

Internal Clinical Guidelines Team

Final Version

Coeliac Disease

Recognition, assessment and management

Clinical Guideline NG20

Methods, evidence and recommendations

September 2015

Final Version

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Health and Care Excellence*

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1 Overview

1.1 Introduction

Coeliac disease is an autoimmune condition associated with chronic inflammation of the small intestine, which can lead to malabsorption of nutrients. Dietary proteins, known as glens, which are present in wheat, barley and rye activate an abnormal mucosal immune response. Clinical and histological improvements usually follow when gluten is excluded from the diet.

Coeliac disease can present with a wide range of clinical features, both gastrointestinal (such as indigestion, diarrhoea, abdominal pain, bloating, distension or constipation) and non-gastrointestinal (such as fatigue, dermatitis herpetiformis, anaemia, osteoporosis, reproductive problems, short stature, neuropathy, ataxia or delayed puberty). Although some people present with typical symptoms, others have few or no symptoms.

People with autoimmune conditions such as type 1 diabetes and autoimmune thyroid disease, or people with a first-degree family history of coeliac disease, have an increased likelihood of coeliac disease.

1.2 Health and resource burden

Coeliac disease is a common condition. Population screening studies suggest that in the UK 1 in 100 people are affected. The complications of untreated coeliac disease can be serious, such as osteoporosis or malignancy.

The treatment of coeliac disease is a lifelong gluten-free diet. Specific education and information, such as advice and education on alternative foods in the diet to maintain a healthy and varied intake, may increase the likelihood of adherence and a positive prognosis. These could be provided by a dietitian with experience in coeliac disease; access to specialist dietetic support is currently poor within the UK.

1.3 Reasons for the guideline

Currently, people with symptoms and/or signs suggestive of coeliac disease are investigated by serological tests, for example, IgA tissue transglutaminase (tTGA) and IgA endomysial antibodies (EMA), with further referral to a gastrointestinal specialist for endoscopic intestinal biopsy to definitively confirm or exclude coeliac disease. There is emerging evidence on the clinical utility of other

tests and diagnostic strategies, such as deamidated gliadin peptides (DGP), point of care tests and the use of combined serological tests to definitively diagnose coeliac disease without carrying out endoscopic intestinal biopsy.

The treatment of coeliac disease is a lifelong gluten-free diet. Adherence to a gluten-free diet has repeatedly been shown to be poor, with 20% to 80% of people with coeliac disease admitting to either occasional or prolonged lapses. Specific education and information, such as advice and education on alternative foods in the diet to maintain a healthy and varied intake, which could be provided by a dietitian with experience in coeliac disease, may increase the likelihood of adherence and a positive prognosis.

People with coeliac disease are at risk of complications and may have other coexisting conditions. The follow-up care of people with coeliac disease after the diagnosis varies widely within the UK ranging from follow-up care in specialist clinics to being discharged back to the community without any provision of a follow-up service.

The majority of people with coeliac disease report a rapid clinical improvement after starting a gluten-free diet. However, 5% to 30% do not report symptomatic improvement after starting treatment, and some will still have persisting symptoms after 6 to 12 months. There is currently no conclusive guidance on differential diagnosis of non-responsive coeliac disease, such as infective gastroenteritis, intestinal bacterial overgrowth, lactose intolerance, intestinal lymphoma, and other immunodeficiency conditions. Approximately 10% of people with non-responsive coeliac disease will have true refractory coeliac disease. The management of people with refractory coeliac disease currently varies widely within the UK.

1.4 Population

This guideline covers the following groups:

- Children, young people and adults with symptoms or signs suggestive of coeliac disease.
- Children, young people and adults with confirmed coeliac disease.
- Children, young people and adults considered to be at high risk of coeliac disease. This includes people with autoimmune conditions such as type 1

diabetes and autoimmune thyroid disease, or those with a first-degree family history of coeliac disease.

- Specific subgroups in whom the investigation and management of coeliac disease is known to be different.

The following groups are not covered within this guideline:

- Children, young people and adults with other gastrointestinal disorders (the guideline will only cover differential diagnosis of non-responsive coeliac disease).
- People with non-coeliac disease gluten sensitivity.

For the purposes of the guideline populations have been defined in the following way: children are those below age 16, young people are those aged 16 and 17 years, and adults are those aged 18 years and over.

1.5 Healthcare setting

All settings where NHS healthcare is commissioned or delivered (including a person's home).

1.6 Medicines

The guideline will assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

1.7 Patient-centred care

This guideline offers best practice advice on the care of children (below age 16), young people (16 - 17 years of age) and adults (18 years and over) with suspected or confirmed coeliac disease.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. If it is clear that the child or young person fully understands the treatment and does not want their

family or carers to be involved, they can give their own consent. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with coeliac disease. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

2 Summary section

2.1 Guideline update

This guidance is a full update of NICE Clinical Guideline 86 (published May 2009) and will replace it in its entirety. All evidence from the previous guideline has been reviewed against the updated inclusion and exclusion criteria and analysed as appropriate. All recommendations from the previous guideline have been stood-down and replaced during the updated evidence review.

New recommendations have been made for the diagnosis, treatment, monitoring, and education of people with coeliac disease

You are invited to comment on the new and updated recommendations in this guideline.

The original NICE guideline and supporting documents are available [here](#).

2.2 Guideline development group members

Guideline development group

Name	Role
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Name	Role
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Susan Spiers (from June 2014)	Associate director
Heather Stegenga (until February 2014)	Technical analyst
Toni Tan (until March 2014)	Technical adviser

2.3 Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer...') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

2.4 Key priorities for implementation

The following recommendations have been identified as priorities for implementation. The full list of recommendations is in section 2.5.

Offer serological testing for coeliac disease to:

- People with any of the following:
 - persistent unexplained abdominal or gastrointestinal symptoms
 - faltering growth
 - prolonged fatigue
 - unexpected weight loss
 - severe or persistent mouth ulcers
 - unexplained iron, vitamin B12 or folate deficiency
 - type 1 diabetes, at diagnosis
 - autoimmune thyroid disease, at diagnosis
 - irritable bowel syndrome (in adults).

- First-degree relatives of people with coeliac disease). **[Recommendation 1]**

When healthcare professionals request serological tests to investigate suspected coeliac disease in young people and adults, laboratories should:

- Test for total immunoglobulin A (IgA) and IgA tissue transglutaminase (tTG) as the first choice
- Use IgA endomysial antibodies (EMA) if IgA tTG is weakly positive
- Consider using IgG EMA, IgG deamidated gliadin peptide (DGP) or IgG tTG if IgA is deficient^a **[Recommendation 5]**

When healthcare professionals request serological tests to investigate suspected coeliac disease in children, laboratories should:

- Test for total IgA and IgA tTG, as the first choice.
 - Consider using IgG EMA, IgG DGP or IgG tTG if IgA is deficient^a
- [Recommendation 6]**

Offer an annual review to people with coeliac disease. During the review:

- Measure weight and height
- Review symptoms
- Consider the need for assessment of diet and adherence to the gluten-free diet
- Consider the need for specialist dietetic and nutritional advice

[Recommendation 17]

Consider the following actions in people with coeliac disease who have persistent symptoms despite advice to exclude gluten from their diet:

- Review the certainty of the original diagnosis.
- Refer the person to a specialist dietitian to investigate continued exposure to gluten.
- Investigate potential complications or coexisting conditions that may be causing persistent symptoms, such as irritable bowel syndrome, lactose intolerance, bacterial overgrowth, microscopic colitis or inflammatory colitis.

[Recommendation 19]

For people undergoing investigations for coeliac disease:

^a IgA deficiency is defined as total IgA less than 0.07 g per litre

- explain that any test is accurate only if a gluten-containing diet is eaten during the diagnostic process **and**
- advise the person not to start a gluten-free diet until diagnosis is confirmed by a specialist, even if the results of a serological test are positive. **[Recommendation 24]**

A healthcare professional with a specialist knowledge of coeliac disease should 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 give them information to help them follow it. This should include:

- information on which types of food contain gluten and suitable alternatives, including gluten-free substitutes
- explanations of food labelling
- information sources about gluten-free diets, recipe ideas and cookbooks
- how to manage social situations, eating out and travelling away from home, including travel abroad
- avoiding cross contamination in the home and minimising the risk of accidental gluten intake when eating out
- the role of national and local coeliac support groups. **[Recommendation 29]**

2.5 Full list of recommendations

The following guidance is based on the best available evidence. Full details of the methods and the evidence used to develop the guidance are provided in section 3.

2.5.1 Evidence for the recognition of coeliac disease

1. Offer serological testing for coeliac disease to:

- People with any of the following:
 - persistent, unexplained abdominal or gastrointestinal symptoms
 - faltering growth
 - prolonged fatigue
 - unexpected weight loss
 - severe or persistent mouth ulcers
 - unexplained iron, vitamin B12 or folate deficiency
 - type 1 diabetes, at diagnosis

- o autoimmune thyroid disease, at diagnosis
 - o irritable bowel syndrome (in adults).
 - First-degree relatives of people with coeliac disease.
- 2. Consider serological testing for coeliac disease in people with any of the following:**
- metabolic bone disorder (reduced bone mineral density or osteomalacia)
 - unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
 - unexplained subfertility or recurrent miscarriage
 - persistently raised liver enzymes with unknown cause
 - dental enamel defects
 - Down's syndrome
 - Turner syndrome.
- 3. Advise people who have tested negative for coeliac disease, particularly first-degree relatives and people with type 1 diabetes, that:**
- coeliac disease may present with a wide range of symptoms **and**
 - they should consult their healthcare professional if any of the symptoms listed in recommendations 1 or 2 arise or persist.

2.5.2 Evidence for serological testing for coeliac disease

- 4. All serological tests should be undertaken in laboratories with clinical pathology accreditation (CPA) or ISO15189 accreditation.**
- 5. When healthcare professionals request serological tests to investigate suspected coeliac disease in young people and adults, laboratories should:**
- test for total immunoglobulin A (IgA) and IgA tissue transglutaminase (tTG) as the first choice
 - use IgA endomysial antibodies (EMA) if IgA tTG is weakly positive
 - consider using IgG EMA, IgG deamidated gliadin peptide (DGP) or IgG tTG if IgA is deficient^a.
- 6. When healthcare professionals request serological tests to investigate suspected coeliac disease in children, laboratories should:**
- test for total IgA and IgA tTG, as the first choice
 - consider using IgG EMA, IgG DGP or IgG tTG if IgA is deficient^a.
- 7. When laboratories test for total IgA, a specific assay designed to measure total IgA levels should be used.**
- 8. Refer young people and adults with positive serological test results^b to a gastrointestinal specialist for endoscopic intestinal biopsy to confirm or exclude coeliac disease.**

^b In young people and adults, a positive serological test result is defined as unambiguously positive IgA tTG alone, or weakly positive IgA tTG and a positive IgA EMA test result. Note: In people who have IgA deficiency, a serologically positive result can be derived from any one of the IgG antibodies.

- 9. Refer children with positive serological test results to a paediatric gastroenterologist or paediatrician with a specialist interest in gastroenterology for further investigation^c for coeliac disease.**
- 10. Refer people with negative serological test results to a gastrointestinal specialist for further assessment if coeliac disease is still clinically suspected.**
- 11. Healthcare professionals should have a low threshold for re-testing people identified in recommendations 1 or 2 if they develop any symptoms consistent with coeliac disease.**
- 12. Laboratories should clearly communicate the interpretation of serological test results and recommended action to healthcare professionals.**
- 13. Do not use human leukocyte antigen (HLA) DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the initial diagnosis of coeliac disease in non-specialist settings.**
- 14. Only consider using HLA DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the diagnosis of coeliac disease in specialist settings (for example, in children who are not having a biopsy, or in people who already have limited gluten ingestion and choose not to have a gluten challenge).**
- 15. Consider referring people with coeliac disease for endoscopic intestinal biopsy if continued exposure to gluten has been excluded and:**
 - serological titres are persistently high and show little or no change after 12 months **or**
 - they have persistent symptoms, including diarrhoea, abdominal pain, weight loss, fatigue or unexplained anaemia.
- 16. Do not use serological testing alone to determine whether gluten has been excluded from the person's diet.**
- 17. Offer an annual review to people with coeliac disease. During the review:**
 - measure weight and height
 - review symptoms
 - consider the need for assessment of diet and adherence to the gluten-free diet
 - consider the need for specialist dietetic and nutritional advice
- 18. Refer the person to a GP or consultant if concerns are raised in the annual review. The GP or consultant should assess all of the following:**
 - the need for a dual-energy X-ray absorptiometry (DEXA) scan (in line with the NICE guideline on [osteoporosis: assessing the risk of fragility fracture](#)) or active treatment of bone disease
 - the need for specific blood tests
 - the risk of long-term complications and comorbidities
 - the need for specialist referral.

^c Further investigation may include, but is not limited to, one or more of the following: an IgA EMA test to confirm serological positivity, HLA genetic testing, an endoscopic biopsy.

2.5.3 Evidence for non-responsive and refractory coeliac disease

19. **Consider the following actions in people with coeliac disease who have persistent symptoms despite advice to exclude gluten from their diet:**
 - review the certainty of the original diagnosis
 - refer the person to a specialist dietitian to investigate continued exposure to gluten
 - investigate potential complications or coexisting conditions that may be causing persistent symptoms, such as irritable bowel syndrome, lactose intolerance, bacterial overgrowth, microscopic colitis or inflammatory colitis.
20. **Diagnose refractory coeliac disease if the original diagnosis of coeliac disease has been confirmed, and exposure to gluten and any coexisting conditions have been excluded as the cause of continuing symptoms.**
21. **Refer people with refractory coeliac disease to a specialist centre for further investigation.**
22. **Consider prednisolone for the initial management of the symptoms of refractory coeliac disease in adults while waiting for specialist advice.**

2.5.4 Evidence for information and support related to coeliac disease

23. **Do not offer serological testing for coeliac disease in infants before gluten has been introduced into the diet.**
24. **For people undergoing investigations for coeliac disease:**
 - explain that any test is accurate only if a gluten-containing diet is eaten during the diagnostic process **and**
 - advise the person not to start a gluten-free diet until diagnosis is confirmed by a specialist, even if the results of a serological test are positive.
25. **Advise people who are following a normal diet (containing gluten) to eat some gluten in more than 1 meal every day for at least 6 weeks before testing.**
26. **If people who have restricted their gluten intake or excluded gluten from their diet are reluctant or unable to re-introduce gluten into their diet before testing:**
 - refer the person to a gastrointestinal specialist **and**
 - explain that it may be difficult to confirm their diagnosis by intestinal biopsy.
27. **Explain to people who are thought to be at risk of coeliac disease that a delayed diagnosis, or undiagnosed coeliac disease, can result in continuing ill health and serious long-term complications.**
28. **Give people with coeliac disease (and their family members or carers, where appropriate) sources of information on the disease, including national and local specialist coeliac groups and dietitians with a specialist knowledge in coeliac disease.**

29. A healthcare professional with a specialist knowledge of coeliac disease should 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 give them information to help them follow it. This should include:

- information on which types of food contain gluten and suitable alternatives, including gluten-free substitutes
- explanations of food labelling
- information sources about gluten-free diets, recipe ideas and cookbooks
- how to manage social situations, eating out and travelling away from home, including travel abroad
- avoiding cross contamination in the home and minimising the risk of accidental gluten intake when eating out
- the role of national and local coeliac support groups.

30. Be aware that people with coeliac disease may experience anxiety and depression. Diagnose and manage these issues in line with the following NICE guidelines:

- [Depression in adults with a chronic physical health problem](#)
- [Depression in children and young people](#)
- [Generalised anxiety disorder and panic disorder \(with or without agoraphobia\) in adults.](#)
- [Social anxiety disorder](#)

2.5.5 Evidence for advice on dietary management of coeliac disease

31. Advise people with coeliac disease (and their family members or carers, where appropriate) to seek advice from a member of their healthcare team if they are thinking about taking over-the-counter vitamin or mineral supplements.

32. Explain to people with coeliac disease (and their family members or carers, where appropriate) that they may need to take specific supplements such as calcium or vitamin D if their dietary intake is insufficient.

33. Explain to people with coeliac disease (and their family members or carers, where appropriate) that:

- they 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.

2.6 Key research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the corresponding sections below.

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

Why this is important

IgA deficiency is significantly more common in people with coeliac disease than in the general population. People with IgA deficiency will have a false negative result when tested for IgA antibody, which may lead to a missed diagnosis of coeliac disease. A missed diagnosis may result in increased use of NHS resources and the person experiencing the risks associated with undiagnosed coeliac disease. IgG antibodies are recommended for use in place of IgA antibodies in people who have IgA deficiency, but there is limited evidence to demonstrate the sensitivity and specificity of tests for IgG antibodies – that is, IgG tTG, IgG EMA and IgG DGP – in people suspected of having coeliac disease with IgA deficiency.

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?

Why this is important

In people with suspected coeliac disease, IgA tTG is most commonly used as the first-choice test to detect the presence of coeliac disease antibodies but some people with coeliac disease will get a false negative result. If this happens, and if there is a strong and ongoing clinical suspicion of coeliac disease, serological testing for IgA EMA or IgA or IgG DGP antibodies should also be requested. However, there is little evidence for the sensitivity and specificity of these antibodies in people who have tested negative for IgA tTG antibodies. A clearer understanding of the sensitivity and specificity of EMA and DGP antibodies in people who have tested negative for IgA tTG will allow clinicians to better interpret test results and make a more informed diagnosis.

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

Why this is important

People with coeliac disease are at an increased risk of malabsorption of key nutrients such as calcium and vitamin D. This is because of the role gluten plays in preventing these nutrients from being properly absorbed. It is not known how long the body takes to properly absorb these vitamins and minerals once a gluten-free diet is started. It is also not known whether the majority of people diagnosed with coeliac disease have enough calcium and vitamin D in their diet, or whether some people with coeliac disease are able to get enough of these nutrients from what they eat. Answering this research question will help healthcare professionals to understand whether calcium and vitamin D should be offered to everyone at the time of diagnosis and for how long these vitamin and mineral supplements should be taken.

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

Why this is important

As a gluten-free diet is the primary treatment option for people with coeliac disease, it is important that a dietitian with a specialist interest in coeliac disease should play a significant role in their care and follow up. Many of the common problems associated with the long-term management of coeliac disease happen because of non-adherence to a gluten-free diet. It is important to explore how to maximise the effectiveness of the dietitian's role in helping people with coeliac disease to adhere to a gluten-free diet.

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

Why this is important

It is currently not known how often people with coeliac disease should have their condition monitored. No research has adequately investigated the effectiveness of different monitoring

frequencies. There is variation across the UK in how often people with coeliac disease have their condition monitored. Further research within this area is important to ensure that people with coeliac disease are having their condition adequately monitored.

3 Methods

This guideline was developed in accordance with the process set out in 'The guidelines manual (2012)'. There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available. In instances where the guidelines manual does not provide advice, additional methods are used and are described below.

3.1 Developing review questions and protocols and identifying evidence

The technical team drafted review questions which were refined and validated by the GDG, using a Population, Intervention, Comparator, Outcome (PICO) framework, and drafted review protocols based on the topics agreed with the stakeholders and included in the scope (see Appendix B) and prepared a protocol for each review question (see Appendix C). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix C) to the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards), and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases, the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database.

Where a question was updated directly from CG68 the search strategies used in the CG68 were updated. However for the review question on signs and symptoms, coexisting conditions and first-degree relatives and long-term consequences, the GDG requested some new search for additional terms and these additional searches had no date restriction. No date restrictions were placed on the searches for all new questions.

Searches in Embase and Medline were limited to English language and studies in humans. None of the other searches were limited by language of publication (although publications in languages other than English were not reviewed). Validated search filters were used to identify particular study designs, such as RCTs. There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching undertaken of journals not indexed on the databases.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 5th December 2014.

3.2 Outcomes

The outcomes prioritised in the review questions and protocols reflect the treatment objectives outlined in each question. The minimum important difference (MID) for both dichotomous and continuous outcomes would be decided by looking at appropriate published evidence or under agreement with the GDG following discussion within committee meetings. On the occasion that no published literature on the minimal important difference was identified and the GDG were unable to specify on a default option was used, for example, in the case of dichotomous outcomes was defined as a relative risk reduction or an increase of 25% or more to be considered clinically important.

For this guideline, the effectiveness of interventions/diagnostic strategies to manage coeliac disease has been assessed against a variety of outcomes. The justification for using these outcomes is based on their relevance to people with the condition and the expert consensus

opinion of members of the multidisciplinary GDG. When assessing the effectiveness of a particular treatment, information about the effect of that treatment on one or more primary outcomes was sought.

3.3 Process

3.3.1 Study identification

Identified titles and abstracts were sifted for relevance and data were extracted by 1 reviewer. A second reviewer checked a random 10% of sifted out titles and abstracts, and all excluded studies with the reason for exclusion, and all data extracted for the included studies.

3.3.2 Data extraction

Basic characteristics of each included study were summarised into standardised evidence tables for each review question (see Appendix D) along with the quality assessment of the evidence. Where outcome data were presented, results were entered as reported in the full-text report of the study.

Some studies were excluded from the guideline reviews after obtaining copies of the publications because they did not meet inclusion criteria specified by the GDG (see Appendix C). These studies are listed in alphabetical order for each question and the reason for exclusion provided for each one.

Missing continuous data

Where the standard deviation of the mean change from baseline was not reported, we imputed this using either the baseline standard deviation (SD) from the control group or the SD from a similar group.

When the standard deviation of the point estimate at study end was not reported, we imputed this using either the baseline standard deviation (SD) from the control group or the SD from a similar group.

Missing dichotomous data

Where the raw numbers for an outcome were not reported and a percentage was reported, the raw numbers were calculated manually from the reported percentage. When a decimal was calculated the number was rounded up if the decimal was over 0.5 and down if below 0.5.

When the outcome is negative (for example, adverse effects or failure rate) the denominator used equalled the total number of the study arm. When the outcome is positive (for example, effectiveness) the denominator used was the number completing in the study arm.

Quality assessment checklists

For randomised controlled trials, the NICE methodological checklist for RCT's was used for quality assessment of the evidence. For cohort studies, the NICE methodological checklist for cohort study was used for quality assessment. For diagnostic studies, the QUADAS checklist was used for quality assessment. For qualitative studies, the CASP checklist for qualitative research design was used for quality assessment. For prognostic studies, a prognostic study checklist designed by Hayden and colleagues (2006) was used.

3.3.3 Meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For continuous outcomes, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis.

Dichotomous outcomes were presented as relative risks (RRs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences with 95% CIs or SDs.

Software

Data for intervention reviews were analysed using Review Manager 5.1 while data for diagnostic reviews was analysed using Meta Disk. An online calculator <http://vassarstats.net/prop1.html> was used to calculator confidence intervals around proportions for single studies.

3.3.4 GRADE process

The body of evidence identified for each therapy or treatment review question (or part of a review question) was presented in the form of a GRADE evidence profile summarising the quality of the evidence and the findings (pooled relative and absolute effect sizes and associated CIs). Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled risk ratios (RRs), pooled odds ratios (ORs), or mean differences. A random-effects model was used as default.

Where quantitative meta-analysis could not be undertaken, the range of effect sizes reported in the included studies was presented in a GRADE profile.

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'The guidelines manual (2012)'. The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well conducted systematic review or meta-analysis of RCTs, or an individual RCT. In the GRADE approach, a body of evidence based on RCTs has an initial quality rating of high, but this may be downgraded to moderate, low or very low if the factors listed above are not addressed adequately. For diagnostic review questions on prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case-control study), and a body of evidence based on such studies would have an initial quality rating of low, which might be downgraded to very low or upgraded to moderate or high, depending on the factors listed above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis or RCT was identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought.

GRADE profiles for interventional evidence

The quality ratings for each study are reported the study's evidence table and are summarised in the footnotes of each GRADE profile. For this guideline, we inserted footnotes to explain the choice we made while assessing the quality of evidence for each outcomes. These footnotes indicated if we upgraded the evidence level, downgraded the evidence level or left the evidence level unchanged, and gave the rationale for doing this.

The quality of the evidence for each outcome was downgraded where appropriate for the reasons outlined in Table 1.

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Example reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about the design or execution of the study, including concealment of allocation, blinding, loss to follow up using intervention checklists in the NICE guidelines manual (2012)
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the statistic, I^2 where ; $I^2 < 33\%$ was categorised as no inconsistency, I^2 between 34% and 66% was categorised as serious inconsistency and $I^2 > 67\%$ was categorised as very serious inconsistency
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is a minimal important difference. This reflects the confidence in the estimate of effect.
Other considerations	Providing no downgrading for other features has occurred, the quality of the evidence could be upgraded if there was evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect.

3.3.4.1 Modified GRADE for diagnostic evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework.

Cohort studies within the GRADE approach start at the low quality level due to accepted inherent study design limitations. Within a modified approach, where evidence from cohort studies has been deemed to be the most appropriate source of information to answer a given review question, studies start from a presumption of 'high quality' The same criteria (risk of bias, inconsistency, imprecision and indirectness) were used to downgrade the quality of evidence as detailed in Table 2 below.

