

Appendix A: Summary of evidence from surveillance

2019 surveillance of coeliac disease (2015) NICE guideline NG20

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

See the evidence tables for all studies considered in surveillance.

Recognition of coeliac disease

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

We found a total of 17 studies on recognition of coeliac disease (CD) (see summary of results in the tables section: [Table 1](#)).

Signs and symptoms

A total of 12 studies were identified covering signs and symptoms which raise suspicion of CD.

Infertility

A meta-analysis(1) (5 studies, n not reported) of the association between CD and infertility. Data were extracted about CD patients in 3 groups; women with infertility (including unexplained infertility), unexplained infertility, and controls. The findings indicated that CD is more prevalent in women with "all-cause" infertility and "unexplained" infertility than in controls.

Enamel defects

A meta-analysis(2) (30 studies, n=unreported) aimed to compare the presence of enamel defects and aphthous stomatitis between coeliac patients and healthy controls. In children (24 studies), CD was associated with both enamel defects and aphthous stomatitis. In adults (3 studies), the association between CD and enamel defects or aphthous stomatitis was non-significant but inconclusive because of the limited evidence on this population. The results should be interpreted with caution due to the high risk of bias identified in all the studies. A further meta-analysis(3) (45 studies, n=2840) found that the prevalence of developmental defects of enamel in people with CD was 50%. In a general analysis, it was observed that patients with CD had a significantly higher prevalence of enamel defects compared to healthy people.

Perinatal risk factors

A secondary study(4) of the Norwegian Mother and Child Cohort Study (650 children with celiac disease and 107,828 controls) assessed the association of foetal growth, birth weight, and mode of delivery with development of CD. Development of CD in children was significantly associated with sex of the child, maternal CD, and type 1 diabetes but not with intrauterine growth.

Genetic biomarkers

A total of 8 studies covered genetic biomarkers and their association with CD risk. The findings of the studies, which included 7 meta-analyses(5–11) and 1 case-control study(12), indicated that the following polymorphisms were associated with increased risk of CD:

- TNF-alpha -308G>A(5) (11 studies, n=2921)
- TNFA promoter haplotypes (-1031T>C,-857C>T,-376G>A,-308G>A,-238G>A) associated with CD independently from human leukocyte antigen(6) (n=511)
- Regulator of G-protein signaling 1 (RGS1) and interleukin-12 A (IL12A) genes(7) 2016 (7 studies)
- TNF-alpha -308 G > A (rs1800629) polymorphism(8) (11 studies, n=1774 controls and n=1147 CD cases)
- Lipoma preferred partner and T-cell activation Rho GTPase activating protein polymorphism(9) (7 studies)
- A double dose of the HLA-DQB1*02 gene(10) (24 studies)
- Myosin IXB (MYO9B) gene polymorphisms (rs1545620, rs1457092, rs2305767 and rs2305764)(11) (7 studies, n=1965 CD patients and n=4894 controls).
- Single nucleotide polymorphisms rs6822844, rs6840978, and rs3184504(12) 2015 (12,986 CD cases and 28,733 controls from 16 independent samples)

Coexisting conditions

A total of 4 meta-analyses and 1 cohort study were identified covering coexisting conditions and CD (Table 1).

One meta-analysis(13) (36 studies, n=9,275) found that the prevalence of positive celiac serology and biopsy-proven CD was significantly higher in subjects with symptoms suggestive of irritable bowel syndrome (IBS) compared to healthy controls. Another meta-analysis(14) (31 studies, n=4383) found a 5.8% prevalence of biopsy-confirmed CD in people with Down's syndrome, with the risk slightly higher in children than in age mixed samples with both children and adults. The third meta-analysis(15) (n=6,024) found that among patients with autoimmune thyroid disease, there was a prevalence of biopsy-confirmed CD of 1.6%.

A systematic review and meta-analysis(16) (9 studies, n=587 cases of biopsy-proven CD) examined prevalence rates of type 1 diabetes (T1D) and CD. Longitudinal cohort studies covering screening for CD in T1D with at least 5 years of follow-up were included. Screening rates, characteristics, and prevalence of biopsy-proven CD in people with T1D were extracted. CD was diagnosed in 40% subjects within 1 year, in 55% within 2 years, and in 79% within 5 years of diabetes duration. Two studies (478 cases) reported higher rates of CD in children aged under 5 years at T1D diagnosis. The duration of follow-up varied across the included studies. CD screening frequency progressively decreased with increased T1D duration. A further cohort study(17) (n=9,180) using The Health Improvement Network found that incidence of CD was higher in individuals with childhood-onset type 1 diabetes compared to those with adult-onset diabetes. Results also indicated that people with type 1 diabetes are at risk of developing CD throughout childhood and adulthood.

Intelligence gathering

A topic expert suggested that Down's syndrome and Turner's syndrome, which are currently included in the list for considering serological testing, should be moved to the list for offering serological testing. No evidence was cited to support this proposal, although new evidence was identified within the current review.

Impact statement

NICE guideline NG20 recommends offering serological testing for CD for a range of signs, symptoms and coexisting conditions. These include type 1 diabetes and autoimmune thyroid disease at diagnosis, as well as IBS. The new evidence supporting testing for CD in people with these coexisting conditions is consistent with the guidance and no impact is anticipated.

The guideline advises considering serological testing for CD for people with unexplained subfertility or recurrent miscarriage, dental enamel defects, and Down's syndrome. The new evidence supporting testing for CD in people with these conditions is consistent with this advice. The evidence showing a higher prevalence of CD in people with Down's syndrome (5.8%) than was found in the guideline evidence review (3.2% versus background population prevalence of 1%), and based on a larger pooled sample size, supports additional topic expert

advice to offer testing for CD to this group. However, the new evidence did not report the relative risk of CD for people with Down's syndrome compared to matched controls without Down's syndrome. In the absence of this and evidence on the cost effectiveness of offering testing for CD to all people with Down's syndrome, there is unlikely to be any impact on recommendation 1.1.2 to strengthen the recommendation for testing for CD in people with this coexisting condition. Further evidence will be reviewed in this area at the next surveillance review.

The evidence indicating maternal CD as a risk factor for childhood CD is consistent with the guideline advice to offer serological testing to first degree relatives of people with CD.

The evidence indicating an association between various genetic biomarkers and CD is likely to need further confirmatory studies in different ethnicities and larger sample sizes in order to trigger an impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Serological testing for coeliac disease

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

A total of 21 studies were identified on serological testing for CD ([Table 2](#)).

Point of care testing

We found 7 studies covering point of care tests (POCT) for CD, with duodenal biopsy used as the reference standard, summarised as follows:

A systematic review and meta-analysis(18) estimated the overall diagnostic accuracy of POCTs for diagnosing CD. The pooled sensitivity and specificity of all POCTs (based on tTG or Deamidated gliadin peptide (DGP) or tTG+Anti-gliadin antibodies) for diagnosing CD were 94.0% and 94.4%, respectively. The pooled positive and negative likelihood ratios for POCTs were 16.7 and 0.06, respectively. The pooled sensitivity and specificity for IgA tTG-based POCTs were 90.5% and 94.8%, respectively.

A diagnostic accuracy study(19) (n=100) of a POCT based on DGPs was concordant with the CD diagnosis made according to European Pediatric Gastroenterology Hepatology and Nutrition Society (ESPGHAN) criteria, and showed 95.8% sensitivity, 98.1% specificity, 97.9% positive predictive value and 96.2% negative predictive value.

A case-finding study(20) (n=350) of an on-site, rapid, whole-blood POCT for active case-finding of CD using IgA/IgG DGP-based fingertip testing was found to be cost effective in primary care when followed by duodenal biopsy.

A multicentre study(21) (n=1055) tested for CD in adults and children using a POCT, Simtomax, which detects IgA and IgG antibodies against DGP. Results were compared with findings from histologic analyses of duodenal biopsies (reference standard). The POCT identified individuals with CD with 79% sensitivity and 94% specificity. The test was more accurate in adults than in children, but the prevalence of CD was far lower (1.2%) in the adult subgroup than in the child group (19.6%).

A prospective diagnostic test accuracy study(22) found that Simtomax identified patients (n=55 people at high risk of CD and n=508 patients who underwent an endoscopy examination for any indication) with CD with similar levels of sensitivity and specificity as standard serologic analysis of anti-tTG. Simtomax also had higher sensitivity than anti-tTG POCTs (Celiac Quick Test and Biocard test).

A further diagnostic accuracy study(23) (n=622) of Simtomax in infertile patients referred for fertility treatment found that the POCT had a sensitivity of 42.9% and a specificity of 86.8%.

Another prospective study(24) (n=1000) assessed the diagnostic performance of an IgA/IgG DGP-based POCT for CD detection. The POCT had comparable sensitivities to serology [IgA tTG and IgA-endomysial antibodies (IgA-EMA)], and correctly identified all CD cases in a gluten sensitive cohort. However, it had a lower specificity than IgA tTG, and IgA-EMA tests.

Anti-Tissue Transglutaminase IgA Antibody (IgA tTG) and HLA-DQ2/8 testing

We found 4 studies covering IgA tTG and HLA-DQ2/8 testing.

