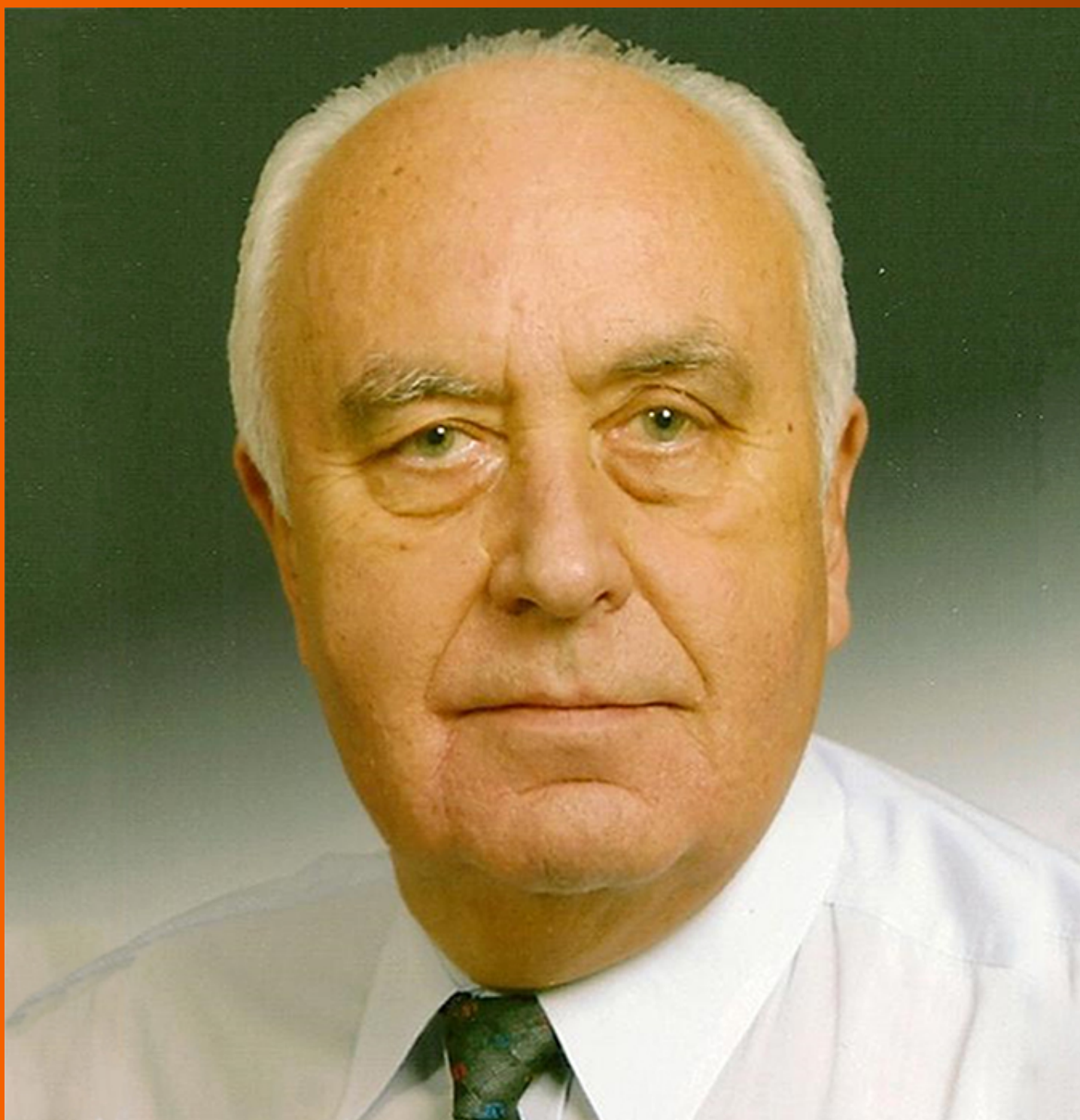


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Diagnosing coeliac disease: Out with the old and in with the new?