Table 2: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Example reasons for downgrading quality
Risk of bias	This includes limitations in the design or execution of the study, including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating)
Inconsistency	The quality of the evidence was downgraded if there were concerns about Inconsistency of effects across studies: This was assessed using the statistic, I^2 where ; $I^2 < 33\%$ was categorised as no inconsistency, I^2 between 34% and 66% was categorised as serious inconsistency and $I^2 > 67\%$ was categorised as very serious inconsistency (this can reduce the quality rating)
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if there is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is minimal important difference. This reflects the confidence in the estimate of effect.
Other considerations	Providing no downgrading for other features has occurred, the quality of the evidence could be upgraded if confounding variables likely to have reduced

GRADE criteria	Example reasons for downgrading quality
	the magnitude of an effect.

3.3.4.2 Modified GRADE for qualitative studies

GRADE has not been developed for use with qualitative studies; therefore a modified approach was applied using the GRADE framework.

Qualitative studies within the non-modified GRADE approach start at the very low quality level due to accepted inherent study design limitations. Within a modified approach where qualitative evidence has been deemed to be the most appropriate source of information to answer a given review question, it is acceptable to initially indicate a high quality level to this study type and to assess the quality of evidence from this point. The same criteria (risk of bias, inconsistency, imprecision and indirectness) were used to downgrade the quality of evidence as detailed in Table 3 below.

Table 3: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Example reasons for downgrading quality
Risk of bias	This includes limitations in the design or execution of the study, including risk of interviewer leading the interviewee or failing to record responses verbatim, or loss to follow up (these can reduce the quality rating)
Inconsistency	Inconsistency of estimate of effect between studies was deemed not applicable to qualitative evidence
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	Imprecision of estimate of effect was deemed not applicable to qualitative evidence
Other considerations	The quality of the evidence was downgraded if there is a large magnitude of effect, confounding variables likely to have reduced the magnitude of an effect; these can increase the quality ratings in observational studies, provided no downgrading for other features has occurred

3.4 Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions, with the exception of those detailed in sections 4.1, 4.2 and 4.3 (which provided data for the health economic question considered in section 4.4) and 7.1 and 7.2 (which were information questions without a substantive health economic component). In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. Search strategies are provided in full in Appendix C. In assessing studies for inclusion, population, intervention and comparator criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies; these are shown in Appendix G.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2012; Appendix E). This checklist is not intended to judge the quality of a study per se, but to determine whether an

existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the guideline. There are two parts of the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table 4).

Table 4: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table 5).

Table 5: Methodological criteria

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Original health economic modelling was conducted for 3 questions that were prioritised by the GDG for detailed analysis: order and sequencing of serological tests (see section 5.2), active case-finding (see section 4.4) and dietetic involvement in follow-up (considered as part of the review on frequency of follow-up; see section 5.4). Each analysis relied on broadly the same model, which was originally developed for the serological testing question and subsequently modified to address other questions. Full details of the methods of the models are provided in Appendix G.

In questions for which no published evidence was identified and original analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering potential differences in resource use and cost between the options alongside the results of the review of evidence of clinical effectiveness

3.5 Agreeing the recommendations

For each review question, recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the guideline development group to agree short clinical and, where appropriate, cost effectiveness evidence statements, which were presented alongside the evidence profiles. Statements summarising the guideline development group's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The 'Linking evidence to recommendations' (LETR) criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered

- consideration of the clinical benefits and harms
- consideration of net health benefits and resource use
- quality of the evidence
- other considerations (including equalities issues).

In areas where no substantial clinical research evidence was identified, the guideline development group considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on guideline development group consensus in relation to the likely cost effectiveness implications of the recommendations. The guideline development group also identified areas where evidence to answer their review questions was lacking and used this information to formulate recommendations for future research

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations are based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences. This discussion should help the patient reach a fully informed decision. Terms used within this guideline are:

- 'Offer' – for the vast majority of patients, an intervention will do more good than harm
- 'Do not offer' – the intervention will not be of benefit for most patients
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Towards the end of the guideline development process, formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The guideline development group identified up to 10 'key priorities for implementation' (key recommendations) and 5 high-priority research recommendations.

4 Evidence for the recognition of coeliac disease

4.1 Signs & symptoms

4.1.1 Review question

What are the clinical signs and symptoms that raise suspicion of coeliac disease?

4.1.2 Methods

The aim of this review question was to establish which presenting clinical features may raise suspicion about the presence of coeliac disease and the need for serological testing. This is an update of the chapter on 'clinical signs and symptoms of coeliac disease' in the 2009 guideline for coeliac disease (CG86). This updated review incorporates studies that were included in the previous guideline together with newly-published evidence.

Studies were considered if they met the following inclusion criteria: the population examined was children, young people, or adults with undiagnosed coeliac disease who presented with clinical signs and symptoms that may raise suspicion for the disease; coeliac disease diagnosis was confirmed by intestinal biopsy. Studies were excluded from analyses if people were receiving treatment for coeliac disease at the time of testing; if the diagnosis of coeliac disease was not confirmed by intestinal biopsy; if the population of interest had non-coeliac gluten sensitivity or wheat allergy.

An exhaustive list of clinical signs and symptoms was suggested by the GDG within the review protocol (see Appendix C) prior to conducting the literature searches for this review question. The comparator was a biopsy-confirmed diagnosis of coeliac disease. The outcome of interest was the diagnostic utility of the odds ratio of having coeliac disease, given the presence of a particular sign or symptom, compared to the odds of not having the disease in the absence of that sign or symptom.

Case-control studies were considered the most appropriate study design to derive signs and symptoms odds ratios for this question and were therefore considered the highest quality within a modified GRADE framework. All other study designs were downgraded from this review, including cohort studies, case-reports, case series, and qualitative studies. Studies could be downgraded due to reasons such as imprecision of odds ratio metrics, the presence of study bias, or inconsistency of effect estimates between studies.

Included studies

A single systematic search was conducted for sections 4.1, 4.2, and 4.3 (see Appendix C) which identified 7230 references. This search was restricted to studies published from 2008 onwards to avoid duplicates of studies considered in the previous coeliac disease guideline (CG86). The references were screened on their titles and abstracts and full papers of 134 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

Overall, 128 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (case-series), not a primary study (descriptive narrative, opinion, etc.), examined the prevalence of coeliac disease in certain populations, studies in which the study population was not suspected of coeliac disease (but may have had an increased risk for developing coeliac disease, such as a commonly comorbid condition, or a family history of coeliac disease), and studies which did not use Marsh grade 3 for the histological

diagnosis of coeliac disease. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

The 6 remaining published papers did meet the eligibility criteria and were included. Data was extracted into detailed evidence tables (see Appendix D) and are summarised below. Two published papers (Olen et al., 2008; Mollazadegan et al., 2009) utilised the same database of Swedish men who underwent medical testing prior to and post conscription. Three published papers (Olen et al., 2008; Mollazadegan et al., 2009; Ludvigsson et al., 2013) also utilised the same control database of Swedish national register of patient information.

The 11 included studies in the previous coeliac disease guideline (CG86) were reviewed against the current protocol. Of these, all were excluded as they did not meet eligibility criteria. Primary reasons for exclusion included inappropriate study design, such as prevalence studies; populations that were already being treated for coeliac disease at the time of inclusion, or who were examined for a sign or symptom after the diagnosis of coeliac disease, and studies in which coeliac disease diagnosis was not biopsy-confirmed.

The overall quality of the evidence from these published papers ranged from very low to moderate, with the majority of evidence to be of low quality.

4.1.3 Evidence review

4.1.3.1 Intussusception in adults

One large nation-wide population study (Ludvigsson et al., 2013) examined the relationship between intussusception and coeliac disease in a group of newly-diagnosed coeliac disease patients (n=29096; mean age 30 years) and healthy control participants (n=144522; age-matched). The prevalence of intussusception was very low in both the coeliac (0.12%) and control (0.10%) groups.

4.1.3.2 Low BMI in adults

One large study (Olen et al., 2009) identified adult males with or without coeliac disease through a national inpatients register of men who were admitted to hospital immediately prior to or post conscription. This study was broken down into two parts; a cohort study and case-control study. Only case-control study data examining the association between low BMI and coeliac disease was used in this analysis. In order to be eligible for the study, data on weight and height had to have been available at the time of study. Only data for those diagnosed with coeliac disease after review of weight and BMI were included in the analyses (n=70; age range 18-50 years). Controls were identified via a government total population register and were matched to patients for age, sex, and country of residence (n=6887; age range 18–50 years).

4.1.3.3 Impaired visual acuity in adults

One large study (Mollazadegan et al., 2009) identified adult males with or without coeliac disease through a national inpatients register of men who were admitted to hospital immediately prior to or post conscription. This study was broken down into two parts; a cohort study and case-control study. Only case-control study data examining the association between impaired visual acuity and coeliac disease was used in this analysis. In order to be eligible for the study, data on visual acuity had to have been available at the time of study. Only data for those diagnosed with coeliac disease after review of visual acuity were included in the analyses (n=69; mean age 18.9 years). Controls were identified via a government total population register and were matched to patients for age, sex, and country of residence (n=6850; mean age 18.7 years).

4.1.3.4 Migraine in children and young adults

Two studies were identified (Alehan et al., 2008; Inaloo et al., 2011) that examined the association between migraine and coeliac disease. Alehan and colleagues (2008) examined the prevalence of coeliac disease in a population of paediatric patients with migraine (n=73; mean age 12.01 years) and healthy control participants (n=147; mean age 11.85 years). One case (0.7%) was identified in the control group, and 4 cases (5.55%) with coeliac disease were identified in the migraine group. Inaloo and colleagues (2011) similarly examined the prevalence of coeliac disease in a population of paediatric migraine patients (n=100; mean age 9.5 years) and healthy control participants (n=1500; mean age 10.6 years). Equal prevalence estimates (2%) of coeliac disease were reported for both the patient and control groups.

4.1.3.5 Dental enamel defects in children and young adults

One study (El-Hodhod et al., 2012) examined the frequency of coeliac disease in paediatric patients with dental enamel defects (n=140; mean age 8.33 years) and healthy controls (n=720; age range 4-12 years). The control children were recruited as part of their routine annual health check in the local children's hospital as part of the well child clinic. All participants underwent an oral hygiene and dental examination and IgA and IgG tTG serological testing for coeliac disease. Positive serological results were followed-up with an endoscopic intestinal biopsy to confirm or exclude the presence of coeliac disease.

4.1.4 Health economic evidence

An economic literature search was not conducted for this question as an economic evaluation would not be the correct framework in which to generate useful evidence on the signs and symptoms of coeliac disease.

4.1.5 Evidence statements

4.1.5.1 Evidence for the relationship between intussusception and coeliac disease in adults

One very low quality published paper (Ludvigsson et al., 2013) of 173618 adults reported no association between coeliac disease and intussusception (OR 1.18, 95% CI: 0.81 to 1.71).

4.1.5.2 Evidence for the relationship between low BMI and coeliac disease in adults

One very low quality study (Olen et al., 2009) of 6957 adult males reported a trend toward an association between low BMI (<18.5) and coeliac disease compared to a healthy age and gender matched population (OR 2.2, 95% CI: 1.0 to 4.8); however as the lower confidence interval lies on 1.0, this was not statistically significant. .

4.1.5.3 Evidence for the relationship between visual acuity and coeliac disease in adults

One very low quality published paper (Mollazedagen et al., 2009) of 6957 adults males reported no associated between impaired visual acuity and coeliac disease compared to a healthy age and gender matched population (OR 1.04, 95% CI: 0.9 to 1.19).

4.1.5.4 Evidence for the relationship between migraine and coeliac disease in children and young adults

One very low quality study (Alehan et al., 2008) of 220 children and adolescents reported an association between migraine and coeliac disease compared to a healthy age and gender matched population (OR 8.46, 95% CI: 0.92 to 77.15); however this association was not statistically significant. A further very low quality study (Inaloo et al., 2011) of 1600 children

and adolescents reported no such association between the presence of migraine and coeliac disease (OR 1.00, 95% CI: 0.23 to 4.24).

4.1.5.5 Evidence for the relationship between dental enamel defects and coeliac disease in adults

One very low quality study (El-Hodhod et al., 2012) of 860 children and young adults reported a significant association between the presence of dental enamel defects and coeliac disease compared to a healthy age and gender matched population (OR 9.36, 95% CI: 9.36 to 52.39).

4.1.6 Evidence to recommendations

All four sub-questions relating to the evidence for the recognition of coeliac disease were presented in tandem and discussed together. Therefore, the linking evidence to recommendation information will be presented for all four components of this question at the end of this chapter.

4.1.7 Recommendations & research recommendations

All four sub-questions relating to the evidence for the recognition of coeliac disease were presented in tandem and discussed together. Therefore, the associated recommendations will be presented for all four components of this question at the end of this chapter.

4.2 Populations at increased risk of coeliac disease

4.2.1 Review question

What populations are at an increased risk of developing coeliac disease?

There is evidence to suggest that certain populations are at an increased risk of developing coeliac disease. It is necessary to identify these populations so that appropriate consideration for serological testing for coeliac disease can be made.

4.2.2 Methods

This review question concerns the identification of possible subgroups of people with coeliac disease. The aim of considering coexisting conditions was to examine whether people with certain conditions have a higher rate of coeliac disease than the general population while the estimation of familial risk is essential in a genetics-based condition such as coeliac disease. This focus on improving the identification of people with possible asymptomatic coeliac disease may also include active case finding in particular subgroups with a higher risk of coeliac disease. Included studies examined the presence of the following:

- Coexisting diseases
- Other factors (i.e. first-degree relatives)

The prevalence of coeliac disease in the populations studied was compared to a general population prevalence of 1.0%. An increased risk of coeliac disease is indicated when the confidence intervals around the prevalence in the population subgroup are all above 1.0% whereas the point estimate and confidence interval below 1.0% or crossing 1.0% indicates no increased risk compared to the general population.

4.2.3 Evidence review

A single systematic search was conducted for sections 4.1, 4.2, and 4.3 (see Appendix C) which identified 7230 references. This search was restricted to studies published from 2008 onwards to avoid duplicates of studies considered in the previous coeliac disease guideline (CG86). The references were screened on their titles and abstracts and full papers of 336 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

Overall, 69 studies which examined the prevalence of coeliac disease in other conditions or first-degree relatives were included (see Appendix C). The remaining 267 studies were excluded. Reasons for exclusion are listed in Appendix F.

Description of included studies

Addison's disease

A single study (Fichna et al., 2010) investigated 85 adults with autoimmune Addison's disease. The age of study participants ranged from 18 to 82 years and 61 (71.8%) were female.

Arthritis

Three studies (Atzeni et al., 2008; Coacciloli et al., 2010; Francis et al., 2002) investigated a total of 222 adults with arthritis. The age of study participants ranged from 20 to 84 years and in total 147 (66.2%) were female. 195 (87.8%) had rheumatoid arthritis and 27 (12.2%) had psoriatic arthritis.

Juvenile arthritis

Three studies (George et al., 1996; Lepore et al., 1996; Robazzi et al., 2013) investigated a total of 224 children and young people with juvenile arthritis. The age of study participants ranged from 2 to 16 years and 148 (66.1%) were female.

Cardiomyopathy in children

A single study (De Menzes et al., 2012) investigated 56 children and young people with cardiomyopathy. The age of study participants ranged from 12 months to 18.8 years and 32 (57.1%) were female.

Cardiomyopathy

Three studies (Chicco et al., 2010; Frustaci et al., 2002; Vizzardi et al., 2008) investigated a total of 637 adults with cardiomyopathy. The age of study participants ranged from 28 to 92 years and 206 (32.3%) were female.

Down's syndrome

Five studies (Bonamico et al., 2001; Cerqueira et al., 2010; Goldacre et al., 2004., Pavlovic et al., 2012; Wouters et al., 2009) investigated a total of 2999 children, young people and adults with Down's syndrome. For children and young people the age ranged from 2 months to 18 years while for adults it ranged from 18 years to 59 years. Across all studies 732 (47.3%) were female, however gender was not specified in one study (Goldacre et al., 2004).

Epilepsy or seizures

Four studies (Cronin et al., 1998; Djuric et al., 2010; Peltola et al., 2009; Pratesi et al., 2003) investigated a total of 605 children, young people and adults with epilepsy or seizures. The age of study participants ranged from 12 months to 64 years and 305 (50.4%) were female.

Dyspepsia

A single study (Giangreco et al., 2008) investigated 726 children and adults with dyspepsia. The age of study participants ranged from 8 to 75 years and 44 (6.1%) were female.

Irritable bowel syndrome

Five studies (Cash et al., 2011; Cristofori et al., 2014; El-Salhy et al., 2011; Sanders et al., 2001; Sanders et al., 2003) investigated 3232 children, young people and adults with irritable bowel syndrome. The age of study participants ranged from 4 to 80 years but was not reported in 2 studies (Sanders et al., 2001; Sanders et al., 2003). 1264 (86.6%) were female; however this was not reported in two studies (Sanders et al., 2001; Sanders et al., 2003).

Other Gastrointestinal (GI) conditions

Five studies (Aziz et al., 2010; Casella et al., 2010; Leeds et al., 2007; Lynch et al., 1995; Simondi et al., 2010) investigated 2547 adults with 'other GI conditions'. The age of study

participants ranged from 18 to 80 years and, where reported, 1324 (52.4%) were female, however mean age and gender were not reported in one study (Lynch et al., 1995) and gender was not reported in Cristofori et al., 2014.

Liver disease

Nine studies (Bardella et al., 1997; Chatzicostas et al., 2002; Dickey et al., 1998; Drastich et al., 2012; Eapen et al., 2011; Gatselis et al., 2012; Germenis et al., 2005; Olsson et al., 1982; Thevenot et al., 2007) investigated 2955 adults with liver disease. The age of study participants ranged from 6 to 85 years although age was not reported in 1 study (Olsson et al., 1982). Where reported, 1342 (46.3%) were female, however gender was not reported in 2 studies (Eapen et al., 2011 & Olsson et al., 1982)

Neurological disease

A single study (Ruggieri et al., 2008) investigated 300 children and young people with known neurological disorders. The age of study participants and gender were not reported.

Sarcoidosis

A single study (Papadopoulos et al., 1999) investigated 78 adults with sarcoidosis. The age of study participants ranged from 22 to 81 years and 34 (43.6%) were female.

Sjogren syndrome

A single study (Szodoray et al., 2004) investigated 111 adults with Sjogren syndrome. The age of study participants ranged from 28 to 77 years and gender was not reported.

Systemic sclerosis

A single study (Forbess et al., 2013) investigated 72 adults with systemic sclerosis. Mean age was 51 years (SD = 13) and 66 (88%) were female.

Auto-immune thyroid disease

Three studies (Saatar et al., 2011; Sategna-Guidetti et al., 1998; Spadaccino et al., 2008) investigated 725 children and adults with autoimmune thyroid disease. The age of study participants ranged from 3.1 to 80 years. 612 (84.4%) were female.

Turner syndrome

Four studies (Bonamico et al., 2002; Dias et al., 2010; Frost et al., 2009; Mortensen et al., 2009) investigated 808 girls and women with Turner syndrome. Mean age ranged from 10 months to 61 years.

Type 1 diabetes

Twelve studies (Adlercreutz et al., 2014; Barbato et al., 1998; Cev et al., 2010; Djurić et al., 2010; Galván et al., 2008; Kakleas et al., 2010; Leeds et al., 2011; Pham-Short et al., 2010; Picarelli et al., 2005; Salardi et al., 2008; Smith et al., 2000; Uibo et al., 2010) investigated 9014 children, young people and adults with type 1 diabetes. The age of study participants ranged from 12 months to 70 years and, where reported 3472 (49.5%) were female, however gender was not reported in one study (Salardi et al., 2008).

First-degree relatives

Nine studies (Almeida et al., 2008; Ascher et al., 1997; Biagi et al., 2009; da Silva Kotze et al., 2013; Esteve et al., 2006; Oliveira et al., 2012; Rubio-Tapia et al., 2008; Szaflarska-Szczepanik et al., 2001; Vaquero et al., 2014) investigated 3358 siblings or parents of people with biopsy-confirmed coeliac disease.

4.2.4 Health economic evidence

An economic literature search was not conducted for this question as an economic evaluation would not be the correct framework in which to generate useful evidence on the clinical conditions which can coexist with coeliac disease.

The populations identified within the clinical evidence review will be carried forward for consideration of the cost-effectiveness of obtaining a diagnosis of coeliac disease in these groups – see section 4.4.4.

4.2.5 Evidence statements

This review found that the following population subgroups had an increased risk of coeliac disease compared with the a background population prevalence of 1.0%

- Autoimmune thyroid disease – pooled prevalence of 2.4% (95%CI 1.5 to 3.8%) low quality evidence from 3
- Dyspepsia – prevalence of 2.1% (95%CI 1.3 to 3.4%) low quality evidence from 1 study
- Down's syndrome - pooled prevalence of 3.2% (95%CI 1.3 to 7.4%) low quality evidence from 5 studies
- Epilepsy or seizures – pooled prevalence of 3.6% (95%CI 1.9 to 6.7%) very low quality evidence from 4 studies
- Sjogren syndrome – prevalence of 4.5% (95%CI 1.9 to 10.1%) low quality evidence
- Turner syndrome – pooled prevalence of 5.5% (95%CI 4.1 to 7.4%) low quality evidence from 5 studies
- Type 1 diabetes – pooled prevalence of 6.0% (95%CI 4.0 to 8.9%) low quality evidence from 12 studies; 3.3% (95%CI 2.4 to 4.6%) in 1 UK-based study
- First-degree relatives – pooled prevalence of 8.2% (95%CI 4.6 to 14.3%) low quality evidence from 9 studies

This review found that the following population subgroups were at no increased risk of coeliac disease compared with a background population prevalence of 1.0%

- Addison's disease - 1.2% (95%CI 0.0 to 6.4%).very low quality evidence from 1 study
- Arthritis - pooled prevalence of 3.0% (95%CI 0.8 to 11.0%) low quality evidence from 3
- Juvenile arthritis - pooled prevalence of 2.3% (95%CI 0.9 to 5.3%) very low quality evidence from 3 studies
- Cardiomyopathy - prevalence of 2.2% (95% CI 0.7% to 6.4%) very low quality evidence from a single study
- Cardiomyopathy in children - prevalence of 1.8% (95% CI 0.3% to 9.5%) very low quality evidence from a single study
- Irritable bowel syndrome - pooled prevalence of 1.8% (95%CI 0.7 to 4.7%) low quality evidence from 5 studies; 4.3% (95%CI 2.7 to 6.7) in 2 UK-based studies
- Other gastrointestinal conditions - pooled prevalence of 2.9% (95%CI 0.5 to 16.6%) low quality evidence from 5 studies

- Liver disease - pooled prevalence of 2.0% (95%CI 0.7 to 5.8%) low quality evidence from 9 studies
- Neurological disease - prevalence of 1.1% (95%CI 0.5 to 2.3%) very low quality evidence from a single study
- Sarcoidosis - prevalence of 0% low quality evidence from a single study
- Systemic sclerosis - prevalence of 0% low quality evidence from a single study

4.2.6 Evidence to recommendations

All four sub-questions relating to the evidence for the recognition of coeliac disease were presented in tandem and discussed together. Therefore, the linking evidence to recommendation information will be presented for all four components of this question at the end of this chapter.

4.2.7 Recommendations & research recommendations

All four sub-questions relating to the evidence for the recognition of coeliac disease were presented in tandem and discussed together. Therefore, the associated recommendations will be presented for all four components of this question at the end of this chapter.

4.3 Conditions associated with undiagnosed / untreated coeliac disease

4.3.1 Review question

What are the long-term consequences of undiagnosed or untreated coeliac disease?

It is estimated that only one fifth of those with coeliac disease are currently diagnosed. This indicates that up to four out of every five people with coeliac disease are currently untreated and at risk of serious long-term health complications. It is imperative to understand the nature of these long-term complications in order to understand the risks of untreated CD, particularly in populations who are deemed 'at risk' for this condition, as explored in section 4.2.

4.3.2 Methods

The aim of this question was both to identify information to be provided to people at the time of diagnoses (in the case of untreated coeliac disease) and to identify those long-term consequences of undiagnosed coeliac disease.

The GDG agreed to include studies which used either biopsy, according to Marsh 3 histological criteria, or positive serological test results to confirm the diagnosis of coeliac disease. The results for both are presented separately within this chapter. The GDG agreed to consider prevalence studies as well as studies estimating risk of having coeliac disease compared to a control group of age and gender matched participants.

The GDG however made a post-hoc decision to include only those studies where an estimation of the risk was presented. The GDG considered that this was easier evidence to interpret and would be more useful in clinical practice. The group also felt that have two different types of evidence for the same reviewing question could be confusing and potentially misleading.

A single systematic search was conducted for sections 4.1, 4.2, and 4.3 (see Appendix C) which identified 7230 references. This search was restricted to studies published from 2008 onwards to avoid duplicates of studies considered in the previous coeliac disease guideline (CG86). The references were screened on their titles and abstracts and full papers of 161 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix F).

Eleven studies (Canavan et al., 2011; Duerksen et al., 2010; Godfrey et al., 2010; Hogen-Esch et al., 2011; Jafri et al., 2008; Kumar et al., 2011, Leboff et al., 2013; Lohi et al., 2009; Sanchez et al., 2011; Silano et al., 2007; Zugna et al., 2013) were included (see Appendix C). The remaining 150 studies were excluded. Reasons for exclusion can be found in Appendix C.

Results are presented as adjusted hazard ratios, odds ratios, risk ratios or standardised incidence ratios.