A systematic review and meta-analysis(25) (60 studies, 13 systematic reviews) reported the evidence on comparative accuracy and safety of methods used in current clinical practice to diagnose celiac disease, including serological tests and human leukocyte antigen (HLA) typing. The review found high-strength evidence to support high accuracy of IgA (TTG) tests and high specificity of endomysial antibodies (EMA) IgA tests. Lower accuracy was reported for DGP-IgA tests. Evidence for algorithms using multiple tests was insufficient because of diverse results, low number of studies, and heterogeneity of populations. Evidence was also insufficient for accuracy in asymptomatic general population screening and special populations such as children and patients with type 1 diabetes, anaemia, and IgA deficiency.

Two small cross sectional studies(26,27) (n=60 and n=121) found contrasting levels of accuracy of IgA (TTG) testing for children and adults. Among children, IgA (TTG) was found to have high accuracy in diagnosing CD, whereas in adults IgA (TTG) was not sensitive (sensitivity 78.6%) to be a reliable diagnostic test in isolation. Both studies used small intestine biopsy as the reference standard.

A cross sectional case-control study(28) (n=143;) investigated whether an HLA-DQ-gluten tetramer-based assay accurately identifies adults with CD compared with adults without CD. The reference standard was duodenal biopsy with flow-cytometry. The results showed that

the test identified patients with and without CD with a high level of accuracy, regardless of whether the individuals were on a gluten free diet (GFD). The authors acknowledged that further validation is needed.

Combined tests

A total of 4 studies examined combined testing for CD.

A cross sectional study(29) (n=242) examined the utility of IgA/IgG anti-TG2, IgA/IgG anti-DGP and IgA/IgG against a mix of TG2 and DGP (anti-TG2/DGP) in finding CD among children. The reference standard was intestinal biopsy. The combined IgA/IgG anti-TG2 against DGP assay had the best performance with a sensitivity of 96%, a specificity of 99.5% and the area under the ROC curve was 0.996.

A further case-control study(30) (n=156; 13 children <2 years, 45 children between 2 and 16 years, and 98 adults over 16 years) found that combining IgG anti-DGP with IgA anti-tTG and defining thresholds for antibody levels improved the serologic diagnosis of CD. Patients with double positivity and high antibody levels had a high probability for having CD. The fraction of CD patients with double positivity and high antibody levels was 59%-67% (depending on the assay) for >3 upper limit of normal (ULN) and 33%-36% (depending on the assay) for >10 ULN, respectively. This fraction was significantly higher in children with CD than in adults.

A case-control study(31) (n=100) assessed the diagnostic accuracy of Polycheck Celiac Panels (PCPs) for diagnosing CD in children. PCPs are immunoenzyme screening assays for the quantitative measurement of coeliac-specific immunoglobulin class G (IgG) or class A (IgA) in serum. The highest specificity and positive predictive value (both 100%) were observed for the detection of Polycheck anti-tTG-IgA antibodies. The highest sensitivity and negative predictive value (both 100%) were achieved by Polycheck anti-DGP-IgG antibody detection. The best performance (98% sensitivity and negative predictive value, 100% specificity and positive predictive value, diagnostic accuracy - AU ROC 99%) was observed for the strategy of using both PCP IgA and IgG and determining positive outcomes of the test with two or more coeliac-specific antibodies detected.

A case-control study(32) (n=199) compared the performance of combined DGP-IgG and DGP IgA with TG2-IgA alone, using four manufacturers' tests, in paediatric coeliac patients at diagnosis and during follow-up under a GFD. The reference standard was biopsy-proven CD. The results indicated that combined testing for TG2-IgA and DGP-IgG did not increase the detection rate of CD in IgA competent children compared to TG2-IgA only. There were significant differences with respect to proportions of children with CD with titres > 10 times the ULN between the manufacturers.

Immunochromatography

A case-control study(33) (n=144) evaluated the anti-tTG occurrence by using the visual immunochromatographic assay (ICA). Using ICA, anti-tTG were detectable in duodenal culture media of most CD patients but sensitivity and diagnostic accuracy achieved with ICA were lower than those obtained with the more established enzyme-linked immunosorbent assays (ELISA), despite being a quicker and more convenient method.

Intelligence gathering

DGP testing

Topic expert feedback indicated the limited value of using DGP in screening for CD. It is considered to be expensive and not easily available in all laboratories.

Genetic testing

Topic experts noted that improved understanding of the genetics of CD can aid the assessment of susceptibility rather than diagnosing CD. Even in non-biopsy cases this has select use and the test can be misused and misinterpreted. It was therefore suggested that genetic interpretation should be part of the NICE guidance. However, no eligible evidence was cited on this topic.

IgA deficient patients

An expert highlighted the need for reliable diagnostic modalities for IgA deficient patients, and that microRNAs are a novel possibility but did not cite any evidence.

Impact statement

Point of care testing

NICE guideline NG20 does not make recommendations on POCTs. In developing the guideline, the committee acknowledged that there is emerging evidence on the clinical utility of other tests and diagnostic strategies, such as DGP, POCTs and the use of combined serological tests to definitively diagnose CD without carrying out endoscopic intestinal biopsy.

The collective new evidence on POCTs is not conclusively in favour of any single POCT over standard serological testing. There is some evidence supporting the use of POCTs in diagnosing CD in primary care but further confirmatory research from larger studies is likely to be needed to signal an impact on the guideline recommendations. However, it should be noted that the Simtomax test is no longer being manufactured.

DGP testing

Intelligence indicates the limited accessibility and high cost of using DGP in testing for CD. In NICE guideline NG20 IgG DGP is not the recommended first choice test in (recommendations 1.2.2 and 1.2.3) and is only advised as a 'consider' recommendation. The new intelligence and lack of conclusive evidence for it is consistent with this advice.

Anti-Tissue Transglutaminase IgA Antibody (IgA tTG)

The guideline recommends (1.2.2 and 1.2.3) testing for total immunoglobulin A (IgA) and IgA tissue transglutaminase (tTG) as the first choice test for both adults and children. It further advises using IgA endomysial antibodies (EMA) if IgA tTG is weakly positive. The new evidence indicating high accuracy of IgA tTG but also the need for it to be complemented by additional tests, including total IgA and IgA EMA, is consistent with this advice.

A systematic review found insufficient evidence to support any single tests in cases of IgA deficiency, which is consistent with the guideline's lower strength of recommendation to consider using IgG EMA, IgG DGP or IgG tTG in these cases, and the related research recommendation in this area remains ongoing.

HLA-DQ2/8 testing

The guideline advises against using HLA=DQ2/8 testing in initial diagnosis in non-specialist settings. The guideline committee found that HLA DQ2/DQ8 genotyping is a relatively expensive test, and that its routine use is associated with significant costs. The committee advised that, in addition to its relative expense, HLA DQ2/DQ8 genotyping is subject to practical difficulties in non-specialist settings, both in gaining access to the test and in interpreting its results. The new evidence from a single cross sectional study, in which the authors acknowledged the need for further validation, is unlikely to impact on this advice.

Combined testing

The new evidence indicating the value of combined testing was derived from retrospective case-control studies and was inconclusive for specific combinations. A large systematic review did not find sufficient evidence for combined tests, including algorithms of multiple tests, due to diverse results, a low number of studies, and heterogeneity of populations. Therefore, no impact on the guideline is anticipated.

Immunochromatography

The guideline does not make specific recommendations for methods of testing. In the development of NICE guideline NG20, the guideline committee further discussed the continual improvement in these ELISA testing kits for the detection of tTG, and expressed that the emergence of new immunofluorescence techniques for the detection of tTG look particularly promising. The new evidence on immunochromatography indicates lower diagnostic accuracy than ELISA in spite of greater convenience, and is unlikely to impact the guideline. Further evidence in this area will be considered at the next surveillance review.

New evidence is unlikely to change guideline recommendations.

Referral of people with suspected coeliac disease

Surveillance proposal

This section of the guideline should not be updated.

Non-biopsy diagnosis

A total of 6 studies examined CD diagnosis without biopsy ([Table 3](#)).

A multicentre international prospective validation study(34) (n=707) aimed to validate the approach of diagnosing CD without biopsies in children with symptoms and levels of TGA-IgA 10-fold or more the ULN, confirmed by detection of endomysium antibodies (EMA) and positivity for HLA-DQ2/DQ8. Consecutive paediatric patients (18 years or younger) on a gluten-containing diet who tested positive for TGA-IgA were included. The reference standard included combined duodenal biopsy and serological tests. Findings of TGA-IgA 10-fold or more the ULN (TGA \geq 10xULN), a positive result from the test for EMA, and any symptom identified children with CD (n = 399) with a positive predictive value of 99.75, but with sensitivity of 61.71; the positive predictive value (PPV) was 100.00 when only malabsorption symptoms were used instead of any symptom (n = 278) but with a lower sensitivity of 43.1. Analyses of HLA antibodies did not increase accuracy. Sensitivity for local TGA \geq 10xULN was 71.01 and for local TGA \geq 10xULN + EMA (+/- HLA) it was 69.30. Specificity for local TGA \geq 10xULN was 93.548 and for local TGA \geq 10xULN + EMA (+/- HLA) it was 96.774.