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Abstract

Coeliac disease (CD) is a complex condition resulting from an interplay between genetic and environmental factors. When diagnosing the condition, serological testing and genotyping are useful in excluding CD, although the gold standard of testing is currently histopathological examination of the small intestine. There are drawbacks associated with this form of testing however and because of this, novel forms of testing are currently under investigation. Before we develop completely novel tests though, it is important to ask whether or not we can simply use the data we gather from coeliac patients more effectively and build a more accurate snapshot of CD through statistical analysis of combined metrics. It is clear that not one single test can accurately diagnose CD and it is also clear that CD patients can no longer be defined by discrete classifications, the continuum of patient presentation needs to be recognised and correctly captured to improve diagnostic accuracy. This review will discuss the current diagnostics for CD and then outline novel diagnostics under investigation for the condition. Finally, improvements to current protocols will be discussed with the need for a holistic “snapshot” of CD using a number of metrics simultaneously.

Key words: Coeliac disease; Diagnostics; Histology; Serology; Microbiome; Metabolome

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Core tip: Due to the complexity of the condition, the diagnosis of coeliac disease can pose unique challenges. This review will discuss the current diagnostics for the condition and then outline novel diagnostics currently under investigation. Finally improvements to the current testing protocols will be discussed with the need for a holistic “snapshot” of the condition, using a number of metrics simultaneously.

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INTRODUCTION

Coeliac disease (CD) is a chronic autoimmune enteropathy which results from a complex interplay between genetic and environmental factors^[1,2]. Inheritance of altered forms of the human leukocyte antigen receptor (HLA-DQ2 or HLA-DQ8) in patients with CD bind epitopes of a dietary protein, gluten, with high affinity. Once cells within the small intestine are sensitised to these epitopes, a destructive autoimmune reaction is triggered which ultimately results in the destruction of the small intestinal wall^[3-5]. The prevalence of CD is increasing, with around 1% of the general population now affected by the condition and presentation of the disease in populations not classically affected^[1,6,7]. The symptoms of CD are varied; but can include diarrhoea, weight loss, abdominal pain and failure to thrive in children. If left untreated, CD can lead to complications associated with nutrient deficiency; such as anemia, alopecia, fertility issues or increased bone fracture risk^[2,8-11]. Long-term untreated CD has been associated with increased risk of enteropathy-associated T-cell lymphoma (EATL) and adenocarcinoma of the small intestine^[12,13]. The only current form of treatment is a strict, lifelong gluten-free diet^[2,14]. This review will focus on the diagnosis of CD, outlining the current diagnostic guidelines and highlighting the benefits and shortcomings associated with these. Novel diagnostics currently under investigation or improvements to the current diagnostics will then be discussed.

CURRENT DIAGNOSTICS - SEROLOGY

The frontline testing for the presence of CD is serological examination. Currently, serological testing for CD is recommended for patients presenting with chronic/intermittent diarrhoea, unexpected weight loss, recurrent abdominal pain or persistent gastrointestinal symptoms. Serological screening for CD is also offered to patients with associated conditions such as autoimmune thyroid disease, irritable bowel syndrome, or type 1 diabetes^[15]. Titres of three main types of antibody are assessed in CD screening; IgA-based antibodies against the enzyme tissue transglutaminase (tTG), IgA and IgG-based antibodies against deamidated gliadin peptides (DGP) and IgA-based antibodies against the endomysium (EMA). Of these tests, high titres of IgA-tTG and IgA-EMA accounts for nearly 95% reliability in serological screening^[10,15]. IgG/IgA-anti-deamidated gliadin peptide (IgG/IgA-DGP) is used as a companion test for improved accuracy by very specifically detecting antibodies directed against immunogenic peptides of gluten in patients with suspected CD^[10,16,17]. Serological testing can also be used as a less invasive method of monitoring treatment progression and adherence to a gluten-free diet after diagnosis^[18].

There are shortcomings associated with serological screening however. Firstly, the patient must be on a diet containing gluten for results to be meaningful^[10,19]. Secondly, many of the tests rely on IgA-based antibodies and IgA deficiency is far more common in CD patients than in the general population, with a prevalence rate of around 2%-3%^[10,19,20]. This can be overcome however by measuring total IgA at the start of testing to ensure sufficient levels and incorporating IgG-based tests into the panel^[19]. Furthermore, it has also been shown that the sensitivity of serological tests for CD is far lower than reported when patients with milder pathology are tested^[21]. Due to these limitations, patients with negative serology but who are still highly suspected of having CD are often referred for further testing, either by examining biopsy material or genotyping (Figure 1).