4.3.3 Evidence review

Osteoporosis

One study (Jafri et al., 2008) investigated 83 children and adults with biopsy-confirmed coeliac disease. The age at diagnosis of coeliac disease range from 12 months to 84 years and 58 (70%) were female.

Four studies (Duerksen et al., 2010; Godfrey et al., 2010; Leboff et al., 2013; Sanchez et al., 2011) investigated 976 people with serology-confirmed coeliac disease. The age of participants ranged from 16 to 87.7 years and 869 (89.0%) were female.

Infertility

One study (Hogen-Esch et al., 2011) investigated 1038 male-female couples with infertility, of whom 10 individuals has unrecognised coeliac disease. The age of study participants ranged from 20 to 45 years.

No studies including biopsy-confirmed coeliac disease were identified.

Malignancy

One study (Silano et al., 2007) investigated 1968 people with biopsy-confirmed coeliac disease. The mean age at diagnosis of coeliac disease was 36.2 ± 13.8 years and 1485 (75.5%) were female.

Three studies (Canavan et al., 2011; Godfrey et al., 2010; Lohi et al., 2009) investigated 14503 people with serology-confirmed coeliac disease. The age of study participants ranged from 30 to 95 years and 8186 (56.4%) were female.

Increased mortality rate

One study (Zugna et al., 2013) investigated 16121 women with biopsy confirmed coeliac disease of whom 3202 (19.9%) were undiagnosed prior to giving birth. The study was concerned with the associated child mortality rate. The age categories used in the study ranged from 15 to 45 years.

No studies including serology-confirmed coeliac disease were identified.

4.3.4 Health economic evidence

An economic literature search was not conducted for this question as an economic evaluation would not be the correct framework in which to generate useful evidence on the clinical conditions which can coexist with coeliac disease.

The populations identified within the clinical evidence review will be carried forward for consideration of the cost-effectiveness of obtaining a diagnosis of coeliac disease in these groups – see 4.4.4.

4.3.5 Evidence statements

4.3.5.1 Biopsy-confirmed coeliac disease

Osteoporosis

Very low quality evidence from a single study reported the risk of osteoporosis, reported as any fracture, to be an adjusted hazard ratio of 2.0 (95% CI 1.0 to 3.9)

Very low quality evidence from a single study reported the risk of osteoporosis, reported as risk of peripheral fractures, to be an adjusted hazard ratio of 2.0 (95% CI 1.0 to 3.9)

Very low quality evidence from a single study reported the risk of osteoporosis, reported as risk of axial fractures, to be an adjusted hazard ratio of 1.7 (95% CI 0.7 to 4.2)

Very low quality evidence from a single study reported the risk of osteoporosis, reported as risk of osteoporotic fractures, to be an adjusted hazard ratio of 6.9 (95% CI 0.7 to 7.65)

Malignancy

Very low quality evidence from a single study reported the risk of malignancy, reported as non-Hodgkin's lymphoma, Hodgkin's lymphoma, small bowel, colon, oesophageal, melanoma, breast, stomach or other cancer to be a standardised incidence rate of 1.3 (95% CI 1.0 to 1.7)

Low quality evidence from a single study reported the risk of malignancy, reported as small bowel cancer to be a standardised incidence ratio of 25 (95% CI 8.5 to 51.4)

Low quality evidence from a single study reported the risk of malignancy, reported as non-Hodgkin's lymphoma to be a standardised incidence ratio of 4.7 (95% CI 2.9 to 7.3)

Low quality evidence from a single study reported the risk of malignancy, reported as Hodgkin's lymphoma to be a standardised incidence ratio of 10 (95% CI 2.7 to 25)

Low quality evidence from a single study reported the risk of malignancy, reported as stomach cancer to be a standardised incidence ratio of 3 (95% CI 1.3 to 4.9)

Very low quality evidence from a single study reported the risk of malignancy, reported as colon cancer to be a standardised incidence ratio of 1.1 (95% CI 0.7 to 1.6)

Mortality

Very low quality evidence from a single study reported the risk of increased child mortality (all cause), to be an adjusted hazard ratio of 1.1 (95%CI 0.9 to 1.3)

Very low quality evidence from a single study reported the risk of increased child mortality (non-accidental), to be an adjusted hazard ratio of 1.3 (95%CI 0.7 to 2.6)

4.3.5.2 Serology-confirmed coeliac disease

Osteoporosis

Low quality evidence from a single study reported the risk of osteoporosis to be an odds ratio of 2.6 (95% CI 1.3 to 5.1)

Low quality evidence from a single study reported the risk of osteoporosis, reported as fracture risk, to be hazard ratio of 1.5 (95% CI 1.1 to 2.1)

Low quality evidence from a single study reported the risk of osteoporosis, reported as T-score less than 2.5 to be a hazard ratio of 2.7 (95% CI 1.2 to 2.0)

Very low quality evidence from a single study reported the risk of osteoporosis, reported as, low bone mineral density (osteoporosis or osteopenia) to be an odds ratio of 1.0 (95% CI 0.1 to 95.8)

Malignancy

Very low quality evidence from a single study reported the risk of malignancy, reported as, coeliac disease related cancers, to be an odds ratio of 2.0 (95% CI 0.3 to 14.4)

Low quality evidence from a single study reported the risk of malignancy, reported as, lymphoproliferative cancers, to be an adjusted risk ratio of 5.9 (95% CI 1.4 to 25.0)

Very low quality evidence from a single study reported the risk of malignancy, reported as, breast cancer, to be an adjusted risk ratio of 0.7 (95% CI 0.1 to 5.1)

Very low quality evidence from a single study reported the risk of malignancy, reported as, all cancers, to be an adjusted risk ratio of 0.7 (95% CI 0.3 to 1.1)

Very low quality evidence from a single study reported the risk of malignancy, reported as mortality due to cancer, to be an adjusted risk ratio of 1.2 (95% CI 0.5 to 2.7)

Infertility

Very low quality evidence from a single study reported the risk of undiagnosed coeliac disease in those with infertility due to ovulation disorders to be an odds ratio of 5.4 (95% CI 0.9 to 32.3)

Very low quality evidence from a single study reported the risk of undiagnosed coeliac disease in those with male factor infertility to be an odds ratio of 5.4 (95% CI 0.9 to 32.3)

Very low quality evidence from a single study reported the risk of undiagnosed coeliac disease in infertile (any cause) women to be an odds ratio of 2.4 (95% CI 0.5 to 12.1)

Very low quality evidence from a single study reported the risk of undiagnosed coeliac disease in infertile (any cause) men to be an odds ratio of 0.9 (95% CI 0.2 to 4.1)

Low quality evidence from a single study reported the risk of undiagnosed coeliac disease in unexplained infertility in women to be an odds ratio of 4.5 (95% CI 1.4 to 19.2)

4.3.6 Evidence to recommendations

All four sub-questions relating to the evidence for the recognition of coeliac disease were presented in tandem and discussed together. Therefore, the linking evidence to recommendation information will be presented for all four components of this question at the end of this chapter.

4.3.7 Recommendations & research recommendations

All four sub-questions relating to the evidence for the recognition of coeliac disease were presented in tandem and discussed together. Therefore, the associated recommendations will be presented for all four components of this question at the end of this chapter.

4.4 Active case-finding

4.4.1 Review question

Should active case-finding be implemented in people with coexisting conditions/subgroups that are associated with an increased risk of coeliac disease?

There are certain populations of people that have an increased risk of developing coeliac disease, as explored in section 4.2. Understanding the utility of case-finding in these populations will inform whether active case finding should be implemented in any of those populations. Case finding aims to increase diagnosis of coeliac disease in people who have the condition but are currently unaware and untreated in order to minimise the potential for the development of serious long-term health consequences of untreated CD, as outlined in section 4.3.

4.4.2 Methods

The aim of this review was to establish if patients with specific health conditions or specific subgroups with an increased risk of coeliac disease should be proactively investigated for coeliac disease.

4.4.3 Evidence review

A systematic search was conducted (see Appendix C) which identified 1483 references. References were screened on their titles and abstracts and full papers of 30 references were obtained and reviewed against the exclusion and inclusion criteria in the review protocol (see Appendix C).

All of these studies were excluded for reasons such as not being a primary study i.e. comment or letter to editor, or inappropriate study design i.e. following-up only serologically-positive individuals with a biopsy. .

In addition, the 1902 papers that were identified in the searches sections 5.1 and 5.2 (serological testing) were re-reviewed based on title and abstract in order to identify any studies that may meet the inclusion and exclusion criteria for the present question. No studies of relevance to the present review question were identified in this database.

4.4.4 Health economic evidence

4.4.4.1 Systematic review of published cost–utility analyses

An economic evaluations filter was applied to the search protocol for this review question with the aim of finding economic evaluations that explored the cost effectiveness of active case-finding for coeliac disease in at-risk subgroups.

The search identified 236 references. The references were screened on their titles and abstracts and 20 full-texts were ordered.

Four cost–utility analyses were found of relevance to the question: Mein & Ladabaum (2004) and Mohseninejad et al. (2013) explored testing people with irritable bowel syndrome (IBS) for coeliac disease; Swigonski et al. (2006) looked at case-finding in children with Down's syndrome; and Dretzke et al. (2004) analysed children newly diagnosed with type 1 diabetes.

4.4.4.2 Original health economic analysis

An original cost–utility model was used to explore the benefits, harms and costs associated with serological investigation of people at increased risk of coeliac disease. A modified version of the model developed to analyse the serological investigation of people with symptoms suggestive of coeliac disease was used (see 5.2.4.2). In addition to the various testing strategies, an arm was simulated in which no testing was offered, in order to estimate the value of case-finding compared with none. The GDG prioritised 4 different populations in which to investigate this question: first-degree relatives of people with coeliac disease, people with irritable bowel syndrome, people with type 1 diabetes and people with autoimmune thyroid disease. This choice was based on the populations in which the GDG believed there was greatest current uncertainty and/or variation in practice.

Parameters that differed between these populations were prevalence of coeliac disease, baseline health-related quality of life and life expectancy. Prevalence estimates were drawn from the evidence synthesis conducted as part of the clinical review identifying populations at an increased risk of developing coeliac disease (see 4.2). On GDG advice, UK-specific data from this review were used, where they were available; if no UK-only studies were found for the population in question, the pooled value for all included studies was used. For first-degree relatives, type 1 diabetes and autoimmune thyroid disease, separate analyses were conducted for adults and children; for irritable bowel syndrome, adults only were considered, as the GDG advised that irritable bowel syndrome is a very uncommon diagnosis in children. Full details of the methods and results of the model are provided in Appendix G.

4.4.5 Evidence statements

No clinical evidence that met the inclusion and exclusion criteria for this question was found.

4.4.5.1 Health economic evidence statements

Evidence for the cost effectiveness of screening first-degree relatives of people with coeliac disease

An original, directly applicable cost–utility analysis with minor limitations estimated that case-finding in adult first-degree relatives of people with coeliac disease results in improved quality of life at increased cost, with an ICER of £14,000 per QALY gained. The ICER remained below £20,000 as long as it could be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.24% or more (compared with a base-case estimate of 1.48%).

An original, directly applicable cost–utility analysis with minor limitations estimated that case-finding in child first-degree relatives of people with coeliac disease results in improved quality of life at increased cost, with an ICER of £18,800 per QALY gained. The ICER remained below £20,000 as long as it could be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.36% or more (compared with a base-case estimate of 1.48%).

Evidence for the cost effectiveness of screening people with type 1 diabetes for coeliac disease

An original, directly applicable cost–utility analysis with minor limitations estimated that case-finding in adults with type 1 diabetes results in improved quality of life at increased cost, with an ICER of £17,100 per QALY gained. The ICER remained below £20,000 as long as it could be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.50% or more (compared with a base-case estimate of 1.48%).

An original, directly applicable cost–utility analysis with minor limitations estimated that case-finding in children with type 1 diabetes results in improved quality of life at increased cost, with an ICER of £20,600 per QALY gained. The ICER fell below £20,000 if it could be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.94% or more (compared with a base-case estimate of 1.48%).

A partially applicable health economic analysis with potentially serious limitations looking at testing for coeliac disease in children newly diagnosed with type 1 diabetes (Dretzke et al., 2004) found that screening with EMA is the most cost-effective option in this group of children.

Evidence for the cost effectiveness of screening people with autoimmune thyroid disease for coeliac disease

An original, directly applicable cost–utility analysis with minor limitations estimated that case-finding in adults with autoimmune thyroid disease results in improved quality of life at increased cost, with an ICER of £26,000 per QALY gained. The ICER fell below £20,000 if it could be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.74% or more (compared with a base-case estimate of 1.48%).

An original, directly applicable cost–utility analysis with minor limitations estimated that case-finding in children with autoimmune thyroid disease results in improved quality of life at increased cost, with an ICER of £28,300 per QALY gained. The ICER fell below £20,000 if it could be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 2.44% or more (compared with a base-case estimate of 1.48%).

Evidence for the cost effectiveness of screening people with irritable bowel syndrome for coeliac disease

An original, directly applicable cost–utility analysis with minor limitations estimated that case-finding in adults with irritable bowel syndrome results in improved quality of life at increased cost, with an ICER of £20,800 per QALY gained. The ICER fell below £20,000 if it could be assumed that a gluten-free diet improves the health-related quality of life of people with subclinical coeliac disease by 1.64% or more (compared with a base-case estimate of 1.48%).

A partially applicable health economic analysis with potentially serious limitations looking at testing for coeliac disease in people with IBS (Mohseninejad et al., 2013), found that screening is likely to be cost effective in people experiencing diarrhoea or mixed symptoms (diarrhoea and constipation) of IBS. Excluding the group of patients with symptoms of only constipation improves the cost effectiveness of screening.

A partially applicable health economic analysis with potentially serious limitations looking at testing for coeliac disease in people with symptoms consistent with an IBS diagnosis (Mein & Ladabaum, 2004), found that screening in this population is cost effective.

Evidence for the cost effectiveness of screening children with Down's syndrome for coeliac disease

A partially applicable health economic analysis with potentially serious limitations looking at testing for coeliac disease as a way to prevent lymphoma in asymptomatic children with Down's syndrome (Swigonski et al., 2006), found that quality of life does not improve and costs increase when compared with not screening this population.

4.4.6 Evidence to recommendations

Relative value of different outcomes	<p>Signs and symptoms</p> <p>The GDG recognised a lack of evidence for the signs and symptoms of coeliac disease (CD), and in particular the most commonly recognised presenting signs and symptoms such as gastrointestinal dysfunction, weight loss, and abdominal pain. The group discussed this and agreed that, because CD is such a well-established disorder in terms of recognition of the common features, there is no impetus to conduct research into this area, and therefore no evidence to support established clinical knowledge.</p> <p>The GDG further recognised that differentiating between symptoms in terms of those that should prompt clinicians to offer serological testing, and those where clinicians should consider serological testing, is further made difficult by the lack of supportive evidence to differentiate between these two classes of recommendations.</p> <p>Coexisting conditions and active case-finding</p> <p>The GDG raised the importance of increasing recognition of CD, which is widely underdiagnosed in the UK. Outlining which particular coexisting conditions have an increased risk of CD is of utmost importance in order to increase awareness for, and testing for, CD in these populations. This can be difficult due to an overlap or masking of CD-like symptoms with symptoms of coexisting conditions. The group noted that they would expect a gain in health-related quality of life after a diagnosis of CD was made in those with coexisting conditions; however no evidence was found for this outcome.</p> <p>Long-term complications</p> <p>The GDG felt that raising awareness of CD to increase diagnosis was of particular importance in order to minimise the likelihood of the development of serious long-term complications.</p>
Trade-off between benefits and harms	<p>Signs and symptoms of CD</p> <p>The GDG was clear about the importance of serological testing for CD in any person where a clinical suspicion has arisen. The group cited the estimate that 4 out of 5 people with CD are currently undiagnosed, and that it is of utmost importance to improve diagnoses of these individuals by increasing both clinical and community awareness of CD and the associated signs and symptoms.</p> <p>The GDG agreed that there were certain signs and symptoms and coexisting conditions that are sufficiently associated with CD that people with them should be offered serological testing, and developed recommendations to reflect this. The GDG further discussed the non-specific nature of many of the signs and symptoms and consequently added 'unexplained' and 'chronic' to the description of some signs and symptoms to ensure that people who may have CD are identified.</p> <p>Neurological symptoms were discussed in detail, as the group recognised that the literature to support suspicion of CD in this</p>

population was scarce. However, it was noted that a considerable number of individuals were detected by neurologists on the basis of recommendations in the previous guideline, which changed their practice substantially and subsequently led to a greater awareness of CD in patients with neurological symptoms. For this reason the GDG was convinced that serological testing should be considered in populations with neurological symptoms, especially ataxia or peripheral neuropathy, which have been reported in numerous case reports.

The GDG agreed a list of further signs, symptoms and coexisting conditions for which they wanted to raise awareness of the link with coeliac disease. Therefore recommendations were developed that identified where offering serological testing for CD should be considered.

The GDG also recognised that prolonged fatigue was a very common presenting feature of a myriad of disorders, both physical and psychiatric. However, members of the group cited research by Hin et al. (1999) which suggests that up to 3% of those who present with unexplained prolonged fatigue were positive for CD antibodies. The group also cited their vast clinical anecdotal experience in which many people who had previously thought of themselves as asymptomatic retrospectively recognised that they had been very tired for up to a decade before diagnosis was made. The importance of addressing the cause of prolonged fatigue was also raised as of high importance in paediatric patients, in whom fatigue is highly uncommon.

Active case-finding

The GDG emphasised that anyone who has symptoms suggestive of CD should be offered serological testing regardless of any coexisting conditions or characteristics. Therefore, the population of interest for the assessment of case-finding strategies should comprise people who are not currently experiencing such symptoms to a degree that leads them to seek advice from healthcare professionals. Following the conventions of the Oslo consensus statement on definitions for coeliac disease and related terms (Ludvigsson et al., 2012), the GDG preferred to refer to this group of people as experiencing 'subclinical' CD. This term is preferable to 'asymptomatic' disease, as it is clear that many people with undiagnosed CD have a history of symptoms that are retrospectively considered significant once a diagnosis has been established; moreover, it is common for people to report an improvement in such symptoms when they start a gluten-free diet (GFD). Therefore, people with subclinical CD should not be considered truly asymptomatic; instead, they are defined as people who experience 'disease that is below the threshold of clinical detection without signs or symptoms sufficient to trigger CD testing in routine practice' (Ludvigsson et al., 2012).

First-degree relatives

Current practice is to offer serological testing to first-degree relatives. The assumption that people do or do not have CD at the time of testing is incorrect. People may undergo seroconversion, which is problematic as a clinician may tell someone that they are not CD positive, but that person may develop CD at a later time. Ruling HLA DQ2/DQ8 out is

important, as a clinician can then definitively conclude that if someone suspected of CD does not have HLA DQ2/DQ8, then they will never develop CD. While this could be very useful, it is pragmatically very difficult as a GP cannot request HLA DQ2/DQ8 testing as this needs to be requested by a specialist. Thus, patients would have to be referred to a specialist to request this test, which becomes expensive and time consuming, and therefore, in the opinion of the GDG, impractical.

Type 1 diabetes

The GDG raised the important notion that it is not sufficient to just test adults who present with gastrointestinal (GI) symptoms, as suggested in the current diabetes guideline. When people present at a diabetic clinic they are commonly only asked about diabetic features i.e. sugar, eyes, feet, etc., and GI symptoms are not discussed as part of a patient's diabetic review so go unnoticed and therefore untested. It is estimated that 15–20% of people have GI symptoms, but people don't realise that these may be relevant to their diabetes and so do not raise it with their diabetes consultant. The group felt strongly that it was very important to have a low threshold for testing people with diabetes to optimise dietary management of their diabetes and their potential CD-related symptoms.

The GDG discussed current recommendations within the diabetes guideline relating to testing for CD when a low BMI is noted. The group discussed that weight loss and low BMI are a feature of CD and noted that, although weight loss can be a symptom of CD, the traditional view of a person with CD being underweight is no longer true and that people with diabetes may present underweight, at a normal weight or overweight. It is therefore important that low BMI should not be highlighted as the only circumstance in which suspicion of CD should be raised in someone with diabetes.

The GDG also discussed testing for CD at the time of diagnosis of diabetes, and noted that this could be problematic in some circumstances. The group recognised that it may be too emotionally or cognitively difficult for the patient to take on the importance of each of their separate diagnoses. For these reasons, the GDG considered that it would be reasonable for a short delay (unlikely to be more than 6 months) between diagnosis of type 1 diabetes and testing for CD. The group chose not to complicate its recommendations with explicit discussion of this issue, as it believed that most clinicians would use their discretion in providing tests and information in an appropriate timeframe, and it did not want to detract from the importance of providing the test for everyone who has received a diagnosis of type 1 diabetes.

Long-term complications

The GDG felt that the available evidence highlighted the very serious nature of the potential long-term complications of undiagnosed CD. Osteoporosis was felt to be the most common potential long-term complication and the GDG felt that the evidence adequately reflected clinical experience.

The GDG noted that, although there is an increased risk of malignancy with undiagnosed CD, the overall risk of developing specific cancers is

	<p>low.</p> <p>The evidence for infertility was somewhat inconsistent. However, due to the serious emotional impact infertility has on a couple trying to conceive, the group still felt that it was important to raise awareness that CD could be contributing to this, and that clinicians should consider serological testing if other causes of infertility have been ruled out.</p> <p>Overall, the group felt strongly that serological testing is inexpensive and non-invasive, and that, if potentially very serious long-term complications could be avoided by having a diagnosis of CD made, the benefit of doing so far outweighs the potential detriment in having to follow a GFD. This trade-off was explored explicitly in original health economic modelling (see below).</p>
Economic considerations	<p>Active case-finding</p> <p>The original health economic analysis for this question was based on a modified version of the model developed to compare various serological testing strategies. Therefore, many of the considerations discussed in that question apply here (see 5.2.6). It was a potential weakness of the analysis that no evidence was found to estimate the diagnostic accuracy of different testing strategies in the populations of interest. Therefore, it was assumed that the sensitivity and specificity of the tests did not differ between populations, and data from the review of diagnostic accuracy in people presenting with symptoms suggestive of CD were used (see 5.1.3 and 5.2.3).</p> <p>In the original health economic model, the benefits of identifying people with subclinical CD are captured in 2 ways. Firstly, the quality of life of the proportion of people who follow advice to adopt a GFD will improve. Secondly, those people are subject to reduced incidence of long-term complications of CD, some of which have an impact on life expectancy.</p> <p>The GDG understood that, in all the populations simulated in the model, a reduction in long-term complications (with attendant improvement in life expectancy) was not, on its own, sufficient to counterbalance the costs and harms of testing (including serological assays and endoscopic biopsy in people who test positive). In contrast, the day-to-day quality of life benefit associated with a true-positive diagnosis only had to be small to make case-finding good value for money.</p> <p>The quality of life evidence used in the model's base case was drawn from an Argentinian study in which quality of life was measured (using the SF-36) at the point of diagnosis and following 3 months' treatment with a GFD. This suggested that people with subclinical CD who adopt a GFD experience quality of life that is, on average, approximately 1.5% better than those who continue to ingest gluten (Nachman et al. 2009). Although the study appears to have been well conducted, the sample of patients of interest to this model is very small; as a result, the estimate of effect is very uncertain. However, this uncertainty is appropriately propagated through the model, which presents a probabilistic synthesis of all parameters.</p> <p>The GDG expressed a clear view that it was appropriate to make a base-case assumption that adopting a GFD improves quality of life in people who were not complaining of symptoms at the time of diagnosis.</p>

Members of the group advised that, in their experience, many people who are diagnosed with subclinical CD report a history of symptoms that, while troublesome, had not led them to seek medical advice. Furthermore, the GDG reported that such people commonly report an improvement in such symptoms when starting a GFD. Finally, the fact that most people who have been diagnosed with subclinical disease elect to continue with a GFD is an indication that they are conscious of a perceptible improvement in quality of life.

The GDG understood that a difference in quality of life of the magnitude used in the model's base case to estimate the benefit of a GFD for people with subclinical CD is very small (1.5%). For comparison, the smallest effect that is detectable by the EQ-5D instrument and UK tariff (that is, the smallest change in quality of life that would result from an improvement in a single domain score) is equivalent to more than a 4% improvement in quality of life. Therefore, it was reasonable to assume that, if the quality of life of an average person with subclinical CD who adopts a GFD improves by a degree that is perceptible to that person, a gain of at least 1.5% – and probably greater – on a quantitative measure could be expected. In this context, the base-case value should be seen as conservative.

In all 4 populations simulated, the original health economic model suggested that case-finding in adults is likely to represent reasonable value for money. Base-case ICERs ranged between £14,000 per QALY gained (first-degree relatives) and £26,000 per QALY gained (autoimmune thyroid disease) for the best serological strategy compared with no testing.

Case-finding was slightly more expensive in children than in adults, largely due to the increased costs associated with endoscopic biopsy in children (which usually requires anaesthesia). Nevertheless, case-finding resulted in improved quality of life, with ICERs ranging between £18,800 per QALY gained (first-degree relatives) and £28,300 per QALY gained (autoimmune thyroid disease).