A multicentre prospective validation study(35) (n=898) aimed to validate total IgA and IgA-TTG (TTG-IgA) and IgG-DGL with IgA-TTG (TTG-DGL) in the non-biopsy diagnosis of CD in children who were about to undergo duodenal biopsy analysis to confirm or rule out celiac disease. The reference standard was duodenal biopsy, and 66% of the children were confirmed as having celiac disease. Patients were assigned to categories of no CD if all assays found antibody concentrations <1-fold the ULN, or CD if at least 1 assay measured antibody concentrations >10-fold the ULN. The TTG-IgA procedure identified patients with CD with a PPV of 0.988 and an NPV of 0.934; the TTG-DGL procedure identified patients with PPV of 0.988 and an NPV of 0.958. An extrapolation model was used to indicate that PPV and NPV would remain over 0.95 even at a disease prevalence of 4%. Limitations were that the sensitivity and specificity for the tests being validated were not clearly reported, the NPV of the TTG-IgA procedure did not meet the prespecified reliability criteria of over 95%, and extrapolation to a lower prevalence population, more comparable to the population that NG20 recommends for referral to a paediatrician for further investigation for CD, was model-based.

A diagnostic test accuracy study(36) (n=240) investigated whether different tissue transglutaminase titres in symptomatic children could predict CD without the confirmation of intestinal biopsy. The reference standard was intestinal biopsy. The PPV of tissue transglutaminase titres at \geq 10 times ULN was 87.7 and similar results were found for other tissue transglutaminase titres (\geq 3x upper limit of normal, >100 U/ml, or >100 U/ml). However, the sensitivity, specificity and negative predictive value were not reported in the abstract.

A diagnostic test accuracy study(37) (n=234) assessed the applicability of the paediatric ESPGHAN criteria for diagnosing CD to adults, and the accuracy of serology in predicting CD. The results indicated that in adult symptomatic patients showing EMA-positivity and genetic susceptibility, anti-tTG titres correlated with histology. Among the prevalent assays used, PPV peaked differently both after normalisation and standardisation, indicating intrinsic

differences in performance, thus preventing uniform prediction of disease. However, a calculated 16 x ULN cutoff showed an improved PPV.

A small diagnostic test accuracy study(38) (n=39) found that in adults, when serological tests, HLA typing, and clinical symptoms indicated CD, in accordance with ESPGHAN criteria, sensitivity of these criteria was 71.4%. Biopsy samples were evaluated according to Marsh scoring.

A further diagnostic test accuracy study(39) (n=731) evaluated whether patients with high probability of CD and high titre of tTGA, had a high probability of intestinal damage that may have negated the need for biopsy for final diagnosis. Using a tTGA cutoff value of 70 IU/ml, the results showed a sensitivity of 83.9% while specificity was 56.1% with an overall accuracy of 77.7%.

Intelligence gathering

Experts highlighted that non-biopsy methods to diagnose CD in children are being used increasingly in the NHS. This less invasive approach avoids the need for endoscopy and general anaesthesia, and is considered to be cost-saving. It was suggested that this may merit a separate paediatric section in NICE guideline NG20.

Impact statement

Non-Biopsy diagnosis

NICE guideline NG20 recommends referral of children with positive serological test results to a paediatric gastroenterologist or paediatrician with a specialist interest in gastroenterology for further investigation for CD. This allows for alternative confirmatory diagnosis to biopsy in certain circumstances. These alternatives could include a non-biopsy approach by using an IgA EMA test to confirm serological positivity or using genetic testing. The guideline committee recognised that an endoscopic intestinal biopsy is not always available as an option in paediatric populations as it can be highly distressing for both the children and their parents and also requires additional care and costs due to the need for general anaesthetic.

Topic experts and stakeholders highlighted that a non-biopsy approach, including serological and genetic testing, to diagnose CD in children is being used increasingly in the NHS. Non-biopsy testing is a less invasive approach, which avoids the need for endoscopy and general anaesthesia, and is considered by some topic experts to be cost saving. The [European Society of Pediatric Gastroenterology, Hepatology, and Nutrition \(ESPGHAN\) Guidelines for Diagnosing Coeliac Disease 2020](#) state that if TGA-IgA is 10 or more times the upper limit of normal then non-biopsy diagnosis may be applied, provided endomysial antibodies (EMA) IgA will test positive in a second blood sample (this approach would be subject to carer/parent approval). The ESPGHAN guideline also states that human leukocyte antigen (HLA) DQ2-/DQ8 determination and symptoms are not obligatory additional criteria for the non-biopsy approach. New evidence indicates that a non-biopsy approach in children has high diagnostic accuracy under the ESPGHAN criteria. This approach could avoid risks and costs of endoscopy for a significant proportion of children with suspected CD, and therefore we will

revisit this section of the guideline when the British Society of Gastroenterology publishes its forthcoming guidance in this area.

For adults NICE guideline NG20 advises referral of young people and adults with positive serological test results to a gastrointestinal specialist for endoscopic intestinal biopsy to confirm or rule-out CD. Despite stakeholder feedback indicating the value of non-biopsy diagnosis in adults, the collective new evidence does not indicate sufficient diagnostic accuracy of this approach in adults to justify a change to the recommendations. Although no ongoing trials were identified in the surveillance review, we recognise that this is a rapidly evolving area of research and further evidence will be considered when available. We will revisit this section of the guideline when the British Society of Gastroenterology publishes its in-progress guidance in this area.

New evidence is unlikely to change guideline recommendations.

Monitoring in people with coeliac disease

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

A total of 6 studies were identified on aspects of monitoring CD ([Table 3](#))

Cardiovascular risk

A systematic review(40) (27 studies) assessed the effect of the GFD on several modifiable cardiovascular risk factors in patients with CD. Lack of control groups in all but one study prevented meta-analysis of results and a narrative summary was presented. Overall study quality was low. Consistent findings across studies included an increase in total cholesterol, high density lipoprotein, fasting glycaemia, and body mass index while remaining within the healthy weight range). Significant changes in low density lipoprotein, triglycerides, and blood pressure were not consistently reported.

Pneumococcal infection

We identified 4 studies examining pneumococcal infection risk in people with CD. A systematic review and meta-analysis(41) (3 studies, representing 3 large databases including the English Hospital Episode statistics) found that compared to inpatients or the general population, hospitalised people with CD had a significantly higher risk of pneumococcal infection.

A population-based cohort study(42) assessed the risk of invasive pneumococcal disease among people with biopsy-proven CD (n=29,012) who were matched with up to 5 controls

(n=144,257). After adjustment for socioeconomic status, educational level and comorbidities the results for people with CD showed a trend towards an increased risk but was non-significant.

A cohort study(43) of young individuals (born between 1989 and 2012) with CD (n=1,294) compared to matched references (n=6,470) assessed the risk of hospitalisations for bacterial pneumonia or pneumococcal infections. Risks of bacterial pneumonia were significantly increased before CD diagnosis and especially the year before CD diagnosis. Risks of pneumococcal infections showed a non-significant increase in CD patients.

A UK based cohort study(44) of patients with CD (n=9,803) compared to matched controls (n=101,755) assessed the risk of community-acquired pneumonia among patients with CD, assessing whether vaccination against streptococcal pneumonia modified this risk. Overall absolute rate of pneumonia was similar in patients with coeliac disease and controls. However, there was a 28% increased risk of pneumonia in coeliac disease unvaccinated subjects compared to unvaccinated controls. This increased risk was limited to those younger than 65, was highest around the time of diagnosis and was maintained for more than 5 years after diagnosis.

Persistent Villous atrophy

A meta-analysis(45) (26 studies, n=not reported) assessed the sensitivity and specificity of tTG IgA and EMA IgA assays in identifying patients with CD who have persistent villous atrophy despite a GFD. Inclusion criteria were studies of subjects with biopsy-confirmed CD, follow-up biopsies, and measurement of serum antibodies on a GFD, biopsy performed on subjects regardless of symptoms, or antibody test results. Villous atrophy was defined as a Marsh 3 lesion or villous height:crypt depth ratio below 3.0. Results indicated that for people with biopsy-confirmed CD undergoing follow-up biopsy on a GFD, tests for serum tTG IgA and EMA IgA levels had low sensitivity (below 50%) in detection of persistent villous atrophy.

Online monitoring and follow-up

A randomised controlled trial (RCT)(46) evaluated the cost effectiveness of online consultations in follow-up of patients with CD (n=304 patients under 25 years old with CD for at least 1 year). Participants were randomised to an online or outpatient consultation. An online consultation included questionnaires for symptom and growth measurement. Antitransglutaminase-type-2 antibodies were determined using a POCT. Controls had a traditional consultation with antitransglutaminase-type-2 antibodies testing in laboratories. The primary outcome was anti-transglutaminase-type-2 antibodies after 6 months. The performance of the online test was significantly inferior to laboratory testing. Nevertheless, the results indicated that online consultations for children and young adults with CD were cost-saving and significantly increased CD-specific health related quality of life (HRQoL), and patient satisfaction.

Intelligence gathering

Adherence

Topic expert feedback highlighted the lack of reliable markers of disease activity and suggested the need to assess GFD adherence by biopsy or non-invasive markers.