CURRENT DIAGNOSTICS - GENOTYPING

Currently, patients who have negative serology (but are suspected of having CD), patients with a family history of CD or patients who are following a gluten-free diet at the time of diagnosis (and unwilling to undergo a gluten challenge) are offered genetic testing for CD in the form of HLA genotyping (Figure 1)^[2,19]. Ninety-nine percent of patients with CD express either of the MHC Class II antigens HLA-DQ2 or HLA-DQ8, variants of the Human Leukocyte Antigen class II receptors^[3,5]. As MHC II molecules are heterodimers, on a genetic level these variants result from the inheritance of several key alleles. HLA-DQ2 results from the expression of two alleles, HLA-DQA1*0501 and HLA-DQB1*02 whose gene products combine to form the altered MHC II receptor. HLA-DQ8 results from the expression of the variant HLA-DQB1*0302 and HLA-DQB1*03 alleles^[22]. These variants are MHC II molecules that favour the binding of negatively charged residues in a 3-anchor point configuration,

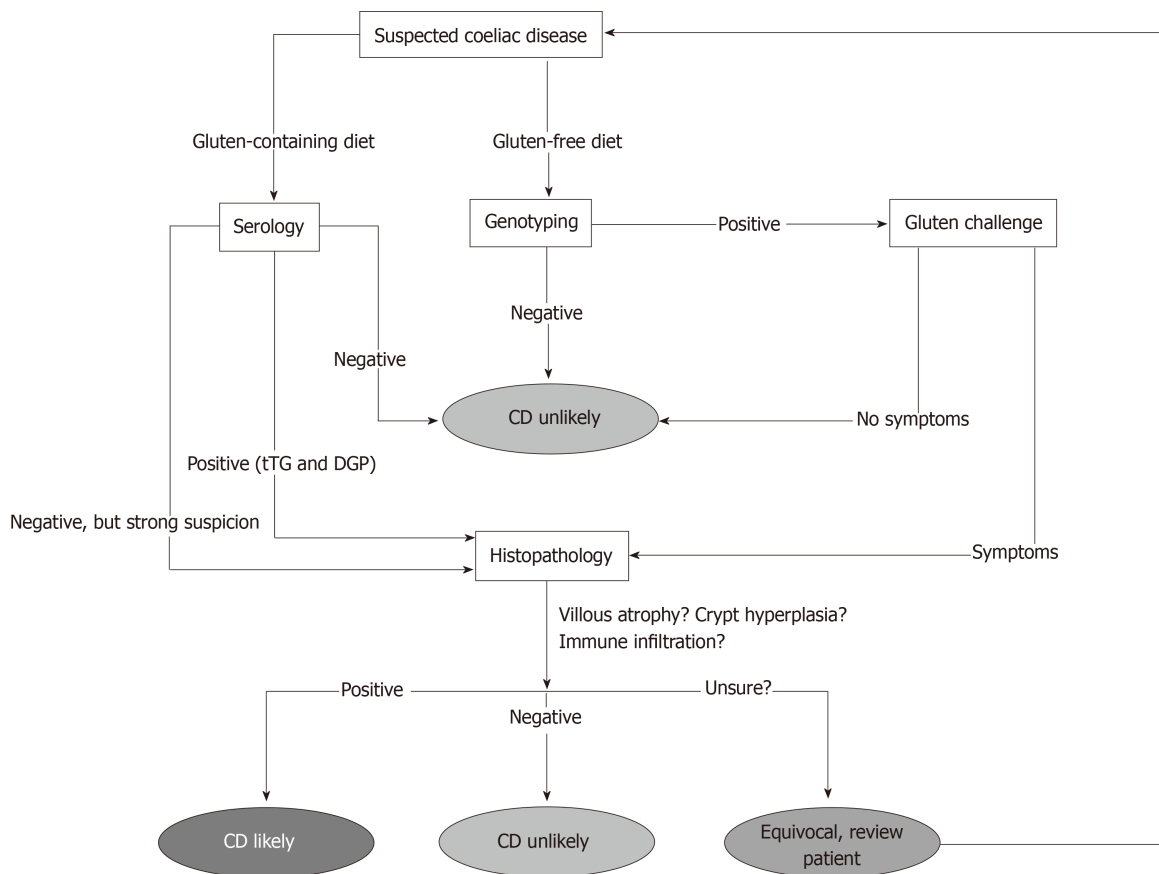


Figure 1 Current diagnostic pathway for suspected coeliac disease. Currently, serology forms the front line of testing for patients currently on a diet containing gluten whilst genotyping can be used for patients who aren't consuming gluten. Histopathology is currently the most conclusive test for the presence of the condition, even though diagnosis can be difficult for patients with mild or equivocal pathology. CD: Coeliac disease; tTG: Tissue transglutaminase; DGP: Deamidated gliadin peptides.

usually at positions 4, 6 and 7 on the gliadin epitope. HLA-DQ8 is a very similar molecule, although with anchor points usually at positions 1, 4 and 9 on the gliadin epitope^[23,24].

HLA-genotyping is therefore useful in excluding a diagnosis of CD in cases where serological or histological results are difficult to interpret or to determine the prevalence of CD amongst relatives^[22,25]. The test can be performed either with blood or buccal samples and a negative result effectively rules out the presence of CD entirely. It is also not dependent on gluten intake, so can be administered without the need for the patient to commence a gluten-containing diet^[15,19].