Although base-case ICERs exceeded £20,000 in type 1 diabetes (children only) and autoimmune thyroid disease (children and adults), the GDG felt these were likely to be somewhat underestimated, as the model only captured health gains that are associated with the diagnosis and management of CD. However, the group believed that, in both these conditions, correct identification of CD would also lead to superior management of the underlying condition, with associated improvement in quality of life. In the case of type 1 diabetes, the glycaemic control of people with subclinical CD is known to be improved by adopting a GFD. Additionally, dietary management is complex in people with both conditions, as each imposes its own requirements; in this context, the GDG believed it is critical for children to have access to appropriate dietetic support, so diagnosis of subclinical CD is very important. In the case of autoimmune thyroid disease, untreated coeliac enteropathy interferes with the absorption of oral medications that are critical to managing the condition. Correct identification of CD, therefore, should be associated with more stable and effective medication requirements, improving the person's quality of life. In both these instances, the GDG felt that, although the additional benefits would be very hard to quantify without a complicated model of 2 concurrent disease processes, they

were examples of 'change in the quality of life [that] is inadequately captured' in the analysis and, therefore, good reasons to recommend case-finding in populations that had base-case ICERs in the range £20–30,000.

In all cases, results were very sensitive to the degree to which a GFD was assumed to improve the health-related quality of life of people with subclinical CD. However, the GDG felt confident that such benefits are observed in practice, so the group was happy to recommend case-finding, on the expectation that the true-positive identification of people with subclinical CD would lead to this kind of health gain.

Although it is theoretically possible that different serological strategies might be optimal in different populations (according to expected prevalence of CD and other population-specific characteristics), little evidence was found to suggest that anything other than the strategies recommended in section 5.2 should be preferred. Therefore, it was not necessary to make separate recommendations about the tests that should be used in a case-finding context; it was sufficient to recommend that serological testing should be offered, and recommendations elsewhere in the guideline would be followed.

One potential exception to this rule was that, in sensitivity analysis for child first-degree relatives of people with coeliac disease, some results suggested that it could theoretically be worth adding routine genotyping (HLA DQ2/DQ8 testing) to the diagnostic strategy. However, the GDG pointed out that, in practice, this would be of very limited value: if one family member is HLA DQ2/DQ8 positive (as the index case almost certainly would be), the chances of the rest of that family being HLA DQ2/DQ8 positive is very high. Therefore, the utility of doing that test in further family members is negligible. This shows that there are some areas in which population-specific diagnostic accuracy data might improve the accuracy of results.

The original health economic model did not cover children with Down's syndrome, as this population was not among the GDG's top priorities for modelling. However, the GDG was presented with details of a published cost–utility analysis (Swigonski et al., 2006), which found that screening was not cost effective in this population. This analysis was confined to a single outcome of preventing lymphoma and the original health economic analysis conducted in other populations had shown that relatively little of the benefit of true-positive identification of CD could be ascribed to this outcome. Therefore, it was unsurprising that Swigonski et al. found insufficient benefit to justify the costs of case-finding. The GDG inferred that a fuller analysis, accounting for a wider range of benefits, would be likely to reach a different conclusion. However, the group did not feel that it had enough evidence to support an 'offer' recommendation, so concluded that case-finding should be considered in this population.

Quality of evidence

The group recognised that overall the quality of evidence available to answer this question was of a low quality. This was recognised to be a product of the lack of evidence available, the retrospective nature of the majority of studies, and the bias inherent in the way study participants were selected, how prevalence estimates were generated, the lack of precision in the presented estimates, and the lack of endoscopic

	<p>intestinal biopsy to prove CD diagnosis in a great number of the studies available.</p>
Other considerations	<p>Irritable Bowel Syndrome (IBS)</p> <p>The GDG felt that it was important that those with a diagnosis of IBS should be tested for coeliac disease, as the two conditions have very similar phenotypic manifestations, notably in terms of gastrointestinal symptoms and abdominal pain. The group discussed that children are not routinely diagnosed with IBS, and are more likely to be labelled with 'recurrent abdominal pain' or 'abdominal migraine'. IBS diagnosis is only typically given to adults with the same symptoms. Children may also have a diagnosis of inflammatory bowel disease. A child could hypothetically present to a number of clinicians and be given a number of different diagnoses for same symptoms because of this lack of consistency in characterising 'IBS-like' symptoms in the paediatric population. It was also raised as common for children to be diagnosed with IBS-like symptoms rather than a diagnosis of IBS. The group further raised the notion that, technically, children should be covered by recommendations on children or adults with recurrent GI symptoms, so whether this is labelled as IBS or not in children it is essentially irrelevant to their being investigated for CD.</p> <p>Repeat serological testing</p> <p>The group thought it highly important that both patients and healthcare professionals should be aware that people with risk factors for CD who test negative initially may remain at increased risk of developing CD in the future.</p> <p>The GDG was aware that some researchers have recommended routine periodic testing of people whose initial serological results are negative, especially those with type 1 diabetes.</p> <p>The original health economic model suggested that testing people with type 1 diabetes for CD at diagnosis could probably be considered to provide reasonable value for money (see above); however, the group was aware that this conclusion was relatively finely balanced, and small adjustments to the parameters of the model would produce different results. In particular, if prevalence of CD was any lower than estimated in the model's base case, it would not be cost effective to offer case finding.</p> <p>The model was not designed to examine the cost effectiveness of periodic repeat testing. However, it could be inferred that the prevalence of CD among people who initially tested negative would be lower than in the incident type 1 diabetes cohort. Therefore, it is extremely unlikely that repeat testing would achieve health gains at a cost that would be considered an effective use of NHS resources. This result would arise partially because of the costs of repeat serology itself, but more particularly because of the costs incurred and quality of life forgone by performing endoscopic biopsies in people with positive serology in a context where those people were more likely to have false-positive findings owing to lower prevalence of CD (that is, the positive predictive value of all serological tests would be lower in a retesting setting).</p>

Nevertheless, the GDG were keen to emphasise that, if people with risk factors for CD who have previously been found to be serologically negative develop CD-like symptoms over time, there should be a low threshold for retesting for CD. The group were mindful of the evidence and experience (noted above) that people with subclinical CD frequently experience mild symptoms that do not lead them to seek medical advice. Therefore, the group recommended that people who initially test negative are advised to treat any future CD-like symptoms seriously, and not to hesitate to seek advice from their healthcare providers. For treating clinicians, it was emphasised that, if a person has risk factors for CD and even mild symptoms that are suggestive of CD, a historical negative serological test should not be used as a reason not to offer repeat serological testing.

4.4.7 Recommendations & research recommendations

1. Offer serological testing for coeliac disease to:

- People with any of the following:
 - persistent unexplained abdominal or gastrointestinal symptoms
 - faltering growth
 - prolonged fatigue
 - unexpected weight loss
 - severe or persistent mouth ulcers
 - unexplained iron, vitamin B12 or folate deficiency
 - type 1 diabetes, at diagnosis
 - autoimmune thyroid disease, at diagnosis
 - irritable bowel syndrome (in adults)
- first-degree relatives of people with coeliac disease.

2. Consider serological testing for coeliac disease in people with any of the following:

- metabolic bone disorder (reduced bone mineral density or osteomalacia)
- unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
- unexplained subfertility or recurrent miscarriage
- persistently raised liver enzymes with unknown cause
- dental enamel defects
- Down's syndrome
- Turner syndrome.

3. Advise people who have tested negative for coeliac disease, particularly first-degree relatives and people with type 1 diabetes, that:

- coeliac disease may present with a wide range of symptoms **and**
- they should consult their healthcare professional if any of the symptoms listed in recommendations 1 or 2 arise or persist.

5 Evidence for testing for coeliac disease

5.1 Accuracy of serological testing

5.1.1 Review questions

What is the sensitivity and specificity of the serological tests for coeliac disease?

Are the sensitivity and specificity of results different in any specified subgroups?

A number of different serological tests exist to test for coeliac disease. Each of these serological tests works by testing for the presence of a positive antigenic response of a given antibody against either IgA or IgG. Each of these serological tests has different sensitivity and specificity to detect coeliac disease. Determining the optimal serological test will ensure a balance of high sensitivity, whereby all those with the disease are accurately diagnosed, and specificity, whereby all those who do not have the disease are excluded.

5.1.2 Methods

The aim of this review question was to determine the sensitivity and specificity of the different serological tests available in the diagnosis of coeliac disease. This is an update of the chapter on 'serological tests in the diagnostic process for coeliac disease' in the 2009 guideline for coeliac disease (CG86). This updated review incorporates studies that were included in the previous guideline together with newly-published evidence.

The second component of this chapter focuses on whether specificity and sensitivity of serological test results is altered in any specified subgroups. Selective IgA deficiency is 10 to 15 times more common in patients with coeliac disease than in healthy subjects (Chow et al., 2012). Therefore, there is a risk of false negative serological results if IgA-dependent assays are used to assess the presence of CD. It has been reported that there has been inadequate evaluation of IgA deficiency while testing for coeliac disease, which has resulted in the underdiagnoses of both coeliac disease and IgA deficiency (McGowan et al., 2008). Therefore, this guideline considered the use of IgA-deficiency testing and IgG-based serological testing in the diagnostic process for coeliac disease.

Studies were only included if they met the following criteria: the population examined was children or adults suspected of having coeliac disease; all participants received both serological testing and an intestinal biopsy. The serological tests considered were:

- IgA tTG
- IgG tTG
- IgA EMA
- IgG EMA
- IgA DGP
- IgG DGP
- HLA DQ2/DQ8 genotyping

The comparator test was an endoscopic intestinal biopsy (reference standard in practice) and outcomes of interest were sensitivity and specificity of the different serological tests to detect coeliac disease.

The GDG expressed the need for a uniform histological reference standard to be used when examining sensitivity and specificity of the serological tests. Marsh grade 3 was identified as the optimal histological reference standard, and thus only studies which used this histological criterion to diagnose coeliac disease were considered. Furthermore, the GDG expressed that

only studies within Europe should be considered. This is due to the high prevalence of non-coeliac enteropathies in countries outside of Europe, particularly India, Africa, and Israel, which is often difficult to discriminate from true coeliac disease.

Within the studies, different diagnostic kits and different cut-off values were used for the analysis^d. Further differences between studies were differing or incompletely reported biopsy strategies, possible variability between laboratories or operators, and studies taking place in several different countries.

The included studies were cohort studies, which provided the best quality evidence within a modified GRADE framework.

For full details of the review protocol please see Appendix C.

Included studies

A systematic search was conducted (see Appendix C) which identified 2527 references. This search was restricted to studies published from 2008 onwards to avoid duplicates of studies considered in the previous coeliac disease guideline (CG86). The references were screened on their titles and abstracts and full papers of 76 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

Overall, 70 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (case-series), not a primary study (descriptive narrative, opinion, etc.), examined the prevalence of coeliac disease in certain populations, studies in which the study population was not suspected of coeliac disease (but may have had an increased risk for developing coeliac disease, such as a commonly comorbid condition, or a family history of coeliac disease), and studies which did not use Marsh grade 3 for the histological diagnosis of coeliac disease. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix C.

The 43 studies included studies in the previous coeliac disease guideline (CG86) were reviewed against the current protocol. Of these, 42 were excluded based on data extracted in the CG86 evidence tables as they did not meet eligibility criteria. Primary reasons for exclusion included inappropriate index tests (IgA AGA and IgG AGA^e), populations that were not suspected of coeliac disease, and studies in which 100% of the participants did not receive both serological testing and an intestinal biopsy.

The search for this question was also designed to identify studies in which there was evidence that the serological tests for coeliac disease performed in any way differently from the general population. No studies of interest were found in this area.

5.1.3 Evidence review

The 6 remaining published papers did meet the stated eligibility criteria and were included. Data was extracted into detailed evidence tables (see Appendix D) and are summarised below). A single study (Hopper et al., 2008) included in the previous coeliac disease guideline did meet eligibility criteria for the current guideline and was included. Data is available in detailed evidence tables derived from the previous coeliac disease guideline (see Appendix D) and are summarised below.

The overall quality of the evidence from these 7 published papers ranged from very low to high, with the majority of evidence to be of moderate quality.

^d : If studies used different cut-off levels, those used were that of the manufacturer's recommended cut-off levels
^e IgA AGA and IgG AGA were assessed in the previous coeliac disease CG86 guideline. Due to low sensitivity and specificity outcome for these tests, they were not recommended for the diagnosis of coeliac disease. On this basis, IgA AGA and IgG AGA were excluded from the present guideline.

5.1.3.1 Evidence for the sensitivity and specificity of IgA tTG in the detection of coeliac disease in adults, children, and mixed age populations

Two studies (Mubarak et al., 2011; Panetta et al., 2011) of 376 children (mean age 3.9 years) with suspected coeliac disease conducted IgA tTG serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. Five children with IgA deficiency were excluded from one study (Panetta et al., 2011), and IgA deficiency was not commented on in by Mubarak and colleagues (2011). Three studies (Hopper et al., 2010; Volta et al., 2010; Swallow et al., 2012) of 2900 adults (mean age 40.4 years) with suspected coeliac disease conducted IgA tTG serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. A total of 16 adults with IgA deficiency were excluded from the analyses. One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA tTG serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.1.3.2 Evidence for the sensitivity and specificity of IgA EMA in the detection of coeliac disease

Two studies (Mubarak et al., 2011; Panetta et al., 2011) of 376 children (mean age 3.9 years) with suspected coeliac disease conducted IgA EMA serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. Five children with IgA deficiency were excluded from one study (Panetta et al., 2011), and IgA deficiency was not commented on in by Mubarak and colleagues (2011). Three studies (Hopper et al., 2010; Volta et al., 2010; Swallow et al., 2012) of 2900 adults (mean age 40.4 years) with suspected coeliac disease conducted IgA EMA serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. A total of 16 adults with IgA deficiency were excluded from the analyses. One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA EMA serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.1.3.3 Evidence for the sensitivity and specificity of IgA DGP in the detection of coeliac disease

One study (Mubarak et al., 2011) of 212 children with suspected coeliac disease conducted IgA DGP serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. One study (Volta et al., 2010) of 144 adults with suspected coeliac disease (mean age 25 years) conducted IgA DGP serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. Two patients with IgA deficiency were excluded from this analysis. One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA DGP serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.1.3.4 Evidence for the sensitivity and specificity of IgG DGP in the detection of coeliac disease

One study (Mubarak et al., 2011) of 212 children with suspected coeliac disease conducted IgG DGP serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. One study (Volta et al., 2010) of 144 adults with suspected coeliac disease (mean age 25 years) conducted IgG DGP serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. One study

(Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgG DGP serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population.

5.1.3.5 Evidence for the sensitivity and specificity of HLA DQ2/DQ8 genotyping in the detection of coeliac disease

One study (Clouzeau-Girard et al., 2011) of 170 children suspected of coeliac disease (median age 18 months) conducted HLA DQ2/DQ8 genotyping and endoscopic intestinal biopsy to determine the association between these coeliac-associated haplotypes and the presence of coeliac disease in this population. A total of 8 children were excluded from the analyses: 2 children were already consuming a GFD; one child had previously been on a gluten-free diet (GFD) and reintroduced gluten only eight weeks earlier; two children had selective IgA deficiency; three children had intestinal biopsies which could not be classified because of bad orientation of the sample.

5.1.3.6 Evidence for the sensitivity and specificity of serological testing in any specified subgroups

One study (Mubarak et al., 2011) was identified which examined serological test accuracy in children under the age of two. This study directly compared the sensitivity and specificity of serological tests in children under two years old to children over the age of two years old.

5.1.4 Health economic evidence

Any economic evaluations regarding the diagnosis of coeliac disease would be more appropriately categorised under the question of which test (or sequence of tests) to use (see 5.2.4), rather than a question concerned with the accuracy of the testing strategies alone. However, the evidence generated in the clinical review for this question forms the basis of the estimates of diagnostic outcome used in the original economic model described in 5.2.4

5.1.5 Evidence statements

5.1.5.1 Evidence for the sensitivity and specificity of IgA tTG in the detection of coeliac disease

Moderate to low quality evidence from 2 studies (Mubarak et al., 2011; Panetta et al., 2011) of 275 children reported that IgA tTG has high levels of sensitivity [96 % (95% CI: 93 to 99)] and moderate specificity [86 % (95% CI: 78 to 91)] in the diagnostic process for children suspected of coeliac disease.

High to moderate quality evidence from 3 studies (Hopper et al., 2008; Volta et al., 2010; Swallow et al., 2012) of 2900 adults reported that IgA tTG has moderate levels of sensitivity [91% (95% CI: 85 to 95)] and specificity [91% (95% CI: 90 to 92)] in the diagnostic process for adults suspected of coeliac disease.

Moderate to low quality evidence from a single study (Burgin-Wolff et al., 2010) of 268 children and adults reported that IgA tTG has high levels of sensitivity [97% (95% CI: 94 to 99)] and moderate specificity [87% (95% CI: 80 to 92)] in the diagnostic process for children and adults suspected of coeliac disease.

5.1.5.2 Evidence for the sensitivity and specificity of IgA EMA

Moderate to low quality evidence from 2 studies (Mubarak et al., 2011; Panetta et al., 2011) of 275 children reported that IgA EMA has high levels of sensitivity [97% (95% CI: 94 to 99)] and moderate specificity [76% (95% CI: 67 to 83)] in the diagnostic process for children suspected of coeliac disease.

High quality evidence from 3 studies (Hopper et al., 2008; Volta et al., 2010; Swallow et al., 2012) of 2900 adults reported that IgA EMA has moderate levels of sensitivity [85% (95% CI: 78 to 90)] and high specificity [98% (95% CI: 98 to 99)] in the diagnostic process for adults suspected of coeliac disease.

Moderate to low quality evidence from a single study (Burgin-Wolff et al., 2010) of 268 children and adults reported that IgA EMA has high levels of sensitivity [98% (95% CI: 96 to 100)] and moderate specificity [85% (95% CI: 78 to 91)] in the diagnostic process for adults and children suspected of coeliac disease.

5.1.5.3 Evidence for the sensitivity and specificity of IgA DGP

High quality evidence from a single study (Mubarak et al., 2011) of 212 children reported that IgA DGP has moderate sensitivity [82% (95% CI: 72 to 89)] and specificity [80% (95% CI: 71 to 88)] in the diagnostic process for children suspected of coeliac disease.

High quality evidence from a single study (Volta et al., 2010) of 144 adults reported that IgA DGP has moderate sensitivity [83% (95% CI: 73 to 93)] and specificity [80% (95% CI: 71 to 88)] in the diagnostic process for adults suspected of coeliac disease.

Moderate quality evidence from a single study (Burgin-Wolff et al., 2010) of 268 children and adults suggests that IgA DGP has moderate sensitivity [78% (95% CI: 71 to 85)] and high specificity [97% (95% CI: 93 to 99)] in the diagnostic process for children and adults suspected of coeliac disease.

5.1.5.4 Evidence for the sensitivity and specificity of IgG DGP

High quality evidence from a single study (Mubarak et al., 2011) of 212 children reported that IgG DGP has moderate sensitivity [89% (95% CI: 80 - 95)] and specificity [81% (95% CI: 71 to 88)] in the diagnostic process for children suspected of coeliac disease.

High quality evidence from a single study (Volta et al., 2010) of 144 adults reported that IgG DGP has moderate sensitivity [83% (95% CI: 73 to 94)] and high specificity [97% (95% CI: 95 to 100)] in the diagnostic process for adults suspected of coeliac disease.

Moderate quality evidence from a single study (Burgin-Wolff et al., 2010) of 268 children and adults reported that IgG DGP has moderate sensitivity [85% (95% CI: 80 to 90)] and specificity [92% (95% CI: 86 to 97)] in the diagnostic process for children and adults suspected of coeliac disease

5.1.5.5 Evidence for the sensitivity and specificity of IgG tTG

There were no published studies that examined the sensitivity and specificity of IgG tTG in populations suspected of coeliac disease.

5.1.5.6 Evidence for the sensitivity and specificity of IgG EMA

There were no published studies that examined the sensitivity and specificity of IgG EMA in populations suspected of coeliac disease.

5.1.5.7 Evidence for the sensitivity and specificity of human leucocyte antigen (HLA DQ2/DQ8) genotyping

High quality evidence from a single study (Clouzeau-Girard et al., 2011) of 170 children considered the sensitivity and specificity of HLA DQ2/DQ8 genotyping in a population of children suspected of coeliac disease. This paper reported a very high sensitivity of 99% (95% CI: 96 to 100) and low specificity of 69% (95% CI: 59 to 79) of HLA DQ2/DQ8 genotyping in children.

5.1.5.8 Evidence for the sensitivity and specificity of serological testing in any specified subgroups

Moderate quality evidence from a single study showed increased specificity in the younger children for IgA EmA (< 2, 93% (95% CI: 66 to 100); >2, 82% (95% CI: 72 to 89)), and increased sensitivity and specificity for IgA DGP (<2, 100% (95% CI: 84 to 100), >2, 87% (95% CI: 77 to 93); <2, 100% (95% CI: 75 to 100), >2, 81% (95% CI: 71 to 88)) and IgG DGP (<2, 100% (95% CI: 84 to 100), >2, 87% 95% CI: (77 to 93; <2, 100% (95% CI: 75 to 100), >2, 81% (95% CI: 71 to 88)), suggesting that the DGP antibodies in particular may have maximum diagnostic accuracy in this population

5.1.6 Evidence to recommendations

Both questions relating to the evidence for serological testing in coeliac disease were presented in tandem and discussed together. Therefore, the linking evidence to recommendation information will be presented for the two components of this question at the end of this chapter.

5.1.7 Recommendations & research recommendations

Both questions relating to the evidence for serological testing in coeliac disease were presented in tandem and discussed together. Therefore, the associated recommendations will be presented for the two components of this question at the end of this chapter.

5.2 Order and sequencing of serological tests

5.2.1 Review questions

Which serological test is the most appropriate to diagnose coeliac disease?

Depending on test results, should more than one test be used, and if so, what should be the sequence of testing?

Following which sequence of tests and test results is it appropriate to refer onwards for endoscopic intestinal biopsy for confirmatory diagnosis?

In section 5.1 the sensitivity and specificity of different serological tests to detect coeliac disease was explored. The purpose of this section is to examine whether a combination of those serological tests investigated in section 5.1 can achieve a greater sensitivity and specificity to detect coeliac disease than when those tests are used in isolation.

5.2.2 Methods

The aim of this review question was to determine when serological test results would indicate a diagnosis of coeliac disease without the need for intestinal biopsy. The second part of this question was designed to determine when serological tests results would indicate a referral for endoscopic intestinal biopsy for confirmatory diagnosis is appropriate. This is an update of the chapter on 'serological tests in the diagnostic process for coeliac disease' in the 2009 guideline for coeliac disease (CG86). This updated review incorporates studies that were included in the previous guideline together with newly-published evidence.

Combinations (including parallel or sequential combinations) of serological and IgA deficiency testing were compared to intestinal biopsy, or other combinations of tests, or test algorithms.

Studies were only included if they met the following criteria: the population examined was children or adults suspected of having coeliac disease; all participants received both serological testing and an intestinal biopsy.

- The serological tests considered (in any combination) were:
 - IgA tTG
 - IgG tTG
 - IgA EMA
 - IgA DGP
 - IgG DGP
 - HLA DQ2/DQ8
 - Total IgA (for IgA deficiency)

The outcomes of interest were sensitivity and specificity of the different combinations of serological tests to detect coeliac disease.

The GDG also expressed the need for a uniform histological reference standard to be used when examining sensitivity and specificity of the serological tests. Marsh grade 3 was identified as the optimal histological reference standard, and thus only studies which used this criterion to diagnose coeliac disease were considered. Furthermore, the GDG expressed that only studies within Europe should be considered. This is due to the high prevalence of non-coeliac enteropathies in countries outside of Europe, particularly India, African and

Middle-Eastern countries, which is often difficult to discriminate from true coeliac disease and may skew sensitivity and specificity estimates of serological tests in these populations.

Within the studies, different kits and different cut-off values were used for the analysis^f. Further differences between studies were different or incompletely reported biopsy strategies, possible variability between laboratories or operators, and studies taking place in several different countries.

The included studies were cohort studies and case-control studies, which provided the best quality evidence.

For full details of the review protocol please see Appendix C.

Included studies

A single systematic search was conducted (see Appendix C) for both review question three and review question four together, which identified 2527 references. This search was restricted to studies published from 2008 onwards to avoid duplicates of studies considered in the previous coeliac disease guideline (CG86). The references were screened on their titles and abstracts and full papers of 17 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

Twelve studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (case-series), not a primary study (descriptive narrative, opinion, etc.), examined the prevalence of coeliac disease in certain populations, or studies in which the study population was not suspected of coeliac disease (but may have had an increased risk for developing coeliac disease, such as a commonly comorbid condition, or a family history of coeliac disease). A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

The 5 remaining published papers did meet eligibility criteria and were included. Data was extracted into detailed evidence tables (see Appendix D) and are summarised below).

The 6 studies included in the previous coeliac disease guideline (CG86) were reviewed against the current protocol. Of these, 5 were excluded as they did not meet eligibility criteria. Primary reasons for exclusion included inappropriate index tests (IgA AGA and IgG AGA),^g populations that were not suspected of coeliac disease, and studies in which 100% of the participants did not receive both serological testing and an intestinal biopsy.

The 1 remaining published paper included in the previous coeliac disease guideline did meet eligibility criteria for the current guideline and was included. Data is available in detailed evidence tables derived from the previous coeliac disease guideline (CG86) and are summarised below.

The overall quality of the evidence from these 6 published papers ranged from low to high, with the majority of evidence to be of moderate quality. Evidence was downgraded due to methodological issues such as unclear recruitment strategy, inconsistency between studies, or imprecision.