Annual monitoring

One expert proposed that advice should be given regarding standard follow-up serology as part of annual review. The American Gastroenterological Association clinical practice update on diagnosis and monitoring of CD was cited in recommending serology at 6 and 12 months post-diagnosis and annually thereafter, with evidence that persistently positive serology usually indicates ongoing intestinal damage and gluten exposure. Blood tests and nutrition screening, in addition to a DEXA scan for osteoporosis were also suggested for further advice.

The following two ongoing studies were identified during the surveillance review and the publication of the results will be tracked and considered when available:

[Noninvasive Markers of Gluten Ingestion in Celiac Disease Patients](#)

[Assessment of Adherence to Gluten Free Diet in Children and Adolescents by Detection of Gluten in Faecal Samples](#)

Impact statement

Adherence

No evidence was identified to address the topic expert feedback highlighting the lack of reliable markers of adherence to GFD in people with CD and no impact on the guideline is anticipated. Further studies in this area will be reviewed at the next surveillance review.

Annual monitoring

Topic experts advised on standard follow-up serology as part of annual review, in addition to nutrition screening and the need for guidance on DEXA scanning for osteoporosis. However NICE guideline NG20 already advises offering annual review to include consideration of the need for assessment of diet and dietary adherence, plus the need for specialist dietetic and nutritional advice. It also advises referral to a GP or consultant to assess the need for a DEXA scan for osteoporosis, and the need for specific blood tests. Therefore, no impact is anticipated on the guideline in the absence of strong evidence to indicate otherwise.

Specific complications

Evidence indicating an increase in risk factors for cardiovascular disease associated with a GFD are unlikely to impact the guideline recommendations, which already advise referring the person to a GP or consultant if concerns are raised in the annual review about the risk of long-term complications such as CVD. The need for specialist dietitian and nutritional advice is also recommended for consideration at annual review.

Risk of pneumococcal infection

New evidence indicates a higher risk of both community and hospital acquired pneumococcal infection for people with CD. Preventive pneumococcal vaccination should be considered for this subgroup, in addition to those with functional hyposplenism. However, vaccination guidance is set at a national level by the UK government through the [Joint Committee on Vaccination and Immunisation](#) and is not within the scope of NICE guideline NG20. Therefore, no impact on the guideline is anticipated. A cross referral will be added to the guideline to the JCVI guidance on pneumococcal vaccination.

Persistent villous atrophy

New evidence indicated that tests for serum tTG IgA and EMA IgA levels had low accuracy in monitoring CD patients for persistent villous atrophy. In the absence of markers for detecting villous atrophy, signs and symptoms for this complication should be assessed at annual review and onward referral should be considered if concerns arise. This is consistent with recommendation 1.4.4 for assessing the risk of long-term complications or comorbidities.

Online monitoring and follow-up

New evidence indicating that the performance of the online consultation was significantly inferior to laboratory testing for anti-transglutaminase-type-2 antibodies is consistent with the guideline recommendations, which do not advise online consultations for monitoring patients with CD. However, it should be noted that online consultations for children and young adults with CD were cost saving and significantly increased CD-specific HRQoL, and patient satisfaction. Further research in this area will be considered at the next surveillance review.

New evidence is unlikely to change guideline recommendations.

Non-responsive and refractory coeliac disease

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

We identified 2 studies on Nonresponsive and refractory CD ([Table 5](#))

Larazotide

A multicentre RCT(47) (n=340) assessed larazotide acetate 0.5, 1, or 2 mg 3 times daily to relieve ongoing symptoms in adults with CD who had been on a GFD for 12 months or longer and maintained their current GFD during the study. The primary end point was the difference

in average on-treatment Celiac Disease Gastrointestinal Symptom Rating Scale score. The primary end point was met with the 0.5-mg dose of larazotide acetate, with fewer symptoms compared with placebo by modified intention to treat. Safety was comparable with placebo. It should be noted that larazotide is not licensed for this indication in the UK.

Immunotherapy

A study comprising two linked RCTs(48) (n=108) assessed the safety and pharmacodynamics of the Nexvax2 therapeutic vaccine in adult patients with CD on a GFD. Compared to placebo, the maximum tolerated dose of Nexvax-2 was 150 mug for twice weekly intradermal administration over 8 weeks, which modified immune responsiveness to Nexvax2 peptides without deterioration in duodenal histology. The gastrointestinal symptoms that followed the first intradermal administration of the vaccine were similar to those associated with oral gluten challenge. It should be noted that ongoing trials of this vaccine have been discontinued because it was no more effective than placebo.

Intelligence gathering

The following study was identified during the surveillance review but has been discontinued because Nexvax-2 was no more effective than placebo:

[A Study of the Safety, Efficacy and Tolerability of Nexvax-2 in Patients With Celiac Disease \(CeD\)](#)

Impact statement

Larazotide

The new evidence from a single RCT indicates that larazotide may be effective in reducing gastrointestinal symptoms of CD in adults after 12 months on a GFD. Further confirmatory research and licensing for use in the UK is likely to be needed to signal any impact on the guideline for this intervention.

Immunotherapy

The initial evidence, based on small phase 1 RCTs for the use of the Nexvax-2 therapeutic vaccine, suggests that it may be tolerable for CD patients, but the cessation of a larger trial due to lack of effectiveness indicates that it will not impact on the guideline.

New evidence is unlikely to change guideline recommendations.

[Information and support](#)

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

An amendment is needed in recommendation 1.6.4 to update the link to NICE guideline [NG134 depression in children](#)

2019 surveillance summary

We identified 2 studies relating to information and support ([Table 6](#))

Dietary adherence

A systematic review and meta-analysis(49) (18 studies) assessed the effect of GFD on HRQoL in CD, specifically taking into consideration determinants that negatively influenced HRQoL. Following a GFD was found to significantly improve but not normalise HRQoL in adults with CD. Dietary adherence improved HRQoL over non-adherence. Better self-reported dietary adherence resulted in higher HRQoL.

Digital educational interventions

An RCT(50) (n=61) aimed to determine the impact of the Text Message Educational Automated Compliance Help (TEACH) text message intervention as a pragmatic approach for patient engagement among adolescents and young people with CD as measured by GFD adherence, patient activation, and quality of life. The TEACH intervention cohort received 45 unique text messages over a 3-month study period while the control group received standard of care treatment. Primary outcome measures included objective markers of GFD adherence included serum tissue transglutaminase IgA and DGP-IgA levels. Results showed there was no statistically significant difference in patient-reported or objectively measured GFD adherence between groups. Among the TEACH intervention group, there was significant improvement in patient activation and quality of life and NIH PROMIS Global Physical Health.

Intelligence gathering

Topic expert feedback highlighted that digital support is being developed to allow people to better manage the diet and report progress, but no evidence was cited in this area..

Impact statement

Supporting dietary adherence

The new evidence indicating that following a GFD may significantly improve HRQoL in adults with CD is consistent with recommendation 1.6.3 for a healthcare professional with a specialist knowledge of coeliac disease to tell people with a confirmed diagnosis of coeliac disease (and their family members or carers, where appropriate) about the importance of a gluten-free diet and to give them information to help them follow it.

The new evidence indicating the value of the TEACH text message intervention for patient engagement has potential but is based on a single small RCT and the findings need to be substantiated by further larger studies to signal an impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Advice on dietary management

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

We identified 5 studies covering dietary management ([Table 7](#))

Inclusion of oats in the gluten free diet

A systematic review and meta-analysis(51) (28 studies; 6 RCTs and 2 non-RCTs n=661, 20 observational studies, n unreported) found that oat consumption for 12 months did not affect symptoms, histologic scores, intraepithelial lymphocyte counts, or results from serologic tests. Subgroup analyses of adults compared to children did not reveal differences. The findings were based on low quality evidence.

An RCT(52) (n=177) evaluated the long-term validity and safety of gluten free oats versus placebo over 15 months in the dietary treatment of children with CD. Direct treatment effect with pure gluten free oats was non-inferior for clinical, serologic, and intestinal permeability variables.

Low FODMAP diet

An RCT(53) (n=50) evaluated the effects of a low fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet (LFD) on gastrointestinal and psychological symptomatology in CD patients over 21 days. Results showed that psychological symptomatology significantly improved in the LFD group, but quality of life did not. General well-being increased in both groups but with a more statistically significant improvement in the LFD group.

Dietary supplements

A pilot RCT(54,55) (n=34) evaluated the effect of the prebiotic oligofructose-enriched inulin (Synergy 1) on fat-soluble vitamins status, parathormone, and calcium-related elements in paediatric CD patients. Participants were randomised into a group receiving 10 g of Synergy 1 or placebo (maltodextrin) together with a GFD. After 3 months, results showed that supplementation of GFD with Synergy 1 significantly improved vitamin D and vitamin E levels. It was also found to significantly increase the bifidobacterium count. No significant side effects were noted.

A multicentre RCT(56) (n=109) evaluated the efficacy and safety of a probiotic mixture in patients with CD with IBS-type symptoms despite a strict GFD. Results showed that a 6-week probiotic treatment was effective in improving the severity of IBS-type symptoms in CD patients on strict GFD and was associated with a modification of gut microbiota.