Unfortunately, the frequency of these genes has been reported to vary geographically, with the DQ2.5 allele being reported at higher frequency in north-western Europeans, such as those from Ireland^[26] and the DQ8 allele showing a higher frequency in Amerindian populations^[27], thus creating differences in expression independent of the presence of CD. In Australia specifically, approximately 20% of the population have been estimated to have the DQ2 allele, whilst less than 5% of the population have been estimated to have the DQ8 allele^[28-30]. At the same time, the cost of the test excludes its use as a front line diagnostic for CD and it also cannot diagnose CD effectively in its own right, as only around 1 in 30 people with the DQ2 or DQ8 variants will eventually develop the condition^[22]. Thus HLA-genotyping only provides a risk profile for developing CD. For this reason, even if the gene test returns a positive result, clinical guidelines state that patients still need to undergo small bowel biopsy to confirm the diagnosis^[2,15,19].

CURRENT DIAGNOSTICS - HISTOLOGY

Histopathological examination of duodenal biopsy material is currently the most conclusive test for the presence of CD. Using image enhancement on modern endoscopes, it is currently recommended that if villous atrophy is suspected during upper-gastrointestinal assessment that 2-3 biopsies are taken from the duodenal bulb

and 4-6 biopsies are taken from along the distal duodenum^[10,15,18,19,31]. Biopsies from these regions are used as they are the first point of contact with the digesta^[10]. The histopathological findings associated with active CD are well documented and include three main findings (Figure 1); blunted or atrophic villi (including complete destruction of the epithelial surface), crypt hyperplasia and mononuclear/lymphocytic infiltration into the lamina propria^[15,18,32].

Villous atrophy and crypt hyperplasia are usually assessed by calculating the crypt-villous ratio, a measure of the height of the villous when compared to the depth of the adjacent intestinal crypt. Using this method, a normal ratio of villous:crypt height in adults is around 3:1 to 5:1, whilst this figure in children is around 2:1. Values significantly less than these give an indication of the degree of villous atrophy present^[33,34]. Lymphocytic infiltration can be assessed by directly examining the numbers of lymphocytes present within the lamina propria in the late stages of the condition (usually T and B lymphocytes) and by assessing the numbers of intraepithelial lymphocytes (IEL)^[15,34]. The IELs are a specialised, critical part of the gut-associated lymphoid tissue and do not need priming by other immune cells to release cytokines^[34-36]. As the population of these cells is expanded in CD, the current diagnostic cut-off is 25 IELs per 100 enterocytes to demonstrate intraepithelial lymphocytosis in the condition^[19,34,37,38].