Sensitivity and specificity values presented here for one of the included studies (Burgin-Wolff et al., 2013) were calculated from raw data values. These differ from the sensitivity and specificity results presented in the paper. The paper presents 'non-classified' data, which relates to the number of participants per test combination that were unable to be classified due to inconsistency between two or more tests (i.e. positive result on one test and negative result in another test(s)). This 'non-classifiable' data was incorporated into the analyses

^f If studies used different cut-off levels, the used were that of the manufacturer's recommended cut-off levels.

^g IgA AGA and IgG AGA were assessed in the previous coeliac disease CG86 guideline. Due to low sensitivity and specificity outcome for these tests, they were not recommended for the diagnosis of coeliac disease. On this basis, IgA AGA and IgG AGA were excluded from the present guideline.

presented here as false negative data, as it is assumed that the 'non-classified' data was classed as negative.

5.2.3 Evidence review

5.2.3.1 Sensitivity and specificity of combination IgA tTG + IgG DGP testing

One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA tTG + IgG DGP combination serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.2.3.2 Sensitivity and specificity of combination IgA EMA + IgG DGP testing

One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA EMA + IgG DGP combination serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.2.3.3 Evidence for the sensitivity and specificity of combination IgA tTG + IgG DGP + IgA DGP testing

One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA tTG + IgG DGP + IgA DGP combination serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.2.3.4 Evidence for the sensitivity and specificity of combination IgA EMA + IgG DGP + IgA DGP testing

One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA EMA + IgG DGP + IgA DGP combination serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.2.3.5 Evidence for the sensitivity and specificity of combination IgA EMA + IgA tTG + IgG DGP testing

One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA tTG + IgA EMA + IgG DGP combination serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.2.3.6 Evidence for the sensitivity and specificity of combination IgA tTG + IgA EMA + IgA DGP + IgG DGP testing

One study (Burgin Wolff et al., 2013) of 268 children and adults (median age 29 years) with suspected coeliac disease conducted IgA tTG + IgA EMA + IgG DGP + IgA DGP combination serological testing and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. IgA deficient patients were excluded from the outset in this study.

5.2.3.7 Evidence for the sensitivity and specificity of combination IgA tTG + IgA EMA + HLA DQ2/DQ8

One study (Clouzeau-Girard et al., 2011) of 170 children suspected of coeliac disease (median age 18 months) conducted HLA DQ2/DQ8 genotyping with IgA tTG + IgA EMA serological testing and endoscopic intestinal biopsy to determine the association between these coeliac-associated haplotypes, serology, and the presence of coeliac disease in this population. A total of 8 children were excluded from the analyses: 2 children were already consuming a gluten-free diet (GFD); 1 child had previously been on a GFD and reintroduced gluten only 8 weeks earlier; 2 children had selective IgA deficiency; 3 children had intestinal biopsies which could not be classified because of bad orientation of the sample.

5.2.3.8 Evidence for the sensitivity and specificity of combination IgA + IgG h-tTG/DGP

One study (Mubarak et al., 2011) of 212 children with suspected coeliac disease conducted serological testing using a combination test with a human recombinant tissue substrate of IgA + IgG tTG/DGP and endoscopic intestinal biopsy to determine the presence of coeliac disease in this population. One case-control study (Porcelli et al., 2011) of 201 adults serologically tested for coeliac disease was also examined. This study population was comprised 41 recently diagnosed people with coeliac disease; 145 'disease-controls' with various other conditions, including autoimmune hepatopathies; viral hepatitis, and other gastrointestinal diseases; and 24 healthy blood donors. All participants underwent serological testing using a combination test with a human recombinant tissue substrate of IgA + IgG tTG/DGP and endoscopic intestinal biopsy to diagnose or exclude the presence of coeliac disease.

5.2.3.9 Evidence for the sensitivity and specificity of the test algorithm If IgA tTG is positive, and then IgA EMA is positive

One study (Hopper et al., 2008) of 2000 adult participants (mean age 55.8 years) with suspected coeliac disease examined a 2-step serological screening strategy in which participants were screened first with IgA tTG and then with IgA EMA if the IgA tTG test was positive. Participants were considered serologically positive for coeliac disease if both serological tests were positive. All patients also underwent an endoscopic intestinal biopsy to confirm the diagnosis of coeliac disease. Fourteen participants were excluded from the analyses due to IgA deficiency.

5.2.3.10 Evidence for the sensitivity and specificity of the test algorithm If IgA tTG is positive or equivocal, and then IgA EMA is positive

One study (Swallow et al., 2012) of 756 adult participants (mean age unknown) with suspected coeliac disease examined a 2-step serological screening strategy in which participants were screened first with IgA tTG and then with IgA EMA if the IgA tTG test was positive or equivocal, according to the strategy recommended by NICE in the coeliac disease guideline CG86. Participants were considered serologically positive for coeliac disease if both serological tests were positive. All participants also underwent an endoscopic intestinal biopsy to confirm the diagnosis of coeliac disease. Fourteen participants were excluded from the analyses due to IgA deficiency.

5.2.3.11 Evidence for the sensitivity and specificity of the test algorithm If both IgA tTG is positive and IgA EMA is positive

Two studies (Hopper et al., 2008; Swallow et al., 2012) of 2756 adult participants (mean age 55.8 years) with suspected coeliac disease examined a 2-step serological screening strategy in which participants were screened with both IgA tTG and IgA EMA. Participants were considered serologically positive for coeliac disease if both serological tests were positive.

All participants also underwent an endoscopic intestinal biopsy to confirm the diagnosis of coeliac disease. Fourteen participants were excluded from the analysis due to IgA deficiency.

5.2.3.12 Evidence for the sensitivity and specificity of the 2-step test algorithm If either IgA tTG is positive, or IgA EMA is positive

One study (Hopper et al., 2008) of 2000 adult participants (mean age 55.8 years) with suspected coeliac disease examined a 2-step serological screening strategy in which participants were screened first with IgA tTG and then with IgA EMA. Participants were considered serologically positive for coeliac disease if either or both serological tests were positive. All participants also underwent an endoscopic intestinal biopsy to confirm the diagnosis of coeliac disease. Fourteen participants were excluded from the analyses due to IgA deficiency.

5.2.4 Health economic evidence

5.2.4.1 Systematic review of published cost–utility analyses

An economic evaluations filter was applied to the search protocol for this research question (an update of a review question considered within the 2009 NICE coeliac disease guideline CG86) with the aim of finding economic evaluations that explored the cost effectiveness of diagnostic strategies for people with signs and symptoms suggestive of coeliac disease.

The search identified 135 references. The references were screened on their titles and abstracts and 10 full-texts were ordered. None of the studies met the inclusion criteria.

No cost–utility analyses were found to address selection criteria

5.2.4.2 Original health economic analysis

An original cost–utility model was developed to explore the benefits, harms and costs associated with different strategies for serological investigation of people with symptoms suggestive of coeliac disease. The model used a cohort (Markov) structure to estimate lifetime costs and effects, incorporating the tests themselves, endoscopic investigation of serologically positive cases, treatment for coeliac disease and the long-term complications of treated and untreated disease (including impact on mortality). Long-term complications modelled were osteoporosis, subfertility and cancer (divided into non-Hodgkin's lymphoma and other cancer). Separate analyses were conducted for adults and children. Full details of the methods and results of the model are provided in Appendix G.

5.2.5 Evidence statements

5.2.5.1 Sensitivity and specificity of combination IgA tTG + IgG DGP testing

Moderate quality evidence from a single study (Burgin-Wolff et al., 2013) reported that the combination test for IgA tTG + IgG DGP has low sensitivity [72%; 95% CI: 65 to 80] and high specificity [96%; 95% CI: 92 to 99] in the diagnostic process for children and adults suspected of coeliac disease.

5.2.5.2 Sensitivity and specificity of combination IgA EMA + IgG DGP testing

Moderate quality evidence from a single study (Burgin-Wolff et al., 2013) reported that the combination test for IgA EMA+ IgG DGP has low sensitivity [73%; 95% CI: 66 to 80] and high specificity [95%; 95% CI: 91 to 98] in the diagnostic process for children and adults suspected of coeliac disease.

5.2.5.3 Evidence for the sensitivity and specificity of combination IgA tTG + IgG DGP + IgA DGP testing

High quality evidence from a single study (Burgin-Wolff et al., 2013) reported that the combination test for IgA tTG+ IgG DGP + IgA DGP has low sensitivity [73%; 95% CI: 66 to 80] and high specificity [99%; 95% CI: 98 to 100] in the diagnostic process for children and adults suspected of coeliac disease.

5.2.5.4 Evidence for the sensitivity and specificity of combination IgA EMA + IgG DGP + IgA DGP testing

High quality evidence from a single study (Burgin-Wolff et al., 2013) reported that the combination test for IgA EMA+ IgG DGP + IgA DGP has low sensitivity [58%; 95% CI: 50 to 66] and high specificity [99%; 95% CI: 98 to 100] in the diagnostic process for adults suspected of coeliac disease.

5.2.5.5 Evidence for the sensitivity and specificity of combination IgA EMA + IgA tTG + IgG DGP testing

High quality evidence from a single study (Burgin-Wolff et al., 2013) reported that the combination test for IgA EMA+ IgA tTG + IgG DGP has low sensitivity [70%; 95% CI: 48 to 64] and high specificity [96%; 95% CI: 98 to 100] in the diagnostic process for children and adults suspected of coeliac disease.

5.2.5.6 Evidence for the sensitivity and specificity of combination IgA tTG + IgA EMA + IgA DGP + IgG DGP testing

High quality evidence from a single study (Burgin-Wolff et al., 2013) reported that the combination test for IgA tTG + IgA EMA+ IgG DGP + IgA DGP has low sensitivity [56%; 95% CI: 48 to 64] and high specificity [99%; 95% CI: 98 to 100] in the diagnostic process for children and adults suspected of coeliac disease.

5.2.5.7 Evidence for the sensitivity and specificity of combination IgA tTG + IgA EMA + HLA DQ2/DQ8

High quality evidence from a single study (Clouzeau Girard et al, 2011) reported that the combination test for IgA tTG + IgA EMA + HLA DQ2/DQ8 has high sensitivity [99%; 95% CI: 96 to 100] and high specificity [96%; 95% CI: 92 to 100] in the diagnostic process for children suspected of coeliac disease.

5.2.5.8 Evidence for the sensitivity and specificity of combination IgA + IgG h-tTG/DGP

High quality evidence from a single study (Mubarak et al., 2012) reported that the combination test for IgA + IgG h-tTG/DGP has high sensitivity [99%; 95% CI: 93 to 100] and specificity [99%; 95% CI: 96 to 100] in the diagnostic process for children suspected of coeliac disease.

Moderate quality evidence from a single study (Porcelli et al., 2011) reported that the combination test for IgA + IgG h-tTG/DGP has 100% sensitivity and moderate specificity [90%; 95% CI: 86 to 95] in the diagnostic process for adults suspected of coeliac disease.

5.2.5.9 Evidence for the sensitivity and specificity of the test algorithm If IgA tTG is positive, and then IgA EMA is positive

High quality evidence from a single study (Hopper et al., 2008) reported that the 2-step algorithm of positive IgA EMA following positive IgA tTG has moderate sensitivity [87%; 95%

CI: 65 to 97] and high specificity [97%; 95% CI: 95 to 98] in the diagnostic process for adults suspected of coeliac disease.

5.2.5.10 Evidence for the sensitivity and specificity of the test algorithm if IgA tTG is positive or equivocal, and then IgA EMA is positive

High quality evidence from a single study (Swallow et al., 2012) reported that the 2-step algorithm of positive IgA EMA following positive or equivocal IgA tTG has moderate sensitivity [86%; 95% CI: 76 to 92] and high specificity [99%; 95% CI: 98 to 99] in the diagnostic process for adults suspected of coeliac disease.

5.2.5.11 Evidence for the sensitivity and specificity of the test algorithm if both IgA tTG is positive and IgA EMA is positive

High quality evidence from 2 studies (Hopper et al., 2008; Swallow et al., 2012) reported that the 2-step algorithm of both positive IgA EMA and positive IgA tTG has moderate sensitivity [86%; 95% CI: 76 to 92] and high specificity [99%; 95% CI: 98 to 100] in the diagnostic process for adults suspected of coeliac disease.

5.2.5.12 Evidence for the sensitivity and specificity of the 2-step test algorithm if either IgA tTG is positive, or IgA EMA is positive

High quality evidence from a single study (Swallow et al., 2012) reported that the 2-step algorithm of either positive IgA EMA, or positive IgA tTG has moderate sensitivity [92%; 95% CI: 84 to 96] and specificity [90%; 95% CI: 89 to 92] in the diagnostic process for adults suspected of coeliac disease.

5.2.5.13 Health economic evidence statements

An original, directly applicable cost–utility analysis with minor limitations suggested that, in adults, the most effective testing strategy is to consider people serologically positive if they are positive on either IgA tTG or IgA EMA. However, the incremental benefit of this strategy comes at a very high cost (base-case ICER in excess of £170,000 per QALY), and much better value for money is achieved by a strategy that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive.

An original, directly applicable cost–utility analysis with minor limitations suggested that, in children, the most effective testing strategy is a combination of IgA tTG, IgA EMA and HLA DQ2/DQ8. However, the incremental benefit of this strategy comes at additional cost, with an ICER of approximately £34,000 per QALY. Of the modelled options, the most cost effective – when QALYs are assumed to be worth £20,000 – was a combination of IgG DGP and IgA tTG. No evidence was available to analyse the combination of IgA tTG and IgA EMA without additional tests in children.

5.2.6 Evidence to recommendations

Relative value of different outcomes

The GDG discussed and agreed that a single histological standard for the diagnosis of coeliac disease was needed in order to ensure consistency between studies. The ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) criterion relies in part on serological results to inform diagnosis; however, the GDG decided that these criteria would be inappropriate as a reference standard to investigate the accuracy of serological tests in the diagnosis of coeliac disease. The GDG agreed that Marsh criteria grade 3 was the most appropriate reference standard for the histological diagnosis of coeliac disease and that only studies using these criteria should be considered as part of the evidence review.

	<p>The GDG further raised the necessity of providing guidance on the operationalisation of 'equivocal' when examining the output of tTG results in order to optimize diagnostic accuracy. There is currently no guidance in interpreting weakly positive (or negative) results, and what defines these weak or equivocal ranges.</p> <p>The group was concerned that it was common for laboratories to assess IgA deficiency when testing for IgA tTG, essentially using IgA tTG as a surrogate marker for total IgA. The benefits of conducting total IgA testing were highlighted as important, because critical immunodeficiency's such as CVID and myeloma can be picked up, as well as those with IgA deficiency, which in itself is relatively common (1/500), and highly important to a person's immunological health and wellbeing.</p>
Trade-off between benefits and harms	<p>Inter-test variability and internal validity of serological testing</p> <p>The GDG discussed the number of different testing kits that are available for each antibody, in particular the transglutaminase ELISA kits and the wide variability in the sensitivity and specificity to diagnose coeliac disease between each of these different kits. The GDG agreed that there is a strong need for each laboratory to internally validate their serological testing assays in order to ensure optimal diagnostic utility. The GDG expressed concern that many laboratories may be using poor testing kits, and that internal validity of testing kits in each laboratory is not being examined, and further, that there is no evidence of quality assurance in labs to make sure that optimal internal validity is being achieved.</p> <p>The GDG 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.</p> <p>The GDG also noted that quality assurance procedures are now being replaced by ISO15189 (http://www.iso.org) which may play a part in increasing the reliability of serological testing by requiring laboratory scientists to examine and monitor internal validity of testing procedures.</p> <p>Equivocal range in tTG serological results</p> <p>The group recognised that each laboratory will have their own definitions of how to define equivocal tTG results, depending on the specific anti-tTG assay used. GDG members believed that, in most laboratories, equivocal can be interpreted as weakly positive. In this circumstance, the majority of laboratories will then conduct an EMA as a confirmatory test (as indicated in the current NEQAS report, 2014).</p> <p>The GDG expressed the purpose of the secondary EMA to be to make sure that the tTG was performed correctly in the first place, as it is known that one can conduct testing using the same ELISA on the same sample 3 separate times, and get slightly different result every time (see Egner et al., 2011). Laboratories tend to do anti-tTG because it is a test which is performed in large numbers and it is both comparatively easy to automate and can be quantified. It is often done in biochemistry labs, who have much experience in automating quantifiable assays, but little experience in more subjective immunological assays such as EMA immunofluorescence. It is also cheaper</p>

and more amenable for most laboratories to do IgA tTG. Actually anti-EMA testing is not significantly more expensive than tTG testing; however the procedure requires specialist immunological training. The problem was raised that theoretically 'equivocal' could be interpreted as slightly below the positive titre threshold, and therefore 'weakly negative'. The group agreed that those who were weakly negative were highly unlikely to have CD whilst those with unambiguously positive tTG were very likely to have CD, and it is those who are 'weakly positive' that they are unsure about and would be most important to have a secondary serological screen of EMA conducted.

The group further discussed the difficulty in determining how to define weakly positive, as each different ELISA uses different manufacturer-recommended cut-off points. It was noted that the ESPGHAN criteria in children uses 10 x the upper limit of normal as strongly positive, and that a similar algorithm could be used to define weakly positive. However 'normal' is still an ambiguous term which will differ between laboratories.

Testing for total IgA

The group discussed that it was very common for laboratories to examine IgA levels when testing for IgA tTG, essentially using IgA tTG as a surrogate marker for IgA deficiency. This was raised as poor practice, and highly problematic, because total IgA levels are measured using an assay that is not designed or validated for measuring these levels (the ELISA is designed to measure tTG, not total IgA). The benefits of conducting total IgA testing were highlighted as highly important, primarily to maximise diagnostic accuracy, but also because critical immunodeficiency's such as common variable immunodeficiency can be picked up, as well as IgA deficiency, which in itself is relatively common in people with coeliac disease. The costs of conducting a separate test for total IgA were discussed and agreed to be negligible (when the test is undertaken as part of multiple tests on the same sample, as would be the case here), further supporting the notion that this test should be carried out separately to IgA tTG in all circumstances. The group also raised the accreditation process that will be introduced under ISO15189, whereby each individual assay must undergo an accreditation process to prove optimal practice and replicable results. Under this accreditation process, it is highly likely that IgA tTG assays will only be accredited to test for IgA tTG. If laboratories that do not have total IgA assays undergo accreditation, they will not have an accredited means of testing for total IgA, which would be a potential violation of good clinical practice standards.

Need for biopsy (in adults)

The group recognised that one component of this review was to determine under which circumstances serology would be accurate enough to diagnose CD, and therefore not require a biopsy to make a diagnosis. The group felt strongly that a biopsy should always be used to confirm a diagnosis for the following reasons:

- Serology is imperfect and there is great variation in the assays used and the inter-test reliability within each laboratory across the country.
- Likelihood of a false-positive diagnosis may be increased. This may lead to a person commencing a strict lifelong gluten-free diet without having the disorder. Therefore it is the responsibility of the clinician to confirm the diagnosis beyond reasonable doubt. Symptoms can be those of IBS and could respond to gluten withdrawal without having coeliac disease – so a

combination of serology and symptom relief on gluten withdrawal is not good enough

- If a patient starts a gluten-free diet without having a biopsy, the diagnosis may subsequently be very difficult to confirm if there is any doubt at a later stage.
- An endoscopic intestinal biopsy allows clinicians to simultaneously check for and exclude comorbid or alternative diagnoses, including very serious conditions such as enteropathy-associated lymphoma and other kinds of intestinal cancers.
- Ongoing symptoms will require re-biopsy. Therefore, if no index biopsy was taken it is impossible to assess whether histological recovery has taken place.

The group 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.

Deamidated gliadin peptides (DGP)

The GDG discussed and agreed that the evidence for deamidated gliadin peptides (DGP) looks promising; however, evidence for these antibodies is still emerging and needs to be strengthened by more studies before any recommendations can be made as to the diagnostic utilities for these.

Combination testing

The GDG discussed combination testing for achieving optimal sensitivity and specificity of diagnosis. It was agreed that there is a lack of evidence for the utility of second-line testing after initial serology is negative in people strongly suspected of coeliac disease.

HLA DQ2.5 DQ2.2 and DQ8 genotyping

The GDG discussed HLA DQ2/DQ8 genotyping and the variability between different centres in terms of how results are reported and fed back to clinicians. In particular, the GDG expressed a need for the standardisation of which HLA DQ2/DQ8 haplotypes were examined. The GDG further expressed that many less common HLA haplotypes exist, however the most common, accounting for around 99% of HLA genotypes relevant to coeliac disease, are HLA DQ2.5, DQ2.2, and DQ8. The GDG wished to specifically refer to these HLA variants when recommending HLA genotyping.

Economic considerations

In the original health economic analysis, the lifetime effectiveness of each strategy – in terms of QALYs accrued – was found to be strongly correlated with the strategy's sensitivity. This is because false-negative diagnoses are associated with reduced QALYs (as a function of both persistent coeliac symptoms and increased likelihood of long-term complications, some of which may impact on life expectancy). Therefore, strategies with fewest false-negative diagnoses are those that accrue most QALYs. Conversely, the total costs of each strategy are strongly correlated with their specificity. This is predominantly because false-positive serological diagnoses incur additional costs due to unnecessary endoscopic biopsies that would be avoided with a more specific approach.

Weighing these factors against each other leads to somewhat different conclusions in adults and children. In adults, greatest value for money (maximal net monetary benefit at £20,000 per QALY) tends to be achieved by strategies that are most sensitive (that is, those that minimise false-negative diagnoses and, therefore, maximise QALYs). In children, the approaches that demonstrate greatest value are those that have higher specificity (that is, those with fewest false-positive diagnoses that, therefore, minimise costs). The reason for this difference is that endoscopic biopsies are much more expensive in the paediatric population, as they are invariably performed under general anaesthesia. However, the GDG also emphasised the importance of correctly identifying children with coeliac disease, and did not believe that minimising false-positive diagnoses could, alone, be the overriding objective of best practice.

In adults, the most effective strategy was the most sensitive – that is, considering people serologically positive if they are positive on either IgA tTG or IgA EMA. However, the incremental benefit of this approach came at a very high cost: the base-case ICER exceeded £170,000 per QALY. However, the model suggested that almost all the benefit of this approach could be achieved at lower cost by a strategy that tests IgA tTG in all people and reserves IgA EMA to classify cases in which IgA tTG results are weakly positive. Indeed, accounting for the costs of the tests themselves and the downstream consequences of true and false diagnoses over the lifetime of the cohort, the model estimated that this approach is associated with lowest net costs of all options. The GDG concluded that it should be recommended as the preferred approach.

Although sensitivity was the main determinant of value in the adult population, small differences in sensitivity between strategies could be outweighed by larger differences in specificity. This was the case with the recommended approach: although there were 2 strategies in the model that had higher sensitivity than IgA tTG with IgA EMA to determine weakly positive cases, the benefits associated with those strategies' superior true-positive rates were smaller than the harms and costs associated with their inferior false-positive rates (lower specificities).

The GDG noted that current provision of serological testing is variable, with different laboratories relying on different assays, either singly or in combination. This means that, in order to recommend the routine use of any particular strategy (especially one involving more than 1 test); it would be necessary to take account of the implications for standardising practice. In particular, the additional costs associated with the new equipment required by some laboratories should be accounted for. Therefore, in addition to the unit cost of each test, the original model included an approximate estimate of additional capital costs that would be incurred, by some laboratories, in expanding their provision to enable them to undertake those tests. Data from a national audit of current provision (NEQAS) were used to estimate the proportion of laboratories for which such additional investment would be necessary. These additional costs had no impact on base-case findings: the strategy using IgA tTG as a first-line test with IgA EMA to discriminate in cases of weak tTG positivity remained optimal. Further exploration of this parameter suggested that the total costs of increasing capacity would have to increase the unit cost of every tTG test undertaken in England and Wales by over £4 per test before it would be preferable to rely on a single-test strategy. This figure was very substantially higher than the base-case estimate of 9p per test;

therefore, the GDG considered that any capital costs required would be clearly justified.

In children, the most effective strategy was one that combined serological assays for IgA tTG and IgA EMA and HLA DQ2/DQ8 genotyping, an approach that had been shown to benefit from very high sensitivity and specificity in the clinical evidence review. However, because HLA DQ2/DQ8 genotyping is a relatively expensive test (over £70 each, some 5–8 times more expensive than any of the serological assays), its routine use is associated with significant costs, with the consequence that the 3-test strategy was associated with a relatively high ICER, around £34,000 per QALY gained compared with the next-cheapest non-dominated option. The GDG 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 GDG noted that many of the strategies that appear attractive in children, from a cost effectiveness point of view, are combination approaches that include one or more DGP assay. The group was aware that all evidence for these tests in children came from a single study (Burgin Wolff et al., 2013). While these results appeared promising, especially as regards the high specificity of the strategies, the group felt that further research would be necessary before such approaches could be universally recommended. Therefore, the GDG chose to make a research recommendation for further research into the accuracy of DGP assays, particularly in younger children.

If DGP-containing strategies are excluded from the paediatric decision-space, IgA tTG is the least expensive strategy in the model. It is also estimated to be more effective than IgA EMA alone (that is, it dominates it). Under this circumstance, the model predicts that the 3-test combination of IgA tTG, IgA EMA and HLA DQ2/DQ8 would become the optimal approach, generating more QALYs than any of the individual tests alone, with an ICER of approximately £6000 per QALY compared with IgA tTG as a single test. However, the GDG reiterated that there are significant practical barriers to the adoption of routine HLA DQ2/DQ8 genotyping in the primary care settings in which most initial testing would be undertaken.