Intelligence gathering

Folic acid supplementation

A topic expert suggested that the guideline aligns with the NICE Clinical Knowledge Summary (CKS) – [Coeliac disease Management](#) on advising high-dose folic acid supplementation (5 mg once daily) for women with CD who are pregnant, or who are planning a pregnancy. The basis for this advice is that women with CD are considered at high risk of conceiving a child with a neural tube defect. However, the CKS topic states that this is based on expert advice, rather than evidence, and what CKS considers to be good medical practice based on the potential risk of poor absorption of folic acid in women with CD.

Role of the dietitian

A topic expert highlighted that the value of the dietitian should be made more prominent in both NICE guideline NG20 and NICE quality standard QS134. The specialist knowledge and training of dietitians includes behavioural modification and counselling skills to support patients around early dietary management of CD. Although pharmacists do not have this background, evidence was cited of their value in the early recognition of CD and for subsequent monitoring (the evidence was ineligible for inclusion in the surveillance review). It was noted that there is an important role for both to play in the community and that this should be reflected in the guideline.

Prescription legislation for gluten free foods

Experts highlighted that under the new legislation:

[The National Health Service \(General Medical Services Contracts\) \(Prescription of Drugs etc.\) \(Amendment\) Regulations 2018](#)

CCGs can, according to NHS England's [Prescribing Gluten-Free foods in Primary Care: Guidance for Clinical Commissioning Groups - frequently asked questions](#): 'restrict further by selecting bread only, mixes only or can choose to end prescribing of all gluten free foods if they feel this is appropriate for their population, while taking account of their legal duties to advance equality and have regard to reducing health inequalities.'

As these products remain more expensive than standard breads and flours, it was felt that CCGs would have difficulty meeting their equality duties and this is likely to put those with lowest incomes at greatest risk of ill health.

Experts suggested that the guideline should include research to assess the correlation between concordance with a GFD and cost and availability of gluten free products.

Gluten free oats

An expert stated that in practice the use of gluten free oats tends to be used after 1-2 years post-diagnosis and that this should be reflected in recommendation 1.7.3.

Impact statement

Folic acid supplementation

No evidence was identified to substantiate the CKS advice for high-dose folic acid supplementation (5 mg once daily) for women with CD who are pregnant, or who are planning a pregnancy. Therefore, no impact on the guideline is anticipated. The CKS advice will be amended to align with NICE guideline NG20. NICE's guideline on [maternal and child nutrition](#) provides further advice in this area.

Role of the dietitian

The role of the dietitian is outlined in NICE guideline NG20 recommendations 1.5.1 and 1.6.2 which include referral to and information on specialist dietitians. There is also a research recommendation in this area which remains ongoing: [How can the role of the dietitian contribute most effectively within a coeliac disease team?](#) No impact is anticipated on existing recommendations until strong evidence indicates otherwise.

Prescription legislation for gluten free foods

The guideline does not make recommendations on prescribing of gluten free foods because policy and legislation in this area is set at a national level by the Department for Health and Social Care, with implementation passed to CCGs at a local and regional level. No impact is anticipated on the guideline.

Oat consumption

NICE guideline NG20 recommendation 1.7.3 advises that people with CD can choose to include gluten-free oats in their diet at any stage and they will be advised whether to continue eating gluten-free oats depending on their immunological, clinical or histological response. New evidence suggests that pure oats can be safely added to the GFD, although the evidence is low quality and is likely to need further confirmatory research to substantiate the findings.

Low FODMAP diet

The findings from a single small RCT over a short duration suggesting that a low FODMAP diet significantly improved psychological symptomatology of people with CD are likely to need further confirmatory research to signal any potential impact on the guideline.

Dietary supplements

The findings of two small RCTs indicating that the prebiotic Synergy 1 improved vitamin D and E levels, and a probiotic mixture improved IBS symptoms, are likely to need substantiation by further confirmatory research before any potential impact on the guideline.

New evidence is unlikely to change guideline recommendations.

Research recommendations

What is the sensitivity and specificity of IgG tissue transglutaminase (tTG), IgG endomysial antibodies (EMA) and IgG DGP tests in detecting coeliac disease in people with IgA deficiency?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
-

What is the sensitivity and specificity of IgA EMA and IgA DGP tests in detecting coeliac disease in people who test negative for IgA tTG?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
-

Should people with coeliac disease be offered calcium and vitamin D supplements for a specific time period soon after their initial diagnosis?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
-

How can the role of the dietitian contribute most effectively within a coeliac disease team?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
-

What is the effectiveness of more frequent monitoring compared with monitoring at 12 months after diagnosis in people with newly diagnosed coeliac disease?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Data Tables

Table 1 Recognition of coeliac disease

Study	Type	n	Risk factor/exposure	Outcome	Result
Irvine, Andrew J; et al. (2017)(13)	SR	9,275	IBS	Association with increased risk of CD	Pooled OR for positive IgA AGAs and biopsy-proven CD in IBS subjects vs. controls 3.21 (95% CI 1.55-6.65) Pooled OR for positive EMA and biopsy-proven CD in IBS subjects vs. controls 2.75 (95% CI 1.35-5.61) Pooled OR for positive tTG, and biopsy-proven CD in IBS subjects vs. controls 4.48 (95% CI 2.33-8.60)
Roy, Abhik; et al. (2016)(15)	SR	6024	ATD	Association with increased risk of CD	Prevalence of biopsy-confirmed CD of 1.6% [CI 1.3-1.9%]. Heterogeneity ($I^2 = 70.7\%$) Prevalence of biopsy-confirmed CD in children with ATD 6.2% [CI 4.0-8.4%]) Prevalence of biopsy-confirmed CD in adults with ATD 2.7% Prevalence of biopsy-confirmed CD in adults and children with ATD 1.0%
Vajravelu, Mary Ellen; et al. (2018)(17)	Cohort	9,180	T1D	Association with increased risk of CD	Overall incidence 196 people (2%) during follow-up. Median time to diagnosis 2.1 years.
Vajravelu, Mary Ellen; et al. (2018)(17)	Cohort	9,180	T1D	Association with increased risk of CD	Incidence (per 10,000 person-years) females (43.0 [95% CI 35.2-52.0]) vs males (26.8 [95% CI 21.5-32.9]). Younger age at diabetes diagnosis within childhood HR 0.91 [95% CI 0.88-0.94]) and female sex among the adult-onset diabetes group (HR 3.19 [95% CI 1.39-7.34]) were associated with greater risk of CD
Pham-Short et al. (2015)(16)	SR	9 studies N=587 cases in children and adolescents	T1D	Association with increased risk of CD	Prevalence of CD 5.1% (95% CI: 3.1-7.4%)
Souto-Souza, Debora; et al. (2018)(3)	SR	2,840	DDE	Association with increased risk of CD	Prevalence of DDE in people with CD was 50% (95% CI 0.44-0.57, $I^2=88\%$) Patients with CD prevalence of enamel defects compared to healthy people RR: 2.31 (95% CI: 1.71-3.12, $I^2=98\%$)
Singh, Prashant; et al. (2016)(1)	SR	Unreported		Association with increased risk of CD	Women with infertility odds of having CD in comparison with control population (OR=3.5; 95% CI, 1.3-9; $P<0.01$) Women with "unexplained infertility" odds of having CD compared with control population (OR=6; 95% CI, 2.4-14.6)

Study	Type	n	Risk factor/exposure	Outcome	Result
Nieri, Michele; et al. (2017)(2)	SR	Unreported	Enamel defects and aphthous stomatitis	Association with increased risk of CD	<p>Frequency of enamel defects in CD OR=5.69 (95%CI from 3.47 to 9.33, P<0.00001, I²=90%, 30 studies)</p> <p>Frequency of enamel defects in CD in children OR 5.63 (95%CI from 3.95 to 8.01, P<0.00001, I²=65%, 24 studies)</p> <p>Frequency of enamel defects in CD in adults (OR=2.16, 95%CI from 0.95 to 4.88, P=0.06, I²=40%, 3 studies)</p> <p>Frequency of aphthous stomatitis in CD (OR=3.79, 95%CI from 2.67 to 5.39, P<0.00001, I²=49%, 21 studies)</p> <p>Frequency of aphthous stomatitis in CD in children OR 4.31 (95%CI from 3.03 to 6.13, P<0.00001, I²=29%, 13 studies)</p> <p>Frequency of aphthous stomatitis in CD in adults OR 47.90 (95%CI from 6.29 to 364.57, P=0.0002)</p>
Emilsson, Louise; et al. (2015)(4)	Cohort	650 children with celiac disease and 107,828 controls	Perinatal risk factors	Association with increased risk of CD	<p>No association between birth weight or height with CD (born small for gestational age was not associated)</p> <p>Mode of delivery (cesarean section, model 1: OR, 0.84; 95% CI 0.65-1.09, and model 2: OR, 0.83; 95% CI, 0.63-1.09)</p> <p>Maternal celiac disease, adjusted for age and sex of the children (OR, 12.45; 95% CI, 8.29-18.71)</p> <p>Type 1 diabetes (model 1: OR, 2.58; 95% CI, 1.19-5.53, and model 2: OR, 2.61; 95% CI, 1.14-5.98)</p>
Du Y.; et al (2018)(14)	SR	4383	Down syndrome	Association with increased risk of CD	<p>Prevalence of biopsy-confirmed CD of 5.8 % (95 % CI = 4.7-7.2 %) in patients with DS</p> <p>Prevalence of CD in children with DS (6.6 %; 17 studies)</p> <p>Prevalence of CD in age mixed samples with both children and adults (5.1 %; 13 studies)</p>
Genetic biomarkers					
Aflatoonian, Majid; et al. (2019)(5)	SR	1147 cases and 1774 controls	TNF-alpha - 308G>A polymorphism	Association with increased risk of CD	<p>A vs G: OR=2.077, 95% CI=1.468-2.939, P=<=0.001; AA vs GG: OR=8.512, 95% CI=3.740-19.373, P=<=0.001</p> <p>AA+AG vs GG: OR=1.869, 95% CI=1.161-3.008, P=0.010</p> <p>AA+AG vs GG: OR=4.773, 95% CI=3.181-7.162, P=<=0.001</p>