Morphological changes in CD mucosa can then be graded according to the Marsh Score^[39,40], with "0" indicating no detectable changes and "3a/3b/3c" indicating severely inflamed tissue affected by autoimmune destruction. It should be noted however that some pathologists will prefer to use descriptive terms instead of the Marsh score in routine assessment of CD rather than the Marsh score^[10]. There has been considerable debate as to the accuracy of the Marsh score system however, as it is based on subjective observations of intestinal histological sections which must be made by an experienced pathologist^[10,39,40,41]. It has been suggested that subjective interpretation of biopsy material may potentially lead to significant inter-observer disagreement and therefore negative or delayed patient outcomes^[41]. Further confounding the histological diagnosis of CD is the patchy presentation of the condition and the fact that the lesions that appear during active CD may not be entirely specific and can often be seen in other enteropathies such as giardiasis or gastroenteritis^[37,42-44]. However, at present the Marsh score system in conjunction with serology is currently the gold standard for the assessment of CD and a vast majority of pathologists are able to readily recognise active lesions (Marsh type 3). The difficulty arises when assessment of milder lesions is required. Thus, equivocal patients with subtle changes may be missed by the current histological criteria, leading to ambiguity in diagnosis.

DO WE NEED NOVEL DIAGNOSTICS, MORE DATA OR JUST IMPROVEMENTS TO THE CURRENT PROTOCOLS?

It is clear that the current testing regimen for CD is complicated, as shown in Figure 1, and it is also clear that each diagnostic has significant drawbacks associated with its use. Therefore, it is at this point that we need to ask a critical question. Do we need to develop completely novel tests for coeliac disease or can we use the data we currently generate from patients more effectively? A number of studies have investigated whether or not the application of statistical analysis to existing measurements can increase the diagnostic sensitivity of CD screening. One such technique is linear discriminant analysis (LDA). This technique, when applied to biological data, aims to assign patients to one or more groups on the basis of a series of measurements from which a linear function has been defined^[45,46]. Discriminant analysis has been shown to be able to predict patient groupings in conditions such as rheumatoid arthritis^[47], Parkinson's disease^[48], diabetes^[49], Alzheimer's disease^[50] and coronary disease^[51]. In CD, improving diagnosis with discriminant function analysis has been previously investigated with IgA/IgG and absorptive serology^[52,53], IEL counts with crypt/villous ratios^[54] and immunohistochemistry data^[55]. More recently, studies in CD have used this technique with capsule endoscopy images^[56], histology data^[57] and gene expression data^[58]. The use of this technique has further highlighted the inherent difficulties in classifying CD patients using the discrete divisions of the Marsh subclassifications^[59]. Clearly, the full spectrum of CD presentation needs to be captured with continuous categories along a scale to be able to accurately diagnose all who present with CD-like symptomatology. Improved and more accurate diagnostics could then also be used to separate other inflammatory conditions, such as Crohn's disease.

As the current technique of sampling from the small intestinal mucosa relies on the

patient being on a gluten-containing diet and actively having CD damage to evaluate, previous research has also focused on determining other biopsy-based tests which could be implemented after a patient has commenced treatment. It has been shown that a rectal challenge with gluten can induce CD-like pathology in the rectal mucosa that is specific enough to attain a diagnosis of CD as both a screening and confirmatory test, with reported sensitivities of 90%-100% and specificities of 91%-100% [60,61]. As sensitised gluten-specific T lymphocytes circulate within the gastrointestinal mucosa, they can be rapidly deployed to sites of localised antigen presentation to initiate a localised inflammatory reaction [60,62]. Although experimental, this test involves the introduction of a slurry of gluten to the rectum that the patient is instructed to retain for as long as possible, preferably for at least 2-4 hours. Biopsies are then taken from the rectal mucosa and the intraepithelial lymphocyte numbers are assessed within the tissue [60-63].

More recently, a novel serological test for CD [64] has also been demonstrated to show high sensitivity and specificity for CD patients who possess the DQ2.5 allele and does not require the patient to be on a gluten-containing diet. Using a whole blood cytokine release assay (primarily used for infectious diseases) focused on IFN- γ , these authors took whole blood from treated CD patients after an oral challenge of gluten and cultured it in the presence of gliadin epitopes. They found that there was no test which could detect changes between the treated CD patients and controls before the gluten challenge; but after gluten was consumed by the treated CD patients, significant elevations in IFN- γ and IFN- γ inducible protein 10 (IP-10; CXCL10) resulted in 85% IFN- γ and 94% IP-10 sensitivity and 100% specificity for DQ2.5+ CD patients. These authors concluded that further clinical studies investigating the utility of these tests were required [64]. Similar testing using tetramers of gluten and HLA has recently been shown to be able to specifically detect gluten-reactive T cells in coeliac patients with a high degree of accuracy and regardless of current gluten intake [65].