In theory, one first-line testing strategy that might be considered in children would be to combine IgA tTG and IgA EMA assays (in a serial algorithm – as in the recommended approach for adults – or in parallel). However, there was no evidence on the accuracy of any strategies combining these tests in children. Moreover, the GDG felt that positive results on any single assay warranted consideration by a specialist in paediatric gastroenterology.

Therefore, the GDG chose to split their recommendation into 2 parts, with first-line testing comprising IgA tTG assay (which should be available and familiar in primary care), followed by referral to a specialist for further investigation (which might include IgA EMA testing and/or HLA DQ2/DQ8 genotyping as well as consideration for endoscopic biopsy). By doing this, the GDG believed that costs associated with genetic testing would be minimised – as specialists would be able to use their experience in ordering the test, rather than taking the more indiscriminate approach that a routine testing strategy implies. In this way, the group inferred that the effectiveness of the recommended strategy would be similar to that achieved under routine 3-step testing, and the costs would be reduced.

A further exploratory analysis using the original health economic model

	<p>attempted to simulate the benefits, harms and costs of a diagnostic algorithm for children that enables a diagnosis of coeliac disease to be made without the need for confirmatory biopsy (as proposed by ESPGHAN). This analysis was more speculative than other simulated strategies, as it was not based on direct evidence of the diagnostic accuracy of the algorithm; instead, it combined evidence on various tests used in isolation and assumed independence between them. The model suggested that this approach is extendedly dominated by some sequences with routine biopsy that had been simulated. However, results were broadly comparable, in terms of costs and effects, to some of the better-value approaches. The GDG was aware that primary evidence on the accuracy of the ESPGHAN algorithm is due to be published in 2015, and concluded that any explicit recommendation endorsing or rejecting the approach should await the availability of this evidence.</p> <p>It should be noted that the original health economic analysis assumed that everyone who is serologically positive undergoes confirmatory biopsy and that biopsy is 100% accurate. Therefore, there is no such thing as a long-term false-positive diagnosis in the model: biopsy immediately corrects the false-positive serology, and the only disbenefits incurred are the costs and disutility associated with an unnecessary endoscopy.</p>
<p>Quality of evidence</p>	<p>The GDG discussed and agreed that the evidence ranged from high to low quality due to methodological issues such as small sample size and potential biases in retrospective studies where the intention to biopsy may be been driven by serological results, or strong clinical suspicion. However, the GDG agreed that, in general, the measures taken to ensure optimal quality results, such as the single histological reference criteria, homogeneous European sample, a single suspected coeliac disease population, and the 100% serology and an endoscopic intestinal biopsy in all participants, ensured that evidence obtained was of the best quality available.</p>
<p>Other considerations</p>	<p>As detailed above, the GDG noted that IgA tTG alone has suboptimal specificity. Therefore, the group concluded that, in adults, a strategy using IgA EMA to classify cases that are weakly positive on IgA tTG should be recommended. Evidence suggested that this approach has excellent specificity and only slightly reduced sensitivity, and the health economic modelling showed that this represented an optimal trade-off between the risks of false-positive and false-negative diagnoses (see below).</p> <p>However, the GDG was aware that evidence on diagnostic accuracy of serological tests can only reflect standards that have been achieved historically. With developments in IgA tTG assays in mind, the GDG noted that it might be possible for a laboratory to demonstrate through its internal validation processes that it is able to achieve levels of specificity from a single IgA tTG test that are comparable with the expected specificity of the 2-step strategy (that is, 99% or better). If this were the case, the GDG thought it would be reasonable for such a laboratory to rely on IgA tTG assays alone, as that approach would benefit from better sensitivity, and specificity would not be compromised. However, the group chose not to make an explicit recommendation detailing this eventuality, as it believed that the circumstances would be rare.</p> <p>The GDG noted that its recommendations for adults and children were closely comparable, with the only difference coming in the handling of weakly positive IgA tTG results – adults with this finding would be subject to an additional</p>

serological test before referral to a gastrointestinal specialist, whereas children would be referred straight away. The group suggested that, in practice, the paediatricians to whom children with weakly positive IgA tTG results are referred may choose to perform additional tests such as IgA EMA in the same way that the group had recommended for adults. However, in the absence of evidence of this approach in children, the group felt that a prescriptive recommendation for either primary care professionals or secondary care specialists would not be helpful. Nevertheless, it was felt that the emergence of these related recommendations from discrete evidence-bases and modelling with somewhat different assumptions provided a degree of convergent validity.

5.2.7 Recommendations & research recommendations

5.2.7.1 Recommendations

4. **All serological tests should be undertaken in laboratories with clinical pathology accreditation (CPA) or ISO15189 accreditation.**
5. **When healthcare professionals request serological tests to investigate suspected coeliac disease in young people and adults, laboratories should**
 - test for total immunoglobulin A (IgA) and IgA tissue transglutaminase (tTG) as the first choice
 - use IgA endomysial antibodies (EMA) if IgA tTG is weakly positive
 - consider using IgG EMA, IgG deamidated gliadin peptide (DGP) or IgG tTG if IgA is deficient^a.
6. **When healthcare professionals request serological tests to investigate suspected coeliac disease in children, laboratories should:**
 - test for total IgA and IgA tTG as the first choice
 - consider IgG EMA, IgG DGP or IgG tTG if IgA is deficient^a.
7. **When laboratories test for total IgA, a specific assay designed to measure total IgA levels should be used.**
8. **Refer young people and adults with positive serological test results^h to a gastrointestinal specialist for endoscopic intestinal biopsy to confirm or exclude coeliac disease.**
9. **Refer children with positive serological test results to a paediatric gastroenterologist or a paediatrician with a specialist interest in gastroenterology for further investigationⁱ for coeliac disease**

^h In young people and adults, a positive serological result is defined as: unambiguously positive IgA tTG alone, **or** weakly positive IgA tTG **and** a positive IgA EMA test result. Note: In people who have IgA deficiency, a serologically positive result can be derived from any one of the IgG antibodies.

ⁱ Further investigation may include, but is not limited to, one or more of the following: an IgA EMA test to confirm serological positivity, HLA genetic testing, an endoscopic biopsy

- 10. Refer people with negative serological test results to a gastrointestinal specialist for further assessment if coeliac disease is still clinically suspected.**
- 11. Healthcare professionals should have a low threshold for re-testing people identified in recommendations 1 or 2 if they develop any symptoms consistent with coeliac disease.**
- 12. Laboratories should clearly communicate the interpretation of serological test results and recommended action to healthcare professionals.**
- 13. Do not use human leukocyte antigen (HLA) DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the initial diagnosis of coeliac disease in non-specialist settings.**
- 14. Only consider using HLA DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the diagnosis of coeliac disease in specialist settings (for example, in children who are not having a biopsy, or in people who already have limited gluten ingestion and choose not to have a gluten challenge).**

5.2.7.2 Research Recommendations

- 1. What is the sensitivity and specificity of IgA DGP and IgG DGP in the detection of coeliac disease in children aged under 2 years?**

Why this is important

The deamidated gliadin peptide (DGP) antibodies are emerging as promising antibodies for the detection of coeliac disease. There is evidence which suggests that these antibodies may be particularly useful in children under the age of two years old (Mubarak et al., 2011). Further research into the sensitivity and specificity of the DGP antibodies in children under two years of age will strengthen this preliminary evidence and may lead to these antibodies being the first point of call in serological testing for coeliac disease in children under two years old.

- 2. What is the sensitivity and specificity of IgG tTG, IgG EMA and IgG DGP tests in detecting coeliac disease in people with IgA deficiency?**

Why this is important

IgA deficiency is significantly more common in people with coeliac disease than in the general population. People with IgA deficiency will have a false negative result when tested for IgA antibody, which may lead to a missed diagnosis of coeliac disease. A missed diagnosis may result in increased use of NHS resources and the person experiencing the risks associated with undiagnosed coeliac disease. IgG antibodies are recommended for use in place of IgA antibodies in people who have IgA deficiency, but there is limited evidence to demonstrate the sensitivity and specificity of tests for IgG antibodies – that is, IgG tTG, IgG EMA and IgG DGP – in people suspected of having coeliac disease with IgA deficiency.

- 3. 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?**

Why this is important

In people with suspected coeliac disease, IgA tTG is most commonly used as the first-choice test to detect the presence of coeliac disease antibodies but some people with coeliac

disease will get a false negative result this happens, and if there is a strong and ongoing clinical suspicion of coeliac disease, serological testing for IgA EMA or IgA or IgG DGP antibodies should also be requested. However, there is little evidence for the sensitivity and specificity of these antibodies in people who have tested negative for IgA tTG antibodies. A clearer understanding of the sensitivity and specificity of EMA and DGP antibodies in people who have tested negative for IgA tTG will allow clinicians to better interpret test results and make a more informed diagnosis.

5.3 Criteria for referral for endoscopic intestinal biopsy

5.3.1 Review question

What are the referral indications for endoscopic intestinal biopsy for further investigation in people with coeliac disease?

Once diagnosed and treated with a gluten-free diet, most people with coeliac disease experience significant improvement in their clinical symptoms, which typically resolve after 3 to 6 months. In some circumstances, people with CD may experience little or no improvement of their symptoms, or a resurgence of clinical symptoms after a period of resolution. In these situations an endoscopic biopsy may be required for further investigation.

5.3.2 Methods

The aim of this review question was to determine what factors may indicate appropriate referral for endoscopic intestinal biopsy for people with coeliac disease.

Studies were only included if the population examined were adults or children with a diagnosis of coeliac disease who were being monitored while on a gluten-free diet and in whom an endoscopic intestinal biopsy may be useful for further investigation.

Outcomes of interest were as follows: complications of coeliac disease; mortality; health-related quality of life; and resource use and cost.

For full details of the review protocol please see Appendix C.

A systematic search was conducted (see Appendix C) which identified 925 references. The references were screened on their titles and abstracts and full text papers of 20 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

All 20 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (case-studies), not a primary study (descriptive narrative, opinion, etc.), or studies in which an endoscopic intestinal biopsy was being conducted for the purposes of initial diagnoses rather than for follow-up investigation. A detailed list of excluded studies and reasons for their exclusion is provided in appendix F.

No data were available in relation to the a-priori specified outcomes of interest. A post-hoc decision was made by the GDG to analyse the following data, which was available from other related review questions (see sections 5.4 and 6.1);

- Change in serological markers on routine monitoring on a gluten-free diet as an indication of histological recovery
- Presenting symptoms of nonresponsive coeliac disease (NRCD) as an indication for the need for further assessment

As these outcomes of interest directly relate to review questions in sections 5.4 (monitoring of people with coeliac disease) and 6.1 (presenting features of non-responsive coeliac disease), relevant evidence was extrapolated from each of these review questions to inform the present review. Overall, 5 papers from the present literature review met the inclusion criteria and were included for analyses. A further 5 studies from review question in section 5.4, and 4 studies from review question 6.1 met the inclusion criteria and were therefore included within the present review.

Cohort studies were considered the best quality evidence for this question and were therefore considered high quality according to a modified GRADE framework. The quality for

each outcome could be downgraded due to risk of bias in terms of methods, inconsistency between studies, indirectness in terms of population, tests and outcomes used, or imprecision in terms of outcomes.

Data were extracted into detailed evidence tables (see Appendix D)

5.3.3 Evidence review

5.3.3.1 Resolution of gastrointestinal and non-gastrointestinal symptoms

Two studies (Dickey et al, 2000; Midhagen et al., 2004) contributed data to the analysis. Dickey (2000) included 53 young people and adults (16 to 81 years of age). None of the study population had IgA deficiency. Midhagen (2004) included 21 adults but was unclear on the age range of participants. None of the study population had IgA deficiency.

5.3.3.2 Change in IgA EMA while on GFD

Four studies (Dickey et al., 2000, Fotoulaki et al., 1999, Midhagen et al., 2001, Trigoni et al., 2014) contributed data to this analysis. Samples sizes ranged from 17 to 70, people with coeliac disease with positive EMA at diagnosis, the percentage with IgA deficiency ranged from 0% to 10%. The age of study participants ranged from 1 to 86 years. The study participants were on a gluten-free diet for between 3 months and 3 years.

5.3.3.3 Change in IgA anti-reticulin antibodies (IgA ARA) while on GFD

A single study (Fotoulaki et al., 1999) contributed data to this analysis. This study included 30 children, young people and adults (age range 1 to 24 years) with coeliac disease diagnosed using ESPGHAN criteria, and 3 (10%) had IgA deficiency. The study participants were on a gluten-free diet for up to 12 months.

5.3.3.4 Change in IgA tTG while on GFD

Four studies (Martin-Pagola et al., 2007, Midhagen et al., 2001, Samasca et al., 2011, Trigoni et al., 2014) contributed data to this analysis. Samples sizes ranged from 14 to 93, people with coeliac disease. None of the study populations had IgA deficiency. Two studies included children and young people (0.95 to 17.5 years of age but the range was not reported in the second study) and 2 included adults (19 to 86 years). The study participants were on a gluten-free diet for between 3 months and 3 years.

5.3.3.5 Change in IgG tTG while on GFD

One study (Martin-Pagola et al., 2007) contributed data to this analysis. This study included 93 children and young people (aged between 0.95 to 17.5 years diagnosis) of whom none of the study populations had IgA deficiency. The study participants had been on a gluten-free diet for an average of 24 months at study follow-up.

5.3.3.6 Change in IgA AGA while on GFD

A single study (Midhagen et al., 2004) contributed data to this analysis. This study included adults (age range 29 to 86 years) with coeliac disease who tested positive for IgA AGA at diagnosis. It was unclear how many participants had IgA deficiency. The study participants were on a gluten-free diet for up to 12 months.

5.3.3.7 Proportion of patients suffering persistent symptoms whilst on gluten-free diet

Four studies (Dewar et al., 2010; Leffler et al., 2007; Abdulkarim et al., 2002; Van Weyenberg et al., 2013) contributed data to this analysis. These studies included adults (age

range 29 to 79 years) with coeliac disease who presented with persistent symptoms despite being on a gluten-free diet for a minimum of 12 months.

5.3.3.8 Presenting symptoms of non-responsive coeliac disease (NRCD)

Four studies (Dewar, 2012; Leffler, 2007; Abdulkarim, 2002; Van Weyenberg, 2013) contributed data to this analysis. Samples sizes ranged from 48 to 113 adults with non-responsive coeliac disease. The mean age of study participants ranged from 42 to 63 years. The study participants were on a gluten-free diet for between 6 months and 6 years.

5.3.4 Health economic evidence

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that explored the cost effectiveness of referral indications for endoscopic intestinal biopsy for further investigation of people with coeliac disease.

The search identified 97 references. The references were screened on their titles and abstracts however none of the studies met the inclusion criteria.

No cost–utility analyses were found to address selection criteria

5.3.5 Evidence statements

5.3.5.1 Evidence for proportion in clinical remission while on GFD

Very low quality evidence from 2 studies (N = 71) found that between 89% and 91% of people diagnosed with coeliac disease were in clinical remission after 12 months on a gluten-free diet

5.3.5.2 Evidence for proportion with negative IgA EMA while on GFD

Very low quality evidence from 2 studies (N = 60) found that between 41% and 58% of adults with coeliac disease were IgA EMA negative after 3 months on a gluten-free diet

Very low quality evidence from a single study (N = 30) found that 57% of mixed age-groups were IgA EMA negative after 3 months on a gluten-free diet

Very low quality evidence from 3 studies (N = 130) found that between 39% and 75% of adults with coeliac disease were IgA EMA negative after 6 months on a gluten-free diet

Very low quality evidence from a single study (N = 30) found that 93%% of mixed age-groups were IgA EMA negative after 6 months on a gluten-free diet

Very low quality evidence from a single study (N = 30) found that 90% of mixed age-groups were IgA EMA negative after 9 months on a gluten-free diet

Very low quality evidence from 3 studies (N = 130) found that between 73% and 87% of adults with coeliac disease were IgA EMA negative after 12 months on a gluten-free diet

Very low quality evidence from a single study (N = 30) found that 100% of mixed age-groups were IgA EMA negative after 6 months on a gluten-free diet

Very low quality evidence from a single study (N = 70) found that 94% of adults were IgA EMA negative after 6 months on a gluten-free diet

5.3.5.3 Evidence for proportion with negative IgA ARA while on a GFD

Very low quality evidence from a single study (N = 30) found that 77% of adults with coeliac disease were IgA ARA negative after 3 months on a gluten-free diet

Very low quality evidence from a single study (N = 30) found that 87% of adults with coeliac disease were IgA ARA negative after 6 months on a gluten-free diet

Very low quality evidence from a single study (N = 30) found that 100% of adults with coeliac disease were IgA ARA negative after 9 months on a gluten-free diet

Very low quality evidence from a single study (N = 30) found that 100% of adults with coeliac disease were IgA ARA negative after 12 months on a gluten-free diet

5.3.5.4 Evidence for proportion with negative IgA tTG while on a GFD

Very low quality evidence from a single study (N = 50) found that 68% of children with coeliac disease were IgA tTG negative after 3 months on a gluten-free diet.

Low quality evidence from a single study (N = 14) found that 57% of adults with coeliac disease were IgA tTG negative after 3 months on a gluten-free diet.

Very low quality evidence from 2 studies (N = 143) found that between 49% and 68% of children with coeliac disease were IgA tTG negative after 6 months on a gluten-free diet.

Low quality evidence from 2 studies (N = 84) found that between 20% and 71% of adults with coeliac disease were IgA tTG negative after 6 months on a gluten-free diet.

Very low quality evidence from a single study (N = 50) found that 82% of children with coeliac disease were IgA tTG negative after 12 months on a gluten-free diet.

Very low quality evidence from 2 studies (N = 84) found that between 49% and 100% of adults with coeliac disease were IgA tTG negative after 12 months on a gluten-free diet.

Very low quality evidence from a single study found that 88% of children with coeliac disease were IgA tTG negative after 24 months on a gluten-free diet.

Very low quality evidence from a single study (N = 70) found that 80% of adults with coeliac disease were IgA tTG negative after 3 years on a gluten-free diet.

5.3.5.5 Evidence for proportion with negative IgG tTG while on a GFD

Very low quality evidence from a single study (N = 93) found that 63% of children with coeliac disease were IgG tTG negative after 6 months on a gluten-free diet.

Low quality evidence from a single study (N = 93) found that 96% of children with coeliac disease were IgG tTG negative after 24 months on a gluten-free diet

5.3.5.6 Evidence for proportion with negative IgA AGA while on a GFD

Low quality evidence from a single study (N = 15) found that 74% of adults with coeliac disease were IgA AGA negative after 3 months on a gluten-free diet

Low quality evidence from a single study (N = 15) found that 93% of adults with coeliac disease were IgA AGA negative after 6 months on a gluten-free diet

Low quality evidence from a single study (N = 15) found that 100% of adults with coeliac disease were IgA AGA negative after 12 months on a gluten-free diet

5.3.5.7 Evidence for symptom presentation of nonresponsive coeliac disease (NRCD)

Five high quality studies found that between 50 – 84% of people experiencing NRCD experience persistent diarrhoea while following a gluten-free diet for a period of at least 6 months.

Five high quality studies found that between 14 – 55% of people experiencing NRCD experience persistent abdominal pain while following a gluten-free diet for a period of at least 6 months.

Five high quality studies found that between 5 – 47% of people experiencing NRCD experience persistent weight loss while following a gluten-free diet for a period of at least 6 months.

Three high quality studies found that between 5 – 43% of people experiencing NRCD experience persistent lethargy while following a gluten-free diet for a period of at least 6 months.

Two high quality studies found that between 10 – 17% of people experiencing NRCD experience persistent nausea with or without vomiting while following a gluten-free diet for a period of at least 6 months.

Three high quality studies found that between 4 – 37% of people experiencing NRCD experience persistent anaemia while following a gluten-free diet for a period of at least 6 months.

5.3.6 Evidence to recommendations

<p>Relative value of different outcomes</p>	<p>The GDG discussed and agreed that currently there was very limited evidence on the a priori selected outcomes of complications of CD, mortality, health-related quality of life, and resource use and cost, in relation to indications for endoscopic intestinal biopsy for further investigation in those with CD.</p> <p>The value of using serological testing to drive indication for biopsy was discussed extensively in terms of the low sensitivity and specificity of these tests as markers of diet adherence and histological recovery (see section 5.4). For example, symptoms may disappear while on a gluten-free diet however an endoscopic intestinal biopsy shows no histological recovery.</p> <p>The value of using symptomology to drive indication for an endoscopic intestinal biopsy was also discussed in detail. It was recognised that not all people with coeliac disease have symptoms at diagnosis, and therefore, symptoms are not a useful marker of clinical response to gluten-free diet. These people may require an endoscopic intestinal biopsy to ensure that there is histological response to the gluten-free diet.</p> <p>The group also cited published research and anecdotal experience of cases that had shown symptomatic improvement despite patients having persistent severely damaged villi, or vice versa, suggesting that clinical improvement should also not be relied upon as an indication for biopsy.</p>
<p>Trade-off between benefits and</p>	<p>The benefit of routine monitoring was discussed and the group agreed this was useful in order to identify those in whom a gluten-free diet is not having an optimal outcome. (See section 5.4). It was discussed by</p>

harms	<p>the GDG that often clinicians will chose to re-biopsy patients after 18 – 24 months as part of a monitoring strategy. Persistently high titres in serology can indicate when further investigations are needed; however persistently high titres may also be misleading and be unrelated to histological outcome. The group agreed however, that in a person with persistently high antibodies, an endoscopic intestinal biopsy would be useful to inform the full clinical picture.</p> <p>People who present with symptoms of non-responsive coeliac disease should be referred to an expert dietitian, as the most common cause of persisting clinical symptoms is gluten ingestion (see section 6.1). Due to the invasive nature of biopsy, the group agreed that a person with non-responsive CD should only be considered for re-biopsy for further investigation after continued gluten ingestion has been ruled out. Most people with coeliac disease report clinical improvement within 2–6 months; anything beyond this was agreed to represent an outlier.</p>
Economic considerations	<p>No economic evidence on referral indications for endoscopic intestinal biopsy for further investigation of coeliac disease was found.</p>
Quality of evidence	<p>Overall the evidence identified for serological monitoring was of very low quality. This is because although it is possible to design a randomised controlled trial comparing two different monitoring strategies. No such study was identified and only lower quality evidence with design limitations was used in this review. The quality of evidence for presenting symptoms for non-responsive coeliac disease was high.</p>
Other considerations	<p>Current clinical practice in the UK is to monitor with serology on an annual basis. Biopsies are often repeated 12 to 24 months after diagnosis. The GDG did not consider the evidence sufficient to change current practice regarding serology and biopsy, despite the fact that they did not believe that serology was an accurate biomarker for response to gluten-free diet.</p>

5.3.7 Recommendations & research recommendations

15. Consider referring people with coeliac disease for endoscopic intestinal biopsy if continued exposure to gluten has been excluded and:

- Serological titres are persistently high and show little or no change after 12 months **or**
- they have persistent symptoms, including diarrhoea, abdominal pain, weight loss, fatigue or unexplained anaemia.

5.4 Routine monitoring

5.4.1 Review questions

How frequently should people with coeliac disease be routinely monitored?

Should the frequency of routine monitoring differ for patients at risk of developing certain complications?

What should routine monitoring consist of?

There exists a great variation in current clinical practice in terms of what constitutes the routine monitoring of those with coeliac disease. Some centres may monitor patients more frequently and choose to biopsy patients within a year of diagnosis to assess histological recovery, while other centres may offer initial dietetic advice and follow-up patients only in the event of continued complications. The relationship between frequency and type of monitoring and the clinical symptoms of coeliac disease is yet to be explored. Optimal follow-up and monitoring should aim to aid those with coeliac disease to achieve histological and symptomatic recovery. The aim of this review is therefore to identify what optimal monitoring practice should consist of.

5.4.2 Methods

The aim of these review questions was to determine how often people with coeliac disease should be followed up. The second component of this question was designed to investigate if any subgroups at risk of developing any particular complications of coeliac disease should be followed up more frequently. The final component of this question examined what assessments and checks should be carried out to monitor coeliac disease, particularly in those at risk of developing complications.

Studies were only included if the population examined included people of any age who were diagnosed with coeliac disease and who were being monitored while on a gluten-free diet. GDG-selected outcomes of interest were as follows; resolution of gastrointestinal and non-gastrointestinal symptoms, growth in children and young people, complications of coeliac disease, dietary adherence, impact on carers and health-related quality of life. All forms of monitoring were considered appropriate for inclusion.

For full details of the review protocol please see Appendix C.

A systematic search was conducted (see Appendix C) which identified 4851 references. The references were screened on their titles and abstracts and full text papers of 63 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

Fifty three studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (case-series with variable length of follow-up), not a primary study (descriptive narrative, opinion, etc.). A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

Randomised controlled trials were considered to be the highest quality evidence available to answer this question and are graded as high in a GRADE framework. No randomised controlled trials were identified so studies with the next best design (cohort studies) for this question were used. The quality for each outcome could be downgraded due to risk of bias in terms of methods, inconsistency between studies, indirectness in terms of population, tests and outcomes used, or imprecision in terms of outcomes.