Study	Type	n	Risk factor/exposure	Outcome	Result
Rossi, Elisa; et al. (2015)(6)	Case-control	511 (244 CD, 267 controls)	TNFA promoter (-1031T>C, -857C>T, -376G>A, -308G>A, -238G>A)	Association with increased risk of CD	TNFA-1031C (OR=0.65, 95% CI:0.44-0.95) -857T (OR=0.42, 95% CI:0.27-0.65) -376A (OR=2.25, 95% CI:1.12-4.51) -308A (OR=4.76, 95% CI:3.12-7.26)
Guo, Cong-Cong; et al. (2016)(7)	SR		RGS1 rs2816316 and IL12A rs17810546	Association with increased risk of CD	Negative association of minor allele C of rs2816316 (C vs. A: OR = 0.77, 95% CI = 0.74-0.80) Positive association of minor allele G of rs17810546 (G vs. A: OR = 1.37, 95% CI = 1.31-1.43)
Guo, C C; et al. (2015)(12)	SR	12,986 CD cases and 28,733 controls	IL2/IL21 (rs6822844 and rs6840978) and SH2B3 (rs3184504)	Association with increased risk of CD	Minor allele T of rs6822844 (T vs G, OR = 0.72, 95%CI = 0.67-0.78, P < 0.001) significantly decreased the risk of CD Minor allele T of rs6840978 (T vs C, OR = 0.76, 95%CI = 0.71-0.83, P < 0.001) in IL2/IL21 significantly decreased the risk of CD Minor allele A of rs3184504 (A vs G, OR = 1.18, 95%CI = 1.12-1.24, P < 0.001) in SH2B3 significantly increased CD susceptibility
Khan, Saif; et al. (2016)(8)	SR	1774 controls and 1147 CD cases	TNF-alpha -308 G > A (rs1800629) Polymorphism	Association with increased risk of CD	Significant associations in four genetic models: Variant allele (A vs. G: p = 0.001; OR = 2.051, 95% CI = 1.452-2.895) Variant homozygous (AA vs. GG: p = 0.001; OR = 6.626, 95% CI = 3.569-12.300), Recessive (AA vs. GG + AG: p = 0.001; OR = 4.766, 95% CI = 3.177-7.152) Dominant (AA + AG vs. GG: p = 0.008; OR = 1.910, 95% CI = 1.181-3.088)
Huang, Shi-Qi; et al. (2017)(9)	SR	Unreported	LPP and TAGAP polymorphisms	Association with increased risk of CD	A allele at rs1464510 OR 1.26 (95% CI: 1.22-1.30) A allele at rs1738074 OR 1.17 (95% CI: 1.14-1.21)
Bajor J.; et al. (2019)(10)	SR	Unreported	HLA-DQB1*02 gene doses	Association with increased risk of CD	Classical CD was more frequent with a double versus single dose of the HLA-DQB1*02 allele OR = 1.758 95%CI: 1.148-2.692, I2 = 0.0% In children gene dose effect was more prominent OR = 2.082, 95%CI: 1.189-3.646, I2 = 0.0% for the comparisons of double versus single dose In children gene dose effect was more prominent in double versus zero dose OR = 3.139, 95%CI: 1.142-8.630, I2 = 0.0% Atrophic histology was more prevalent with a double versus zero dose OR = 2.626, CI: 1.060-6.505, I2 = 21.3%

Study	Type	n	Risk factor/exposure	Outcome	Result
Liao N.; et al. (2015)(11)	SR	1965 CD patients 4894 controls	MYO9B polymorphisms (rs1545620, rs1457092, rs2305767 and rs2305764)	Association with increased risk of CD	rs1545620 was associated with CD risk in Europeans in: Dominant comparison model (OR=1.31, 95% CI: 1.10-1.58, Pz=0.003) Recessive comparison model (OR=1.36, 95% CI: 1.08-1.72, Pz=0.009) Homozygote comparison model (OR=1.55, 95% CI: 1.20-2.01, Pz=0.001) Allelic comparison model (OR=1.24, 95% CI: 1.10-1.40, Pz=0.001)

Abbreviations: CD -coeliac disease; SR - systematic review; CI – confidence interval; OR – odds ratio; ATD – autoimmune thyroid disease; A, G, AA, GG; genetic nomenclature not defined in abstract; LPP - Lipoma preferred partner; TAGAP - T-cell activation Rho GTPase activating protein

Table 2 Serological testing for coeliac disease with intestinal biopsy as the reference standard

Study	Type	n	Diagnostic test	Outcome	Result
Point of care tests (POCT)					
Polanco, Isabel; et al. (2017)(19)	DTA	100	POCT that detects IgA and immunoglobulin G (IgG) antibodies to DGP and total IgA	Diagnostic accuracy	95.8% (85.7-99.4%) sensitivity 98.1% (89.7-99.7%) specificity 97.9% (88.7-99.6%) positive predictive value 96.2% (87.0-99.4%) negative predictive value Positive likelihood ratio 49.8 (7.2-347.5) Negative likelihood ratio 0.04 (0.01-0.17)

Study	Type	n	Diagnostic test	Outcome	Result
Mooney, Peter D; et al. (2015)(22)	DTA	Group 1, n=55 patients at high risk of CD who tested positive for endomysial antibody Group 2 n=508 patients who underwent an endoscopy examination for any indication	Group 1: Biocard test and the Celiac Quick Test, which measure anti-tTG, and the Simtomax test which measures DGP antibodies	Diagnostic accuracy for identifying CD	<u>DGP (Simtomax) test:</u> Group 1 94.4% sensitivity Group 2 92.7% sensitivity (95% CI 83.0-97.3) 85.2% specificity (95% CI, 81.5-88.3) PPV 49.2% (95% CI, 40.3-58.2) NPV 98.7% (95% CI, 96.8-99.5) <u>Celiac Quick Test:</u> Group 1 77.8% sensitivity (P = .03 vs the DGP test) <u>Biocard test:</u> Group 1 72.2% sensitivity (P = .008 vs the DGP test) <u>Measurement of serum anti-tTG:</u> sensitivity 91.2% (95% CI 81.1-96.4) specificity 87.5% (95% CI 84.0-90.4) PPV 53.0% (95% CI, 43.6-62.2) NPV 98.5% (95% CI, 96.5-99.4)
Esteve M.; et al. (2018)(20)	DTA	350	POCT based on IgA/IgG DGP	Diagnostic accuracy	Sensitivity 100% Specificity 93% PPV 14% NPV 100%
Tangermann P.; et al.(2019)(21)	DTA	1055 (888 adults, 167 children)	Simtomax POCT test	Diagnostic accuracy	Adults and children (prevalence 4.1%): 79% sensitivity (95% CI, 64%-89%) 94% specificity (95% CI, 93%-96%) PPV 37% NPV 99% Adults with CD (prevalence 1.2%): 100% sensitivity 95% specificity Children with CD (prevalence 19.6%): 72% sensitivity (95% CI 53%-86%)
Lau M.S.; et al. (2018)(24)	DTA	Group 1: 1000 Group 2: 61	IgA/IgG DGP based POCT	Diagnostic accuracy	Group 1: 41 patients (4.1%) were diagnosed with CD POCT sensitivity 82.9% POCT specificity 85.4% IgA tTG sensitivity 78.1% IgA tTG specificity 96.3% IgA-EMA sensitivity 70.7% IgA-EMA specificity 99.8% Group 2: The POCT had 100% sensitivity and NPV in detecting CD in group 2.

