeliac disease, is associated with a modestly increased risk of mortality.

Conclusions
Despite the increase in the prevalence of coeliac disease and improved recognition and rates of diagnosis, numerous avenues of investigation are necessary to better understand the pathogenesis and improve the treatment of patients with this condition. Advances in the pathophysiology of coeliac disease could enable preventive strategies in individuals at high risk for disease development. The development of non-dietary
therapies might alleviate symptoms among patients with coeliac disease and inadvertent gluten exposure, and an effective replacement of the gluten-free diet could greatly enhance the quality of life of those many patients who find adhering to the diet challenging. Technologies for the detection of gluten in food and to monitor for recent gluten exposure (such as the detection of gluten peptides in stool or urine) could enhance the design of future clinical trials and might be of major value in patients’ daily activities.

Contributors
All authors contributed equally to the literature search and to writing the manuscript.

Declaration of interests
DSS receives an educational grant from Dr Schär, a gluten-free company, for an investigator-led study, but reports that this company has no control over outcomes. PIIHRG is on the scientific advisory board for ImmunoSanT, Celimmune, and ImmunogenX. BL declares no competing interests.

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