Ten papers met this revised criteria and were included. Another 2 studies were identified through searches for other questions or reference checking and so a total of 12 studies were included. No randomised controlled trials were identified, and cohort studies were rated as low quality. Data were extracted into detailed evidence tables (see Appendix D)

Data were available for 2 of the a priori GDG specified outcomes resolution of gastrointestinal and non-gastrointestinal symptoms and dietary adherence but no data were identified for the other four GDG requested outcomes.

A post-hoc decision was taken to analyse the following as data were available;

- Change in serological markers on routine monitoring on a gluten-free diet
- Change in histology on routine monitoring on a gluten-free diet
- Nutritional status while on gluten-free diet
- Healthcare professionals involved in routine monitoring

5.4.3 Evidence review

5.4.3.1 Resolution of gastrointestinal and non-gastrointestinal symptoms

Two studies (Dickey et al., 2000; Midhagen et al., 2004) contributed data to the analysis. Dickey et al., 2000 included 53 young people and adults (16 to 81 years of age), of whom 39 (74%) were female. None of the study population had IgA deficiency. Midhagen and colleagues (2004) included 21 adults but was unclear on the proportion of female participants and the age range. None of the study population had IgA deficiency.

5.4.3.2 Adherence to gluten-free diet

Five studies (Dickey et al., 2000, Monzani et al., 2011, Trigoni et al., 2014, Zanchi et al., 2013; Galli et al., 2014) contributed data to this analysis. The sample sizes ranged from 28 to 315 and the proportion of female participants ranged from 61% to 74%. None of the study populations had IgA deficiency. The studies had mixed age groups with Monzani et al., (2011) including children, (1 to 16.8 years of age), Zanchi et al., (2013) including children and adults (6 to 45 years of age) while the remaining 3 studies included only adults (16 to 81 years of age).

5.4.3.3 Growth in children and young people

- No studies reported this outcome

5.4.3.4 Complications of coeliac disease

- No studies reported this outcome

5.4.3.5 Impact on carers

- No studies reported this outcome

5.4.3.6 Health-related quality of life

- No studies reported this outcome

5.4.3.7 Diagnostic accuracy to detect non-adherence

Two studies (Monzani et al., 2011, Zanchi et al., 2013) reported on the accuracy of serological tests to detect non-adherence to a gluten-free diet. Monzani et al., 2011 included 28 children and young people, of whom 17 (61%) were female between the ages of 1 and 16.8 years. None of the children had IgA deficiency. Zanchi et al., (2013) included 315 children and adults with an age range of 6 to 45 years of whom 227 (65%) female. IgA

deficiency status was not reported. The findings of both studies are summarised in table 1 below.

5.4.3.8 Change in IgA EMA while on GFD

Four studies (Dickey et al., 2000, Fotoulaki et al., 1999, Midhagen et al., 2001, Trigoni et al., 2014) contributed data to this analysis. Samples sizes ranged from 17 to 70, including people with coeliac disease with positive EMA at diagnosis, the percentage of female participants ranged from 55% to 74%; the percentage with IgA deficiency ranged from 0% to 10%. The age of study participants ranged from 1 to 86 years. The study participants were on a gluten-free diet for between 3 months and 3 years.

5.4.3.9 Change in IgA anti-reticulin antibodies (IgA ARA) while on GFD

A single study (Fotoulaki et al., 1999) contributed data to this analysis. This study included 30 children, young people and adults (age range 1 to 24 years) with coeliac disease diagnosed using ESPGHAN criteria. 17 (57%) were female and 3 (10%) had IgA deficiency. The study participants were on a gluten-free diet for up to 12 months

5.4.3.10 Change in IgA tTG while on GFD

Four studies (Martin-Pagola et al., 2007, Midhagen et al., 2001, Samasca et al., 2011, Trigoni et al., 2014) contributed data to this analysis. Samples sizes ranged from 14 to 93, people with coeliac disease. The percentage of females ranged from 54.5% to 71% and none of the study participants had IgA deficiency. Two studies included children and young people (0.95 to 17.5 years of age but the range was not reported in the second study) and 2 studies included adults (19 to 86 years). The study participants were on a gluten-free diet for between 3 months and 3 years

5.4.3.11 Change in IgG tTG while on GFD

One study (Martin-Pagola et al., 2007) contributed data to this analysis. This study included 93 children and young people (0.95 to 17.5 years of age at time of diagnosis) of whom 62% were female and none of the study participants had IgA deficiency. The study participants were on a gluten-free diet for 24 months at the time of follow-up.

5.4.3.12 Change in IgA AGA while on GFD

A single study (Midhagen et al., 2004) contributed data to this analysis. This study included adults (age ranged from 29 to 86 years) with coeliac disease who tested positive for IgA AGA at diagnosis. It was unclear how many were female or had IgA deficiency. The study participants were on a gluten-free diet for up to 12 months

5.4.3.13 Change in histology on routine monitoring on a gluten-free diet

Four studies (Dickey et al., 2000, Midhagen et al., 2004, Martini et al., 2002, Galli et al., 2014) contributed data to this analysis. Samples sizes ranged from 18 to 101 people with coeliac disease. The percentage of females ranged from 55% to 78% and none of the study participants had IgA deficiency. The age of study participants ranged from 18 to 86 years. The study participants were on a gluten-free diet for at least 12 months.

5.4.3.14 Nutritional status while on GFD

A single study (Shepherd et al., 2012) contributed data to this analysis. This study included 50 adults (18 to 71 years) diagnosed with coeliac disease of whom 38 (76%) were female. All were adherent to a gluten-free diet.

5.4.3.15 Health care professional involvement

A single study (Wylie et al., 2005) contributed data to this analysis. This study included 99 adults (23 to 86 years of ages) diagnosed with coeliac disease of whom 69 (70%) were

female. This study examined the change after the introduction of a dietitian to coeliac disease team.

5.4.4 Health economic evidence

5.4.4.1 Systematic review of published cost–utility analyses

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that examined the cost effectiveness of monitoring people with coeliac disease.

The search identified 632 references. The references were screened on their titles and abstracts and three full texts were ordered. None of the studies met the inclusion criteria.

No cost–utility analyses were found to address selection criteria.

5.4.4.2 Original health economic analysis

An original cost–utility model was used to explore the benefits, harms and costs associated with serological investigation of people at increased risk of coeliac disease. A modified version of the model developed to analyse the serological investigation of people with symptoms suggestive of coeliac disease was used (see section 5.2.4.2). The long-term consequences of disease were modelled, with the single parameter of adherence to GFD varied to reflect the effectiveness of dietitian-led follow-up (as reported by Wylie 2005). Full details of the methods and results of the model are provided in Appendix G.

5.4.5 Evidence statements

5.4.5.1 Evidence for resolution of gastrointestinal and non-gastrointestinal symptoms

Very low quality evidence from 2 studies (N = 71) found that 90.1% (95%CI 80.7% to 95.2%) of people diagnosed with coeliac disease were in symptomatic remission after 12 months on a gluten-free diet

5.4.5.2 Evidence for dietary non-adherence on GFD

Very low quality evidence from four studies (N = 486) found that 23.6% (95%CI 9.2 to 48.5%) of people diagnosed with coeliac disease were not adhering to a gluten-free diet.

5.4.5.3 Evidence for diagnostic accuracy to detect partial adherence to GFD

Very low to low evidence from a single study (N = 28) reported that DGP IgA/G had high sensitivity to discriminate between strictly adherent and partially adherent at 6 – 8 months and 9 – 12 months. The same study reported that anti TTG IgA had high sensitivity at 2 – 4 months and that AGA IgA was highly sensitive at 2 – 4 months. Where calculable, all other levels of sensitivity and specificity were low.

Very low to low evidence from a single study (N = 315) reported that both the anti TTG ELISA test and a ‘rapid’ version had low sensitivity and high specificity to discriminate between strictly adherent and partially adherent at 24 months.

5.4.5.4 Evidence for proportion with negative IgA EMA while on GFD

Very low to low quality evidence from 4 studies (N = 150) including people with newly-diagnosed coeliac disease found that the proportion who tested negative for IgA EMA antibodies increased over time on a gluten-free diet. The proportion ranged from between

30.3% (95%CI 17.3%, 47.4%) at 3 months to between 89.4% (95%CI 82.2% to 93.9%) at 12 months.

5.4.5.5 Evidence for proportion with negative IgA ARA while on a GFD

Low quality evidence from a single study (N = 30) including people with newly-diagnosed coeliac disease found that the proportion who tested negative of IgA ARA antibodies increased over time on a gluten-free diet. The proportion ranged from 76.7% (95% CI 57.3% to 89.4%) at 3 months to 100% (No 95% CI) at 12 months.

5.4.5.6 Evidence for proportion with negative IgA tTG while on a GFD

Very low quality evidence from 3 studies (N = 115) including people with newly-diagnosed coeliac disease found that the proportion who tested negative of IgA tTG antibodies increased over time on a gluten-free diet from 85%% (95%CI 53.1 to 76.1%) at 3 months to 76.5% (95% CI 42.2% to 93.6%) at 12 months.

5.4.5.7 Evidence for proportion with negative IgG tTG while on a GFD

Low quality evidence from a single study (N = 93) including people with newly-diagnosed coeliac disease found that the proportion who tested negative of IgG tTG antibodies increased over time on a gluten-free diet. The proportion ranged from 63.4% (95%CI 52.8% to 73.0%) at 6 months to 96.7% (95%CI 90.2% to 99.2%) at 24 months.

5.4.5.8 Evidence for proportion with negative IgA AGA while on a GFD

Low quality evidence from a single study (N = 15) including people with newly-diagnosed coeliac disease found that the proportion who tested negative of IgG AGA antibodies increased over time on a gluten-free diet. The proportion ranged from 60.0% (95% CI 32.9% to 82.5%) at 3 months to 100% (No CI) at 12 months.

5.4.5.9 Evidence for histological recover while on a GFD

Low quality evidence from four studies (N = 237) including people with newly-diagnosed coeliac disease found between 56% and 89% demonstrated either mucosal recover or improvement in Marsh grading.

5.4.5.10 Evidence for nutritional status while on a GFD

Very low quality evidence from a single study (N = 50) found that 10% of adults with coeliac disease had nutritionally deficient diets after 12 months on a gluten-free diet

5.4.5.11 Evidence for healthcare professional involvement in monitoring people with coeliac disease

Very low quality evidence from a single study (N = 99) found an increase of 12% in those adhering to a gluten-free diet after 12 months with a dietitian-led coeliac disease clinic. The same study (N = 80) found a 52% increase in those satisfied with their care after 12 months with a dietitian-led coeliac disease clinic.

5.4.5.12 Health economic evidence statements

An original, partially applicable cost–utility analysis with potentially serious limitations suggested that the introduction of a dietitian-led coeliac disease clinic results in increased health benefits at increased cost, with an ICER of £15,200 per QALY gained. The model was reliant on a single, very low-quality study for its effectiveness evidence.

5.4.6 Evidence to recommendations

Relative value of different outcomes	<p>The GDG discussed and agreed that currently there was very limited evidence on the a priori selected outcomes such as resolution of gastrointestinal and non-gastrointestinal symptoms and adherence to a gluten-free diet. Both outcomes were deemed to be critical but also difficult to interpret on their own. For example, symptoms may disappear while on a gluten-free diet but biopsy results still show no change.</p> <p>Adherence to a gluten free-diet is also difficult to monitor accurately as commonly used tools such as 3- or 7-day diaries and self-report questionnaires are not very accurate as people may believe that they are adherent but inadvertently are ingesting some gluten. Sensitivity to gluten is an important factor in terms of serology or biopsy monitoring as some people with coeliac disease are highly sensitive to gluten while others are less so.</p>
Trade-off between benefits and harms	<p>One of the major benefits of routine monitoring is the increased level of contact between the person with coeliac disease and healthcare professionals. This facilitates the provision of information and ongoing support essential for a condition such as coeliac disease. The value of knowing that the gluten-free diet appears to be working, through reduction in antibody titres over time, can be reassuring to people with coeliac disease and/or their carers. This is a powerful motivation factor in helping people with coeliac disease adhere to a gluten-free diet.</p> <p>Routine monitoring can also identify those in whom the gluten-free diet is not having an optimal outcome (see sections 5.3 and 6.1). Persistently high serological titres can indicate when further investigations are indicated and, in many cases, when further dietary education and counselling is needed (see section 7). However, the group discussed that the evidence does not indicate a strong nor conclusive relationship between serological titres and dietary adherence, in that a number of patients who were shown to be strictly adhering to a GFD still had persistently high serological titres. The GDG also discussed shared clinical experience in which patients who were very strict adherers to the GFD still had high serological titres. In these patients, serological testing does not accurately reflect histological recovery. It can therefore be potentially harmful to the patient's adherence to the GFD when they feel that they are doing everything in their power to exclude gluten from their diet and this is not being reflected in their serological testing. The group therefore recognised that serology may be used to inform a clinical picture of a patient, but it should not be used alone to determine GFD adherence.</p> <p>The group raised the notion that it is also important to consider what the routine monitoring consists of. Satisfaction with routine monitoring increased in one study when a dietitian was involved. A qualitative study cited by the GDG (Rajani et al., 2013) also supports this evidence and found that regular clinics with the full coeliac disease multi-disciplinary lead to increase satisfaction with the service. The chapter on nutritional status and diet (section 7.3) also highlighted a need for additional nutritional supplements particularly in newly diagnosed people with coeliac disease. The GDG agreed that nutritional deficiencies in diet should be identified through appropriate ongoing</p>

	<p>monitoring based on an individual's needs and supplementations should not be initiated without a full assessment from the healthcare professional team including the dietitian.</p>
<p>Economic considerations</p>	<p>The GDG understood that the original health economic modelling undertaken for this question was exploratory in nature, and totally reliant on a single parameter from a very low-quality study (Wylie et al., 2005) to estimate the effectiveness of dietitian-led follow-up (in terms of improved adherence to GFD).</p> <p>The GDG discussed that, if the improvement in adherence to GFD reported by Wylie et al. (2005) can be believed, then dietitian-led follow-up is very likely to be a cost-effective strategy. However, the shortcomings of this evidence make it difficult to be confident of the size of effect that would be seen in practice. Therefore, the GDG concluded it was critical to recommend additional research on this topic.</p> <p>The GDG also noted that the package of follow-up care reported by Wylie et al. (2005) comprised multiple elements, including dietetic review, DEXA scanning, blood tests and gastroenterological referral for a proportion of patients. It was not possible to identify what contribution each of these components made to the reported effect. However, when it came to the outcome that was critical to the health economic model – adherence to GFD – the GDG was content to assume that the involvement of a dietitian was an important factor.</p>
<p>Quality of evidence</p>	<p>Overall, the evidence identified for routine monitoring was of very low quality. This is because although it is possible to design a randomised controlled trial comparing two different monitoring strategies, no such study was identified and only lower quality evidence with design limitations was identified. The GDG highlighted, based on their own expertise and clinical experience, that people with coeliac disease benefit from regular dietetic assessment to monitor adherence to the gluten free diet, review symptoms, and provide nutritional advice, and that this would represent a gold-standard for annual review. However, in the current context of a lack of good quality evidence to support this, and the significant implementation ramifications of offering all people with coeliac disease access to a specialist dietitian, the GDG agreed that the recommendation should reflect that dietetic input should be considered as part of an annual review. The GDG highlighted this as a priority for further research to stimulate investigation into the utility of dietetic support as an integral component of an annual review for people with coeliac disease.</p>
<p>Other considerations</p>	<p>Current clinical practice in the UK is to monitor with serology on an annual basis. Intestinal biopsies are often repeated 12 to 24 months after diagnosis. The GDG did not consider the evidence sufficient to change current practice regarding serology and biopsy.</p> <p>However, the GDG acknowledged that nutritional deficiencies at baseline may dictate follow up with a dietitian. The GDG also acknowledged that, while dietitians are routinely employed in secondary care, there are fewer in primary care, leading to a resource gap.</p>

5.4.7 Recommendations & research recommendations

5.4.7.1 Recommendations

16. Do not use serological testing alone to determine whether gluten has been excluded from the person's diet.

17. Offer an annual review to people with coeliac disease. During the review:

- measure weight and height
- review symptoms
- consider the need for assessment of diet and adherence to the gluten-free diet
- consider the need for specialist dietetic and nutritional advice.

18. Refer the person to a GP or consultant if concerns are raised in the annual review. The GP or consultant should assess all of the following:

- the need for a dual-energy X-ray absorptiometry (DEXA) scan (in line with the NICE guideline on [osteoporosis: assessing the risk of fragility fracture](#)) or active treatment of bone disease
- the need for specific blood tests
- the risk of long-term complications and comorbidities
- the need for specialist referral.

5.4.7.2 Research recommendations

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

Why this is important

As a gluten-free diet is the primary treatment option for people with coeliac disease, it is important that a dietitian with a specialist interest in coeliac disease should play a significant role in their care and follow up. Many of the common problems associated with the long-term management of coeliac disease happen because of non-adherence to a gluten-free diet. It is important to explore how to maximise the effectiveness of the dietitian role in helping people with coeliac disease to adhere to a gluten-free diet.

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

Why this is important

It is currently not known how often people with coeliac disease should have their condition monitored. No research adequately investigated the effectiveness of different monitoring frequencies. There is variation across the UK in how often people with coeliac disease have their condition monitored. Further research within this area is important to ensure that people with coeliac disease are having their condition adequately monitored.

6 Evidence for non-responsive and refractory coeliac disease

6.1 Causes of non-responsive coeliac disease

6.1.1 Review questions

- a) What are the potential causes of non-responsive coeliac disease (NRCD)?
- b) In people with confirmed refractory coeliac disease (RCD), what investigative procedures should be undertaken?

NRCD can manifest where persons with coeliac disease do not experience symptomatic or histological improvement after excluding gluten from their diet, or when the symptomatic respite afforded by gluten exclusion dissipates and people again become symptomatic. Understanding the potential causes for NRCD is highly important in order to identify and rectify the causes of increased symptoms and investigate the potential for refractory coeliac disease.

RCD is often deconstructed into separate sub-classifications and prognosis varies substantially depending on subtype. Subtype is determined by the presence (RCD II) or absence (RCD I) of aberrant small intestinal intraepithelial lymphocytes (IEL's). People with RCD II have a proportion of aberrant intra epithelial lymphocytes (IEL's) that lose surface expression of CD3 and CD8, which is frequently associated with the presence of a monoclonal IEL population. This subtype is associated with a significantly reduced survival expectancy compared to those with RCD I, and this is predominantly driven by the increased risk of enteropathy associated T-cell lymphoma (EATL). Survival rate of those who develop EATL is poor, with a 2 year survival estimated between 15% - 20%. Investigative procedure which allow for the sub-classification of RCD, and monitoring for development of lymphoma and other enteropathies is of great importance to the clinical management of people with this condition.

6.1.2 Methods

The aim of this review question was to determine:

- The proportion of differing causes of persistent symptoms in people with a confirmed diagnosis of coeliac disease who have been advised to exclude gluten from their diet
- The clinical utility of investigative tests in people with refractory coeliac disease

NRCD is defined as a continuation of symptoms and/or signs of coeliac disease (CD) despite reporting being on a gluten-free diet (GFD). There are no current consensus criteria for the precise definition of RCD. We have defined RCD in this review as the persistence or later development of severe villous atrophy in people with CD despite a strict gluten-free diet, where adherence/inadvertent gluten ingestion and potential concomitant conditions have also been ruled out.

Studies reviewed were only included if the population examined was people in whom a biopsy-confirmed diagnosis of coeliac disease had been made. Studies considered for question 6.1.1 (a) investigated people who were deemed to have non-responsive coeliac disease (NRCD), and the potential causes for this non-responsiveness. Studies considered for question 6.1.1 (b) focused on investigative procedures for the sub-classification and monitoring of people with confirmed RCD.

Cohort studies were considered to be the highest quality evidence available and are graded as high in a modified GRADE framework. The quality for each outcome could be

downgraded due to risk of bias in terms of methods, indirectness in terms of population, tests and outcomes used, inconsistency between studies, or imprecision in terms of outcomes.

For full details of the review protocol please see Appendix C.

Included Studies

A systematic search was conducted (see Appendix C) which identified 1859 references. The references were screened on their titles and abstracts and full text papers of 39 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

Twenty seven studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (case-control studies with healthy or symptom-free uncomplicated CD, or other patient comparator groups), not a primary study (descriptive narrative, opinion, etc.). A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

The 12 remaining published papers did meet the eligibility criteria and were included. Data were extracted into detailed evidence tables (see Appendix D).

6.1.3 Evidence review

6.1.3.1 Causes of nonresponsive coeliac disease

Four studies (Dewar et al., 2012; Leffler et al., 2007; Abdulkarim et al., 2002; Van Weyenberg et al., 2013) contributed data to this analysis. Samples sizes ranged from 48 to 113 adults with NRC. The mean age of study participants ranged from 42 to 63 years. The study participants were on a gluten-free diet for between 6 months and 6 years.

6.1.3.2 Subtyping of RCD into RCD type I and RCD type II

Three studies (Daum et al., 2009; Arguelles-Grande et al., 2013; Malamut et al., 2009) contributed data to this analysis. Samples sizes ranged from 14 to 73 adults with confirmed RCD. The mean age of study participants ranged from 48 to 67 years. Only participants on a strict gluten-free diet were included in all studies at the time of testing.

6.1.3.3 Sensitivity and specificity of investigative procedures to detect enteropathy-associated –cell lymphoma (EATL) and ulcerative jejunitis (UJ)

One primary study with one publication (Daum et al., 2007), and two primary studies with two publications (Hadithi et al., 2006, 2007; Van Weyenberg et al., 2011, 2013) contributed to this analysis. Samples size ranged from 14 to 68 adults with a confirmed diagnosis of RCD. Mean age of participants ranged from between 48 to 63 years. Only participants on a strict gluten-free diet were included in all studies at the time of testing.

6.1.3.4 Cumulative survival at 5 years post diagnosis of RCD

Four studies (Daum et al., 2009; Malamut et al., 2009; Van Weyenberg et al., 2011; Arguelles Grande, 2013) contributed to this analysis. Sample sizes ranged from 12 to 67 participants with RCD type I and 6 to 43 participants with RCD type II. Mean age of participants ranged from 50 to 56 years.

6.1.3.5 Predictive factors of EATL development in patients with RCD

Two studies (Liu et al., 2009; Malamut et al., 2009) contributed data to this analysis. Sample sizes were 41 and 57 participants with RCD, respectively. Mean age of participants at diagnosis of RCD ranged from 48 to 63 years.

6.1.3.6 Predictive factors for clinical worsening in patients with RCD

One study (Arguelles Grande et al., 2012) contributed to this analysis. This study examined 73 participants with RCD, with a mean age of 56 years. The mean time since RCD diagnosis was 5 years.

6.1.4 Health economic evidence

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that explored potential causes of non-responsive coeliac disease or the cost effectiveness of investigations for individuals diagnosed with refractory coeliac disease.

The search identified 113 references. The references were screened on their titles and abstracts and none of the studies met the inclusion criteria.

No cost–utility analyses were found to address selection criteria.

6.1.5 Evidence statements

6.1.5.1 The potential causes of nonresponsive coeliac disease (NRCD)

High quality evidence from 3 studies of 148 participants with NRCD suggested that between 10% to 12% of patients presenting with NRCD could be accounted for by a misdiagnosis of coeliac disease.

High quality evidence from 4 studies of 165 adults with NRCD suggested that between 36% to 82% of patients presenting with NRCD could be accounted for by noncompliant or inadvertent gluten ingestion.

High quality evidence from 3 studies of 148 adults with NRCD suggested that between 6% to 11% of patients presenting with NRCD could be accounted for microscopic colitis.

High quality evidence from 3 studies of 148 adults with NRCD suggested that between 6% to 14% of patients presenting with NRCD could be accounted for by bacterial overgrowth.

High quality evidence from 3 studies of 148 adults with NRCD suggested that between 7% to 12% of patients presenting with NRCD could be accounted for by lactose intolerance.

High quality evidence from 2 studies of 117 adults with NRCD suggested that between 6% to 7% of patients presenting with NRCD could be accounted for by inflammatory colitis.

High quality evidence from 2 studies of 149 adults with NRCD suggested that between 2% to 12 % of patients presenting with NRCD could be accounted for by pancreatic insufficiency.

High quality evidence from 3 studies of 148 adults with NRCD suggested that between 9% to 18% of patients presenting with NRCD could be accounted for by true refractory coeliac disease (RCD).

6.1.5.2 Investigative procedures in patients with confirmed refractory coeliac disease: Change to clinical management

6.1.5.2.1 *Aberrant T-cell receptor gene rearrangement (TCR) by polymerase chain reaction (PCR)*

High quality evidence from 3 studies of 146 adults with RCD showed that aberrant T-cell receptor gene rearrangement (TCR) assessed by polymerase chain reaction (PCR) has

between 97% to 100% sensitivity and 100% specificity to discriminate RCD type II from RCD type I.

6.1.5.2.2 Immunohistochemistry to detect aberrant IEL immunophenotype

High quality evidence from 3 studies of 146 adults with RCD showed that immunohistochemistry to detect an aberrant CD3+ CD8- immunophenotype has between 56% to 100% sensitivity, and 100% specificity to discriminate RCD type II from RCD type I.

6.1.5.3 Investigative procedures in patients with confirmed refractory coeliac disease: Detection of lymphoma

6.1.5.3.1 Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (F-18-FDG-PET)

High quality evidence from a study of 30 adults with RCD reported 18-F FDG PET to have a sensitivity of 100% and specificity of 90% (95% CI: 79 to 100) to detect the presence of EATL in people with RCD.