Study	Type	n	Diagnostic test	Outcome	Result
Grode L.; et al. (2019)(23)	DTA	622	POCT Simtomax	Diagnostic accuracy	Index POCT Sensitivity 42.9% (95% CI 9.9-81.6) and a specificity 86.8% (95% CI 83.9-89.4). Positive and negative predictive values were 3.57% (95% CI 0.7-10.1) and 99.3% (95% CI 98.1-99.8)
Singh P.; et al. (2018)(18)	SR	Not reported	POCT tests	Diagnostic accuracy	Pooled sensitivity of all POCTs (based on tTG or DGP or tTG+Anti-gliadin antibodies) 94.0% [95% CI 89.9-96.5] Pooled specificity of all POCTs (based on tTG or DGP or tTG+Anti-gliadin antibodies) 94.4% (95% CI, 90.9-96.5) Pooled positive likelihood ratio for all POCTs 16.7. Pooled negative likelihood ratio for all POCTs 0.06. Pooled sensitivity for IgA tTG-based POCTs 90.5% (95% CI, 82.3-95.1) Pooled specificity for IgA tTG-based POCTs 94.8% (95% CI, 92.5-96.4)
IgA tTG tests and HLA					
Maglione, Margaret A; et al. (2016)(25)	SR	60 primary studies, 13 SRs	Serology	Diagnostic accuracy	tTG IgA test: sensitivity 92.5% and specificity 97.9% EmA IgA test: sensitivity 79%, specificity 99.0% DGP-IgA test: sensitivity 87.8%, specificity 94.1%
Hashmi, Muhammad Almas; et al. (2016)(26)	DTA	60	anti-tissue transglutaminase IgA (TTG)	Diagnostic accuracy	Sensitivity of TTG 86.84%, Specificity of TTG 81.82% PPV 89.19% NPV 78.26% TTG titre more than 50 iu/ml had a 100% positive predictive value
Javaeed A.; et al. (2015)(27)	DTA	121	IgA tTG	Diagnostic accuracy	anti-tTG: Sensitivity 78.6% Specificity 98.1% PPV 84.6% NPV 97.2%
Sarna, Vikas K; et al. (2018)(28)	DTA	143	HLA-DQ-gluten tetramer-based assay	Diagnostic accuracy	Optimised cut-off values identified subjects with CD on a GFD vs subjects without CD on a GFD: 97% sensitivity (95% CI 0.92-1.00) 95% specificity (95% CI 0.84-1.00) The values identified subjects with CD on a gluten-containing diet vs controls with: 100% sensitivity (95% CI 1.00-1.00) 90% specificity (95% CI 0.83-0.98)
Combined tests					

Study	Type	n	Diagnostic test	Outcome	Result
Dahlbom, Ingrid; et al. (2016)(29)	DTA	242	IgA/IgG anti-TG2, IgA/IgG anti-DGP and IgA/IgG against a mix of TG2 and DGP (anti-TG2/DGP)	Diagnostic accuracy	IgA/IgG anti-TG2 assay: Sensitivity of 96% Specificity of 99.5% Area under the ROC curve 0.996 (95% CI 0.992-1, p < 0.0001)
Oyaert, Matthijs; et al. (2015)(30)	DTA	156; 13 <2 year; 45 2-16 years; 98 over 16 years	combined IgA tTG and IgG anti-DGP	Diagnostic accuracy	Patients with double positivity and high antibody levels (>3 times, >10 times ULN) had a high probability for having CD (likelihood ratio >=649 for >3 times ULN and for >10 times ULN).
Konopka, Ewa; et al. (2016)(31)	Case-control	100	Serology (Poplycheck celica panels)	Diagnostic accuracy	Specificity and positive predictive value were both 100% for the detection of Polycheck anti-tTG-IgA antibodies. Sensitivity and negative predictive value were both 100% for Polycheck anti-DGP-IgG antibody detection. For the strategy of using both PCP IgA and IgG and determining positive outcomes of the test with two or more coeliac-specific antibodies detected: 98% sensitivity and NPV 100% specificity and PPV Area under ROC 99%.
Bufler, P; et al. (2015)(32)	DTA	411 children with CD 98 children without CD	DGP-IgG and DGP IgA with TG2-IgA	Diagnostic accuracy	Sensitivity to diagnose CD for TG2-IgA (100 %) Sensitivity to diagnose CD for DGP-IgG (90 - 100 %) Sensitivity to diagnose CD for DGP IgA (67 - 86 %) Specificity for all tests (97 - 100 %)
Immunochromatography					
Di Tola, Marco; et al. (2018)(33)	DTA	103	ICA	Diagnostic accuracy	anti-tTG detected by ICA: Sensitivity 84.5% Specificity 100% Diagnostic accuracy 88.9%
Abbreviations: CD -coeliac disease; DTA – diagnostic test accuracy; SR - systematic review; CI – confidence interval; OR – odds ratio; AUC – area under curve; ULN – upper limit of normal; PPV – positive predictive value; TNFA - Tumour Necrosis Factor alpha; IGA - immunoglobulin A; IgG - immunoglobulin G; ROC – receiver operating characteristic; ICA – Immunochromatographic assay					

Table 3 Referral of people with suspected coeliac disease

Study	Type	n	Intervention/ Diagnostic test	Outcome	Result
Non-biopsy diagnosis					

Study	Type	n	Intervention/ Diagnostic test	Outcome	Result
Werkstetter, Katharina Julia; et al. (2017)(34)	DTA	707	Symptoms and levels of immunoglobulin A against tissue transglutaminase (TGA-IgA) 10-fold or more the upper limit of normal (ULN), confirmed by detection of endomysium antibodies (EMA) and positivity for HLA-DQ2/DQ8	Diagnostic accuracy	Non-biopsy PPV of 99.75 (95% CI, 98.61-99.99) PPV was 100.00 (95% CI, 98.68-100.00) when only malabsorption symptoms were used instead of any symptom (n = 278). When levels of TGA-IgA were 10-fold or more the ULN, PPVs ranged from 99.63 (95% CI, 98.67-99.96) to 100.00 (95% CI, 99.23-100.00) Sensitivity for Local TGA \geq 10xULN 71.01 Sensitivity for Local TGA \geq 10xULN + EMA (+/- HLA) 69.30 Specificity for Local TGA \geq 10xULN 93.548 Specificity for Local TGA \geq 10xULN + EMA (+/- HLA) 96.774
Elitsur, Yoram; et al. (2017)(36)	DTA	240	Serology	Diagnostic accuracy	tissue transglutaminase titres at \geq 10x upper limit of normal: Sensitivity 75.4 Specificity 48.8 PPV 87.7 NPV 29.0 Accuracy rate 70.8 % Similar data in the other tissue transglutaminase titres (\geq 3x upper limit of normal, >100 U/ml, or >100 U/ml and >10x upper limit of normal)
Efthymakis, Konstantinos; et al. (2017)(37)	DTA	234	Serology	Diagnostic accuracy	Anti-tTG levels correlated with histology (r s = 0.397, p < 0.001) AUC was similar before and after normalisation (0.803 vs 0.807) Applying the ESPGHAN criterion (\geq 10 x ULN): PPV 97.66% ROC curve analysis showed an optimal cutoff of \geq 16 x ULN, PPV 98.86%
Gulseren, Yasemin Derya; et al. (2019)(38)	DTA	39	Serology	Diagnostic accuracy	Sensitivity 71.4% with ESPGHAN criteria Sensitivity 81% when ESPGHAN's IgA tTG threshold value for children was taken into consideration (>200 IU/mL)
Bansal E.; et al. (2018)(39)	DTA	731	Serology	Diagnostic accuracy	Using a tTGA cutoff value of 70 IU/ml: Sensitivity 83.9% Specificity was 56.10% Overall accuracy of 77.7%
Wolf J; et al. (2017)(35)	DTA	898	Serology	Diagnostic accuracy	total-IgA and IgA-TTG: PPV 0.988 NPV 0.934 IgG-DGL with IgA-TTG: PPV 0.988 NPV 0.958

Study	Type	n	Intervention/ Diagnostic test	Outcome	Result
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Abbreviations: CD -coeliac disease; DTA – diagnostic test accuracy; SR - systematic review; CI – confidence interval; OR – odds ratio; AUC – area under curve; ULN – upper limit of normal; PPV – positive predictive value; TNFA - Tumour Necrosis Factor alpha; IGA - immunoglobulin A; IgG - immunoglobulin G; ROC – receiver operating characteristic; ESPGHAN – European Pediatric Gastroenterology Hepatology and Nutrition Society

Table 4 Monitoring in people with coeliac disease

Study	Type	n	Risk factor/ Exposure	Intervention/ Diagnostic test	Comparator	Outcome	Result
Cardiovascular risk							
Potter, Michael D E; et al. (2018)(40)	SR	27 studies (n not reported)	GFD			Blood pressure, glycaemia, body mass index, waist circumference, and serum lipids	Consistent findings across studies included an increase in total cholesterol, high density lipoprotein, fasting glycaemia, and body mass index (while remaining within the healthy weight range)
Pneumococcal infection risk among patient with CD							
Simons, Malorie; et al. (2018)(41)	SR	3 studies (n not reported)	Pneumococcal infection risk			Pneumococcal infection	Odds of pneumococcal infection were higher among hospitalised CD patients compared with controls: OR 1.66; 95% CI 1.43-1.92 No evidence of heterogeneity (Q[1] = 1.17, P = .56, I2 = 0%)
Rockert Tjernberg, A; et al. (2017)(42)	Cohort	29,012 CD 144,257 controls	Pneumococcal infection risk			Pneumococcal infection	46% increased risk for IPD [HR 1.46, 95% CI 1.05-2.03]
Canova C.; et al. (2019)(43)	Cohort	1294 CD patients and 6470 reference individuals	Bacterial pneumonia or pneumococcal infections			Association with increased risk of CD	Risk of bacterial pneumonia among CD patients (HR 1.82; 95%CI 0.98-3.35) Risks of bacterial pneumonia the year before CD diagnosis (OR 6.00, 95%CI 1.83-19.66)
Zingone F; et al. (2016)(44)	Cohort	9803 CD and 101,755 controls				Association with increased risk of CD	Risk of pneumonia in CD unvaccinated subjects compared to unvaccinated controls: 28% increased risk (HR 1.28, 95% CI 1.02-1.60)
Diagnosis of persistent villous atrophy among patients with CD using intestinal biopsy as reference standard							