Due to the complexity of the coeliac reaction, it is clear that not one single test can fully capture the coeliac continuum, data from many different parameters would need to be combined for the most accuracy. So where should this data come from and how could it be used as a single diagnostic? Histology of the duodenal mucosa should always play a part in CD diagnosis, however we must first define what a normal duodenal mucosa is before we can begin to compare pathological specimens. The upper and lower borders of the mucosal surface need to be defined, in particular where the exact border of the crypt and the villus meet, perhaps through the use of mRNA expression [59]. At the same time, the surface of the duodenum is a complex and 3-dimensional environment which is poorly represented on a 2-dimensional microscope slide. Computerised analysis is needed to fully understand the 3-dimensional structure of the duodenal mucosa and how this relates to our 2-dimensional representations [59,66]. Once we can overcome these shortfalls, we need to take numerical values of histological parameters from slides instead of making subjective assessments or attempting to put patients into discrete categories. These numbers can then be used to improve diagnostics as previously shown [57].

There is a wealth of data which could potentially be collected from CD patients, with the most recent being insights into the microbiome of these patients. In the mouth of CD patients, it has been shown that differences occur in the microbial population and that these organisms display proteolytic activity against gliadin, possibly generating immunogenic peptides in the process [67]. In the small intestine, although it was demonstrated that the microbiome did not differ in children with CD when compared to healthy controls, this same effect has not been well investigated in adults to date [68]. It is hypothesised however that changes in the small intestinal microbiome may be involved in the pathogenesis of CD through immune reactions generated against translocated bacterial proteins, resulting from decreased intestinal barrier integrity [69-71]. Within the large intestine, shifts in microbial populations have been shown in CD with a number of genera, including *Lactobacillus*, *Streptococcus* and *Clostridium* demonstrating proteolytic activity against gluten proteins. Members of these strains may possibly be used in the treatment of the condition by digesting immunogenic fragments of gliadin [72]. Significant changes in the colonic microbiome, including increases in the *Veillonellaceae* family and other taxa involved in starch metabolism, have also been observed in patients who have started treatment with a gluten-free diet in CD [73]. If it is possible to numerically categorise these changes in CD patients when compared to non-CD patients, this data could then be used in a diagnostic sense. At the same time, the collection of faeces and saliva is more efficient and less invasive than intestinal tissue sampling.

Along a similar vein is the categorisation of the CD metabolome; that is, the complete set of metabolites present in a patient sample at a given time point [74,75]. This holistic assessment of end-products can therefore indirectly take into account a variety of changes which may occur from genotype to phenotype [74]. In CD, the

metabolites studied are most commonly from pathways associated with malabsorption, energy metabolism and alterations in intestinal permeability and these can be assessed in a diverse range of fluids, including saliva, CSF, amniotic fluid, breath condensate and faecal extract^[74,75]. As there is currently no one particular metabolite which has been shown to have a high predictive value for CD, assessing panels of these potential biomarkers currently holds the most promise for novel diagnostic tests^[74-77]. Most recently, this approach has identified a phospholipid signature in HLA at-risk infants which has diagnostic capacity for CD well before antibodies or clinical symptoms appear^[78].

“Fingerprinting” of microbial and metabolomic signatures in CD therefore has potential to generate a large amount of data from individuals from a relatively non-invasive test. With the use of LDA, the more variables which can be added to build diagnostic equations, the more accurate the outcome^[45]. Combining these new definitions of CD with current diagnostics would allow for a snapshot of CD presentation from all angles. Measuring these parameters (histology, mRNA expression, microbiome change, metabolome change) simultaneously would allow for the most accurate diagnosis and secure the best outcome for patients, as shown in Figure 2.