Study	Type	n	Risk factor/ Exposure	Intervention/ Diagnostic test	Comparator	Outcome	Result
Silvester, Jocelyn A; et al (2017)(45)	SR	CD		tTG IgA and EMA IgA assays		Diagnostic accuracy for villous atrophy	For persistent villous atrophy Sensitivity 0.50 for the tTG IgA assay (95% CI, 0.41-0.60) Specificity: 0.83 for the tTG IgA assay (95% CI, 0.79-0.87) Sensitivity 0.45 for the EMA IgA assay (95% CI, 0.34-0.57) Specificity 0.91 for the EMA IgA assay (95% CI, 0.87-0.94)

Online monitoring and follow-up

Vriezina, Sabine; et al. (2018)(46)	RCT	304		Online consultation with POCT	Laboratory testing	Anti-transglutaminase-type-2 antibodies after 6 months	Intervention inferior
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Abbreviations: CD -coeliac disease; RCT - randomised controlled trial; SR - systematic review; CI - confidence interval; OR - odds ratio; HR - hazard ratio; ULN - upper limit of normal; PPV - positive predictive value; POCT - point of care test; IPD - invasive pneumococcal disease; GFD - gluten free diet; OR - odds ratio; HR - hazard ratio

Table 5 Nonresponsive and refractory coeliac disease

Study	Type	n	Intervention	Comparator	Outcome	Result
Larazotide for people with CD						
Leffler, Daniel A; et al. (2015)(47)	RCT	342	Larazotide acetate 0.5, 1, or 2 mg 3 times daily	Placebo	Difference in average on-treatment Celiac Disease Gastrointestinal Symptom Rating Scale score	0.5 mg dose of larazotide acetate, superior (p=0.005)
Immunotherapy for people with CD						

Study	Type	n	Intervention	Comparator	Outcome	Result
Goel, Gautam; et al. (2017)(48)	RCT	108	Nexvax2 vaccine	Placebo	Primary endpoint was the number and percentage of adverse events in the treatment period in an intention to treat analysis	<p>Maximum tolerated dose for Nexvax2 was 150 mug.</p> <p>In the ascending dose cohorts in the three-dose study, patients with at least one treatment-emergent adverse event:</p> <p>6 (55%) of 11 placebo recipients, 5 (56%) of 9 who received Nexvax2 60 mug, 7 (78%) of 9 who received Nexvax2 90 mug, 5 (63%) of 8 who received Nexvax2 150 mug 3 (100%) placebo recipients 1 (33%) of 3 Nexvax2 150 mug recipients in the biopsy cohort.</p> <p>In the ascending dose cohorts of the 16-dose study patients with at least one treatment-emergent adverse event:</p> <p>5 (71%) of 7 placebo-treated participants 6 (75%) of 8 who received Nexvax2 150 mug 10 (100%) who received Nexvax2 300 mug, 6 (86%) of 7 placebo recipients 5 (71%) of 7 Nexvax2 150 mug recipients in the biopsy cohort.</p>
Abbreviations: RCT – randomised controlled trial; GI - gastrointestinal						

Table 6 Information and support

Study	Type	n	Intervention	Comparator	Outcome	Result
Dietary adherence						

Study	Type	n	Intervention	Comparator	Outcome	Result
Burger, Jordy P W; et al. (2017)(49)	SR	18 studies (n not reported)	GFD adherence			<p>GFD HRQoL for PGWB-Total (MD 7.34, 95% CI [1.96; 12.72]; p = 0.008)</p> <p>SF-36 MCS (MD 7.37, 95% CI [1.84; 12.90]; p = 0.009)</p> <p>SF-36 PCS (MD 5.72, 95% CI [1.50; 9.95]; p = 0.008)</p> <p>Treated patients HRQoL compared with controls for PGWB-Total: (MD -0.72, 95% CI [-2.71; 1.27]; p = 0.48), SF-36 MCS (MD -4.09, 95% CI [-6.17; -2.01]; p = 0.0001)</p> <p>PCS (MD -4.57, 95% CI [-6.97; -2.17]; p = 0.0002)</p> <p>Symptom-detected GFD adhering patients HRQoL compared with screening-detected patients (MD -3.73, 95% CI [-6.77; -0.69]; p = 0.02)</p> <p>Strict adhering patients HRQoL compared with non-strict adhering patients for SF-36 MCS (MD 7.70, 95% CI [4.61; 10.79]; p < 0.00001)</p> <p>SF-36 PCS (MD 3.23, 95% CI [1.33; 5.14]; p = 0.0009)</p>

Digital technology interventions

Haas, Kelly; et al. (2017)(50)	RCT	61	Text message intervention (TEACH) comprising 45 unique text messages	Standard care	Markers of GFD adherence: serum tissue transglutaminase IgA and deamidated gliadin peptide IgA levels	There was no statistically significant difference in patient-reported or objectively measured GFD adherence
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Abbreviations: RCT – randomised controlled trial; GFD – gluten free diet; TEACH – text message intervention; HRQoL – health related quality of life; MCS – mental component score; MD – mean difference; PCS – physical component score; PGWB – psychological general well-being

Table 7 Advice on dietary management

Study	Type	n	Intervention	Comparator	Outcome	Result
Inclusion of oats in the gluten free diet						

Study	Type	n	Intervention	Comparator	Outcome	Result
Pinto-Sanchez, Maria Ines; et al. (2017)(51)	SR	28 (6 RCT, 2 non-RCT, 20 observational) n not reported	Oat consumption	GFD without oats	Symptom scores	Oat consumption for 12 months did not affect symptoms (SMD: reduction in symptom scores in patients who did and did not consume oats, -0.22; 95% CI, -0.56 to 0.13; P = .22), Histologic scores (RR for histologic findings in patients who consumed oats, 0.24; 95% CI, 0.01-4.8; P = .35) Intraepithelial lymphocyte counts (SMD, 0.21; 95% CI, reduction of 1.44 to increase in 1.86)
Lionetti, Elena; et al. (2018)(52)	RCT	177	Pure unreactive oats	Placebo	Clinical (BMI, GSRS score), serologic (IgA antitransglutaminase antibodies, and IgA anti-avenin antibodies), and intestinal permeability	Intervention non-inferior to placebo. Direct treatment effect for clinical, serologic, and intestinal permeability variables: BMI: median, -0.5; 95% CI, -0.12 to 0.00 GSRS score: median, 0; 95% CI, -2.5 to 0.00 IgA: median, -0.02; 95% CI, -0.25 to 0.23 IgA anti-avenin antibodies: median, -0.0002; 95% CI, -0.0007 to 0.0003 intestinal permeability test: median, 0.004; 95% CI, -0.0002 to 0.0089
Low FODMAP diet for people with CD						
Roncoroni, Leda; et al. (2018)(53)	RCT	50	Low FODMAP GFD	Regular GFD	Psychological symptomatology and quality of life evaluated by the Symptom Checklist-90-R (SCL-90) and the Short Form (36) Health Survey (SF-36) questionnaires. Gastrointestinal symptomatology and general well-being evaluated by visual analogue scale (VAS) scores	Improved with intervention: A reduced global SCL-90 index (p < 0.0003). SF-36 scores did not differ between groups after treatment. The VAS for abdominal pain lower with intervention VAS for faecal consistency enhanced with intervention General well-being increased in both groups but more with intervention (p = 0.03)
Dietary supplements						
Drabinska, Natalia; et al. (2018)(54)	RCT	34	Oligofructose-enriched inulin (Synergy 1)	Placebo	Quantitative gut microbiota characteristics	Bifidobacterium count increased significantly (p < 0.05) in the Synergy 1 group

Study	Type	n	Intervention	Comparator	Outcome	Result
Drabinska, Natalia; et al. (2018)(55)	RCT	34	Oligofructose-enriched inulin (Synergy 1)	Placebo	Fat-soluble vitamins status, parathormone, and calcium-related elements	Concentration of 25(OH)D increased significantly (p < 0.05) by 42% with intervention but not in placebo. Concentration of vitamin E increased significantly (p < 0.05) by 19% with intervention, but not in the placebo group
Francavilla R.; et al. (2019)(56)	RCT	109	Probiotics	Placebo	IBS Severity Scoring System (IBS-SSS); GSRS; BSFS; and IBS Quality of Life Questionnaire (IBS-QOL)	IBS-SSS decreased with intervention (-15.9%+/-14.8% vs. 8.2%+/-25.9%; P<0.001) GSRS decreased with intervention (-19.8%+/-16.6% vs. 12.9%+/-31.6%; P<0.001) Treatment success was significantly higher in patients receiving probiotics, as compared with placebo (15.3% vs. 3.8%; P<0.04)
Abbreviations: SR – systematic review; RCT – randomised controlled trial; IBS – irritable bowel syndrome; GFD – gluten free diet; SSS – severity scoring system; GSRS - Gastrointestinal Symptom Rating Scale; SMD – standardised mean difference; QOL – quality of life; VAS – visual analogue scale; FODMAP - Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols; BSFS - Bristol Stool Form Scale; BMI - body mass index; RR – relative risk						

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