CONCLUSION

Having accurate diagnostics for CD is critical moving forward, with increasing prevalence of the condition and the risk of serious effects if treatment is not commenced early enough. Current diagnostics have significant drawbacks however and the accuracy of these tests needs to be improved to successfully detect CD in all patients who present with the condition. This is particularly true for those who lack classical symptomology or those who have very mild histopathology. This is also true for tracking treatment progression and healing in patients once a gluten-free diet has been commenced. We need to move away from the discrete definition of CD and towards a continuous scale to fully capture the complete spectrum of patient presentation. To do this, we need diagnostic tests which are holistic; that is, they can take a range of measures from a patient at once and can then be combined to improve diagnostic accuracy. This is where new diagnostic tests need to be defined which can assess CD less invasively. Of most interest is the changes which appear in the microbiome of CD patients and if these changes can be numerically defined, this could lead to a range of novel tests for the condition, either alone or in combination with the traditional CD diagnostics.

With our original question in mind then, novel diagnostic advances in CD are welcomed, particularly if they can assess the condition less invasively and increase the accuracy and speed of screening. The current diagnostics for the condition need to be revisited for the next generation of CD patients and their accuracy needs to be improved, particularly for equivocal presentation. It is hoped then that a balance can be found between novel tests and traditional methods to provide an accurate snapshot of the condition and improve the outcomes of CD patients.

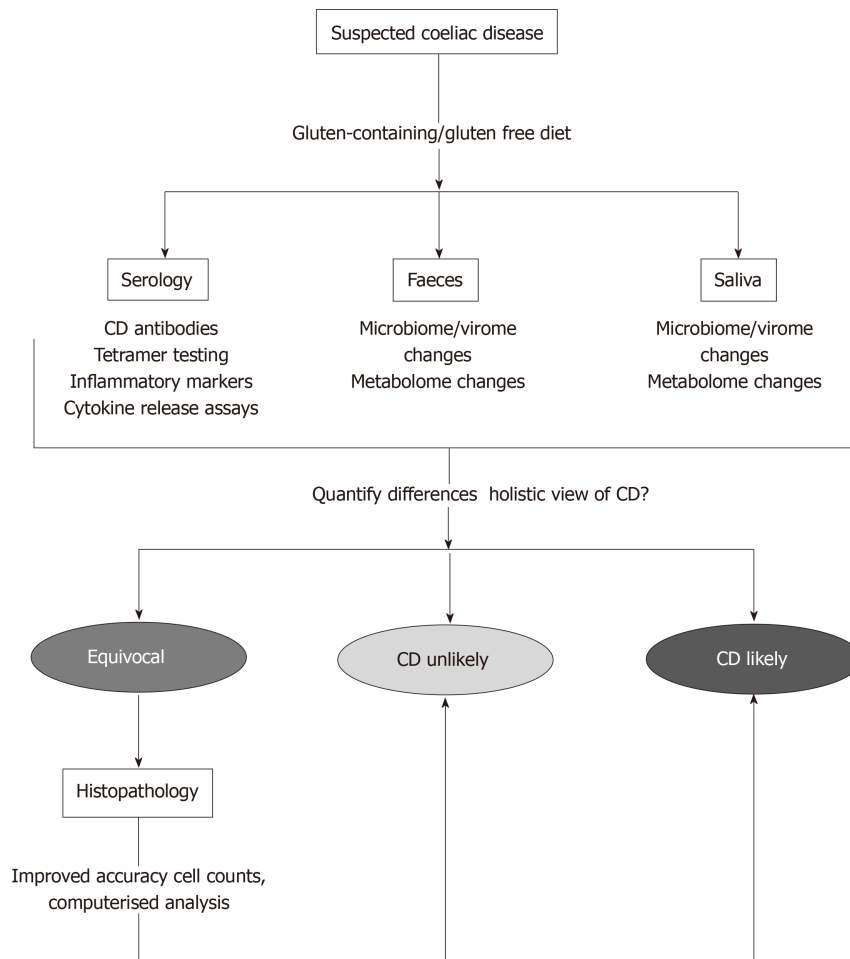


Figure 2 Proposed diagnostic pathway for suspected coeliac disease. Several less invasive measures could be investigated at once using markers in serum, faeces and saliva. If reliable differences could be quantified in coeliac disease, then patients could be diagnosed rapidly and with increased accuracy. For equivocal patients, histopathology of the small intestine would still be used, although increasing the accuracy of these measures through cell counts and computerised analysis would need to be considered. CD: Coeliac disease.

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