6.1.5.3.2 Computerised tomography (CT)

Low quality evidence from 2 studies of 37 adults with RCD reported abdominal CT to have a sensitivity of between 50% (95% CI: 36 to 69) and a specificity of 76% (95% CI: 36 to 100) to detect EATL in people with RCD.

6.1.5.3.3 Magnetic resonance (MR) enteroclysis

Low quality evidence from a single study of 28 adults with RCD and uncomplicated CD reported MR enteroclysis to have a sensitivity of 88% (95% CI: 47 to 99) and a specificity of 97% (95% CI: 87 to 99) to detect EATL in people with RCD.

6.1.5.3.4 Double balloon enteroscopy

High quality evidence from a single study of 35 adults with RCD reported double balloon enteroscopy to have a sensitivity and specificity of 100% to detect EATL in people with RCD.

6.1.5.3.5 Capsule endoscopy (CE)

Very low quality evidence from 2 studies of 48 adults with RCD reported capsule endoscopy to have a sensitivity of between 50% (95% CI: 19 to 100) and a specificity of 100% to detect EATL in people with RCD.

6.1.5.4 Health-related outcomes: Cumulative survival at 5 years post diagnosis

High quality evidence from 4 studies of 112 participants reported that people with a diagnosis of RCD type I have between 95% (95% CI: 76 to 100) cumulative survival rate at 5 years post diagnosis of RCD.

High quality evidence from 4 studies of 68 participants reported that participants with a diagnosis of RCD type II have a 53% (95% CI: 12 to 94) cumulative survival rate at 5 years post diagnosis of RCD.

6.1.5.5 Health-related outcomes: predictive factors for lymphoma

6.1.5.5.1 Aberrant immunophenotype

Moderate quality evidence from 2 studies of 98 participants with RCD reported that an aberrant immunophenotype has a significant predictive value (OR: 4.59; 95% CI: 0.51 to 20.7) for the development of lymphoma in people with RCD.

6.1.5.5.2 Age

Moderate quality evidence from studies of 98 participants with RCD reported age to have no significant predictive value (OR: 1.13; 95% CI: 0.9 to 1.7) for the development of lymphoma in people with RCD.

6.1.5.5.3 Ulcerative jejunitis

Moderate quality evidence from a single study of 57 people with RCD reported the presence of ulcerative jejunitis to have no significant predictive value (OR: 1.8; 95% CI: 0.7 to 4.7) for the development of lymphoma in people with RCD.

6.1.5.5.4 Gender

Moderate quality evidence from a single study of 41 people with RCD reported gender to have a no predictive value (OR: 2.17; 95% CI: 0.45 to 10.44) for the development of lymphoma in people with RCD.

6.1.5.5.5 Persistent monoclonality

Moderate quality evidence from a single study of 41 people with RCD reported the presence of persistent monoclonality to have significant predictive value (OR: 3.6; 95% CI: 0.6 to 21.6) for the development of lymphoma in people with RCD.

6.1.5.5.6 Persistent concurrent aberrant immunophenotype and monoclonality

Moderate quality evidence from a single study of 41 people with RCD reported the presence of persistent monoclonality to have significant predictive value (OR: 9; 95% CI: 0.51 to 48.75) for the development of lymphoma in people with RCD.

6.1.5.5.7 Persistent >80% CD3+ CD8- IEL's

Moderate quality evidence from a single study of 41 people with RCD reported the presence of persistent >80% CD3+ CD8- IEL's to have significant predictive value (OR: 21.33; 95% CI: 2.94 to 154.6) for the development of lymphoma in people with RCD.

6.1.5.5.8 Persistent concurrent >80% CD3+ CD8- IEL's and monoclonality

Moderate quality evidence from a single study of 41 people with RCD reported the presence of persistent concurrent >80% CD3+ CD8- IEL's and monoclonality to have significant predictive value (OR: 45.33; 95% CI: 4.05 to 506.86) for the development of lymphoma in people with RCD.

6.1.5.6 Health-related outcomes: predictive factors for clinical worsening in RCD

6.1.5.6.1 Age \geq 50 years

Moderate quality evidence from a single study of 73 people with RCD reported an age of greater than or equal to 50 years to have no predictive value (OR: 1.55; 95% CI: 0.8 to 3.0) for clinical worsening in RCD.

6.1.5.6.2 Monoclonality

Moderate quality evidence from a single study of 73 people with RCD reported monoclonality to have significant predictive value (OR: 4.33; 95% CI: 1.7 to 10.98) for clinical worsening in RCD.

6.1.5.6.3 **Severe villous atrophy**

High quality evidence from a single study of 73 people with RCD reported the presence of severe villous atrophy to have no predictive value (OR: 1.54; 95% CI: 0.25 to 0.8) for clinical worsening in RCD.

6.1.5.6.4 **Aberrant IEL immunophenotype**

Moderate quality evidence from a single study of 73 people with RCD reported the presence of an aberrant immunophenotype to have significant predictive value (OR: 3.01; 95% CI: 1.5 to 6.01) for clinical worsening in RCD.

6.1.5.6.5 **Non-EATL lymphoma**

Moderate quality evidence from a single study of 73 people with RCD reported the presence of non-EATL lymphoma to have no predictive value (OR: 2.76; 95% CI: 0.8 to 9.19) clinical worsening in RCD.

6.1.5.6.6 **Presence of focal proximal erythema on capsule endoscopy**

Low quality evidence from a single study of 48 people with RCD reported the presence of focal proximal erythema on capsule endoscopy to have significant predictive value (OR: 6.7; 95% CI: 1.2 to 38.7) for worsening clinical outcome.

6.1.5.6.7 **Absence of progression of capsule to distal intestina during capsule endoscopy**

Low quality evidence from a single study of 48 people with RCD reported the absence of progression of the capsule to distal intestina during capsule endoscopy to have significant predictive value (OR: 16.5; 95% CI: 1.2 to 224.9) for worsening clinical outcome.

6.1.6 **Evidence to recommendations**

Relative value of different outcomes

Accurate diagnosis of nonresponsive and refractory coeliac disease was of the highest importance to the GDG, as these two conditions have very important and different implications. Mortality is a primary outcome of concern for refractory disease. Identifying methods of subtyping of refractory disease into type I and type II was also highlighted as a highly important outcome of interest for the GDG, as those with RCD II have a poorer prognosis and require closer monitoring.

Identifying the cause of symptoms in nonresponsive CD was also highlighted as a key outcome of concern for the GDG in order to be able to address and rectify ongoing symptoms and improve the quality of life of patients.

Trade-off between benefits and harms

Identifying the proportion of differing causes of NRCD

Non responsive coeliac disease was found to be most often associated with exposure to gluten. The group discussed potential reasons for this and considered that for those who were incidentally ingesting gluten, increased education about the GFD is needed. For this reason, the group thought it was important that people should be referred to a specialist dietitian to review diet and any potential consumption of gluten which may be causing ongoing problems. When gluten ingestion has been ruled out, investigation for other potential causes highlighted in this review, such as IBS or microscopic colitis, should be undertaken.

Patients who are experiencing ongoing symptoms often have a poor quality of life, and the group discussed that it was important that further investigation was undergone as quickly as possible in order to identify any potential causes before considering diagnosis of true refractory coeliac disease. The GDG also recognised that true refractory coeliac disease was a condition only diagnosed in adults, whereas any children continuing to have symptoms are almost always inadvertently ingesting gluten or have a contributing comorbid condition.

Change to clinical management

The importance of establishing the certainty of diagnosis was discussed as potentially problematic. In the absence of accurate biopsy orientations, a re-biopsy may be required. In order for the biopsy to be accurate, a gluten-challenge may need to be undertaken. This is often distressing and problematic for people. It can be difficult for people to understand when they are told to make sure that all gluten is excluded from the diet and then recommended to resume eating gluten for the purposes of diagnostic testing. The group felt that the benefit of making certain the diagnosis in order to identify causes of ongoing problems would outweigh the potential discomfort of patients while they underwent a gluten challenge for the 6 week period recommended before investigations.

Patient outcome at follow up

The group raised the notion that in making a referral to a specialist centre to follow-up refractory CD patients would be particularly beneficial to both people with RCD and treating clinicians. This is because numbers of patients with confirmed RCD are so small that referral of these people to a specialist centre will allow the few centres to build up sufficient expertise in this area, and to ensure correct and appropriate immunology tests are done to determine the diagnosis and subtype. At present, very few centres will have this expertise.

Health-related quality of life

Health-related quality of life was particularly discussed in terms of the impact that ongoing symptoms and potential mortality and cancer risk has on patients with RCD. Investigative procedures which assess subtyping of RCD into type I and type II were discussed as particularly important in order to understand and communicate prognosis to patients. As RCD II is associated with an increased risk of EATL, investigative procedures for this were also highlighted as essential for monitoring and assessment. The utility of these procedures was discussed as problematic, as the evidence suggests, because these have low sensitivity and specificity to detect EATL. Harms of these procedures were also discussed in terms of their invasive nature, which could cause these patients, who are likely very unwell, further discomfort. The capsule endoscopy method in particular was discussed as potentially harmful to patients who do have EATL or another major intestinal obstruction due to the capsule not being able to pass through and thus requiring surgery for its removal. The group discussed the very poor prognosis of those diagnosed with EATL and agreed that the most important consideration for any patient was to diagnose or exclude EATL as soon as possible.

Economic considerations	No economic evidence was found
Quality of evidence	Overall the evidence identified for causes of non-responsive coeliac disease was high. The evidence for investigations for refractory coeliac disease, however, varied from low to high quality. This is because populations that were not truly refractory were included in some of the studies, and because the confidence intervals for estimated sensitivity and specificity were often very wide, reflecting the lack of power to detect clinically meaningful results.
Other considerations	<p>The GDG discussed and agreed that currently there was no clear consensus over how non-responsive and refractory coeliac disease should be defined and diagnosed. The presence of symptoms is often cited as necessary for recognition; however it was recognised by the GDG that some people may not be symptomatic, such as those detected through case-finding or incidentally and thus would not show clinical remission. It was also recognised that clinical remission may not reflect histological remission (see 5.4). The group expressed concern that as such, refractoriness may be over diagnosed when the most likely cause is inadvertent exposure to gluten. The input of a specialist dietitian was highlighted as essential in order to make certain that gluten has been completely excluded from the diet.</p> <p>The GDG acknowledged that because RCD populations are rare it is difficult to obtain adequate sample sizes to detect true sensitivity and specificity estimates of imaging procedures to detect malignancy.</p> <p>The GDG also acknowledged that computerised tomography (CT) was a poor tool to use for detection of malignancy, but may be useful in conjunction with other imaging modalities. The limitations of capsule endoscopy were also discussed in terms of the presence of lesions such as ulcerative jejunitis and malignancy being contraindications for the capsule to successfully pass through the intestines. If the capsule becomes lodged in the intestine, an operation is required to remove it and this can be distressing for people with RCD. Some members of the group stated that in certain circumstances, capsule endoscopy may be of some, albeit limited, utility.</p>

6.1.7 Recommendations & research recommendations

19. Consider the following actions in people with coeliac disease who have persistent symptoms despite advice to exclude gluten from their diet:

- review the certainty of the original diagnosis
- refer the person to a specialist dietitian to investigate continued exposure to gluten
- investigate potential complications or coexisting conditions that may be causing persistent symptoms, such as irritable bowel syndrome, lactose intolerance, bacterial overgrowth, microscopic colitis or inflammatory colitis.

- 20. Diagnose refractory coeliac disease if the original diagnosis of coeliac disease has been confirmed, and exposure to gluten and any coexisting conditions have been excluded as the cause of continuing symptoms.**

- 21. Refer people with refractory coeliac disease to a specialist centre for further investigation**

6.2 Pharmacological interventions

6.2.1 Review question

What is the effectiveness of pharmacological treatments for people with refractory coeliac disease?

There is currently very little known about the optimal pharmacological treatment strategy for patients with refractory coeliac disease. Current clinical practice is to treat with steroids such as prednisone and monitor clinical response, however further information and guidance on this and other potential treatment strategies is needed in order to ensure that patients with this condition receive the best pharmacological management.

6.2.2 Methods

The aim of this review was to establish the effectiveness of pharmacological interventions for the symptoms of refractory coeliac disease.

A systematic search was conducted which recovered a total of 928 results (after duplicates were removed). Results were screened on title and abstract, and a total of 68 full-text papers were ordered to be assessed for eligibility against the inclusion and exclusion criteria specified in the review protocol. Two additional studies were identified from cross-referencing narrative reviews. These were not retrieved from our search because the abstract and title did not report the drug used in the studies.

Of the 71 full-text articles obtained, 57 were excluded for reasons specified in Appendix F. Overall, 14 small case series were selected for inclusion, of which only 4 studies included more than 30 people with refractory coeliac disease (see summary table X). Only 6 studies were prospective, while the remaining 8 were retrospective reports of people treated at particular institutions for refractory coeliac disease.

Among the 14 studies included, there was a potential for overlap of participants reported in 3 pairs of the studies which were included (see footnotes on tables below). The GDG acknowledged that this was likely due to the rarity of this condition. The later publications included longer follow-up of participants included in earlier studies but tended to be retrospective and report on the outcomes of all people treated at a centre with a larger number of pharmacological treatments or combinations of these treatments. These later studies also tended to report some outcomes across all people treated at a centre, regardless of which drug or combinations of drugs they received.

It was not possible to pool results due to the heterogeneous nature of the included studies, owing to factors such as small differences in definitions applied to refractory coeliac disease and differences in the reporting of outcomes (such as different definitions of clinical, immunological and histological response). A summary of the results is included in table X below.

Randomised controlled trials are the optimal study design to answer this review question. However, due to the rarity of true refractory coeliac disease, the GDG was aware of only case series in this field with very small numbers of participants per study. As such, a modified GRADE assessment of individual studies was applied for this question.

The outcomes specified in the review protocol were extracted, where available, and included:

- Resolution of gastrointestinal and non-gastrointestinal symptoms
- Complications of coeliac disease
- Adverse effects
- Health-related quality of life

- Impact on carers
- Serological response
- Histological response

The reporting of these outcomes varied across the included studies and no study reported on the impact of pharmacological treatments on health-related quality of life or on carers. Full evidence tables are found in Appendix D.

6.2.3 Evidence review

6.2.3.1 Immunosuppressants (azathioprine, cyclosporine, cladribine, tioguanine, methotrexate)

Six small case series in up to 22 adults examined the effectiveness of immunosuppressive therapy to treat the symptoms of refractory coeliac disease in a group of people with biopsy-confirmed coeliac disease and a diagnosis of refractory coeliac disease.

6.2.3.2 Corticosteroids (prednisone, prednisolone, budesonide)

Six small case series in up to 22 adults examined the effectiveness of corticosteroids to treat the symptoms of refractory coeliac disease in a group of people with biopsy-confirmed coeliac disease and a diagnosis of refractory coeliac disease.

6.2.3.3 Aminosalicylates (mesalamine/mesalazine)

One very small case series in four adults examined the effectiveness of mesalamine to treat the symptoms of refractory coeliac disease in a group of people with biopsy-confirmed coeliac disease and a diagnosis of refractory coeliac disease.

6.2.3.4 Combinations (corticosteroids + immunosuppressants or multiple immunosuppressants)

Five small case series in up to 18 adults examined the effectiveness of corticosteroids and immunosuppressants in combination to treat the symptoms of refractory coeliac disease in a group of people with biopsy-confirmed coeliac disease and a diagnosis of refractory coeliac disease.

One very small case series in 6 adults examined the effectiveness of both prednisone and mesalamine in combination to treat the symptoms of refractory coeliac disease in a group of people with biopsy-confirmed coeliac disease and a diagnosis of refractory coeliac disease. One very small case series in 10 adults examined the effectiveness of cladribine plus pre-treatment with azathioprine or prednisone to treat the symptoms of refractory coeliac disease in a group of people with biopsy-confirmed coeliac disease and a diagnosis of refractory coeliac disease.

6.2.3.5 Cytokine modulators (unspecified anti-TNF α)

One very small case series in 4 adults examined the effectiveness of anti-TNF to treat the symptoms of refractory coeliac disease in a group of people with biopsy-confirmed coeliac disease and a diagnosis of refractory coeliac disease.

6.2.4 Health economic evidence

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that explored the cost effectiveness of pharmacological therapy for refractory coeliac disease.

The search identified 63 references. The references were screened on their titles and abstracts and none of the studies met the inclusion criteria.

No cost–utility analyses were found to address selection criteria.

6.2.5 Evidence statements

Overall, the studies included were very low quality and contained no control group. Additionally, it is likely that there was an overlap of people reported in some of the included studies.

6.2.5.1 Immunosuppressants (azathioprine, cyclosporine, cladribine, tioguanine, methotrexate)

Very low quality evidence from 6 small case series (n=22 or less) reported that immunosuppressants may reduce symptoms and villous atrophy in some people with refractory coeliac disease, but also reported some adverse effects of the treatment.

6.2.5.2 Corticosteroids (prednisone, prednisolone, budesonide)

Very low quality evidence from 6 small case series (n=47 or less) reported that corticosteroids alone may reduce symptoms and villous atrophy in some people with refractory coeliac disease.

6.2.5.3 Aminosalicylates (mesalamine/mesalazine)

Very low quality evidence from 1 very small case series (n=4) reported that mesalamine may reduce symptoms in some people with refractory coeliac disease.

6.2.5.4 Combinations (corticosteroids + immunosuppressants or multiple immunosuppressants)

Very low quality evidence from 5 small case series (n=18 or less) reported that corticosteroids and immunosuppressants in combination may reduce some symptoms and villous atrophy in some people with refractory coeliac disease.

Very low quality evidence from 1 very small case series (n=6) reported that both prednisone and mesalamine may reduce some symptoms in some people with refractory coeliac disease.

Very low quality evidence from 1 very small case series (n=10) reported that cladribine plus pre-treatment with azathioprine or prednisone reduces symptoms and villous atrophy in a small proportion of people with refractory coeliac disease.

6.2.5.5 Cytokine modulators (unspecified anti-TNF α)

Very low quality evidence from 1 very small case series (n=4) reported that anti-TNF α may reduce symptoms in some people with refractory coeliac disease.

6.2.6 Evidence to recommendations

Relative value of different outcomes	The GDG felt that all outcomes of interest for this question were equally valuable and important to address.
Trade-off	The GDG was concerned with the state of the evidence on the

<p>between benefits and harms</p>	<p>pharmacological treatment for refractory coeliac disease. The evidence was of very low quality (see 'quality of evidence' below) and on very small numbers of participants.</p> <p>As a result of the limited and low quality evidence, the GDG did not feel it was possible to make recommendations about treatment based on the evidence. They were also concerned that many clinicians are not experienced in dealing with people with this rare condition and that other factors such as nutritional management may play a role. Consequently, the GDG felt that advice should be sought from specialists with experience in managing people with this rare condition.</p> <p>Despite feeling that they could not make recommendations about pharmacological management based on the evidence, the GDG was cognisant that people with refractory coeliac disease are typically in very poor condition and felt it was important that these people received some treatment, even while waiting for advice from a specialist. However, they found this difficult because of the very poor evidence to support the use of any pharmacological treatment for refractory coeliac disease so made this decision based on their clinical expertise.</p> <p>While the GDG was concerned about encouraging the use of drugs for which there is little evidence, they felt that because there was not enough evidence to support a change in clinical practice, they should recommend the use of prednisone or prednisolone. However, they expressed concerns about the long-term effects of these drugs so recommended that they only be used while clinicians are awaiting advice from a specialist. The GDG felt that people with suspected refractory coeliac disease should not be started on prednisolone or prednisone without the expectation of an early review. Due to the poor clinical condition of these people, the GDG felt that it was reasonable to use these drugs for short term management given that these people would be under close and frequent clinical review.</p> <p>Furthermore, regarding the use of immunosuppressants, the group felt that these drugs should not be prescribed without advice and follow-up of a specialist because prescribing these drugs requires experience and specific expertise, particularly with the associated risk of adverse events.</p> <p>The GDG felt mesalazine was promising as an option and that there is less potential for harm related to this drug, but there is very little evidence to make recommendations about its use. They felt that further research into its use should be supported.</p> <p>They also felt that budesonide should not be prescribed routinely as it is not commonly used and there is little evidence on its use.</p> <p>Overall, the GDG felt that there is a need for high-quality evidence to inform the management of patients with refractory coeliac disease.</p>
<p>Economic considerations</p>	<p>No economic evidence on pharmacological management of coeliac disease was found.</p>
<p>Quality of</p>	<p>The available evidence on the pharmacological management of</p>

evidence	refractory coeliac disease is observational and of very low quality. The evidence is based on case series with no control or case reports (though the later were excluded from the guideline) and are, therefore, likely to be subject to bias. In addition, the included case series are predominantly retrospective studies where it was unclear why the participants were allocated to different drugs or different combinations of drugs. Furthermore, for most studies, it is unclear if participants were recruited consecutively so reporting bias is a possibility. Many of the studies were retrospective reports of all people with refractory coeliac disease treated at specific centres and the focus of the study was not specifically on the efficacy of specific treatments rather the study reported some outcomes for all participants regardless of treatment. Consequently, this made it difficult to attribute the affect that each individual treatment had on participant outcomes.
Other considerations	The GDG was aware that prednisolone is the only drug that is licensed for coeliac disease unresponsive to gluten withdrawal.

6.2.7 Recommendations & research recommendation

22. Consider prednisolone for the initial management of the symptoms of refractory coeliac disease in adults while waiting for specialist advice.

6.3 Nutritional interventions

6.3.1 Review question

What is the effectiveness of nutritional management or nutritional support for people with refractory coeliac disease?

It is currently unknown whether any specific dietary interventions beyond the gluten-free diet can alleviate symptoms of refractory coeliac disease. This chapter sought to investigate the clinical efficacy of any such dietary interventions for this population.

6.3.2 Methods

The aim of this question was to determine whether people with refractory coeliac disease would benefit from additional nutritional support or nutritional management.

A systematic search was conducted which identified 2161 references studies. After removing duplicates the references were screened on their titles and abstracts and 38 references were obtained and reviewed against the inclusion and exclusion criteria (for the full review protocol please see Appendix C).

All 38 studies were excluded as they did not meet the inclusion criteria, such as, inappropriate study population (e.g. participants did not have refractory coeliac disease), the intervention wasn't one of interest or not primary research study (e.g. expert opinion). A list of excluded studies and reasons for their exclusion is provided in Appendix F.

6.3.3 Evidence review

No evidence that met the inclusion and exclusion criteria for this question was found.

6.3.4 Health economic evidence

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that explored the cost-effectiveness of nutritional support or nutritional management of people with refractory coeliac disease.

The search identified 173 references. The references were screened on their titles and abstracts and none of the studies met the inclusion criteria.

No cost–utility analyses were found to address selection criteria.

6.3.5 Evidence statements

No evidence that met the inclusion and exclusion criteria for this question was found.

6.3.6 Evidence to recommendations

Relative value of different outcomes	No evidence was included to answer this review question. The GDG based its decisions on the knowledge and experience of the group.
Trade-off between benefits and harms	The GDG did not feel able to make a recommendation on this topic. True refractory coeliac disease is quite rare (as most people are found to have either been still being exposed to gluten, or are found to have another condition), therefore they could not be sure that additional

	nutritional support or nutritional management would be of benefit. The GDG also noted that as stipulated in section 5.4 (Monitoring of people with CD), all people with coeliac disease, regardless of whether they are refractory to treatment, should be offered access to specialist dietetic advice and that as such these patients should at least be getting some dietetic support.
Economic considerations	No health economic evidence was found and this question was not prioritised for de novo modelling.
Quality of evidence	No evidence was available.

6.3.7 Recommendations & research recommendations

No recommendations were made for this review question.

6.4 Autologous stem-cell transplants

6.4.1 Review question

What is the effectiveness of autologous stem cell transplant for people with refractory coeliac disease?

Stem cell research in refractory coeliac disease is a very new and potentially promising area of clinical medicine. This chapter sought to investigate the clinical efficacy of native stem cell replacement to treat refractory coeliac disease.

6.4.2 Methods

The aim of this review question was to determine the efficacy of chemotherapy followed by transplantation of native stem cells (from the patient's own body) for the treatment of confirmed refractory coeliac disease.

A systematic search was conducted (see Appendix C) which identified 1035 references studies. After removing duplicates the references were screened on their titles and abstracts and 22 references were obtained and reviewed against the inclusion and exclusion criteria (for full review protocol see Appendix C).

Twenty studies were excluded as they did not meet the eligibility criteria such as inappropriate study population (e.g. patients were already diagnosed with cancer) or not primary research study (e.g. expert opinions). A list of excluded studies and reasons for their exclusion is provided in Appendix F.

The overall quality of the 2 included published papers (from one study) was of very poor quality with very low confidence in the effect estimates. This is due to the methodological issues of the study design such as non-randomised and non-comparative, prone to selection bias, poor reporting on data and analysis, unclear recruitment strategies.

Moreover, the study only focused on a specific subgroup of people with refractory coeliac disease (RCD) (i.e. RCD type II, unresponsive to cladribine therapy), and hence, this limited inconclusive evidence cannot be generalised to the overall RCD patient population.

6.4.3 Evidence review

Two papers from 1 primary study (Tack et al., 2011; Al-Toma et al., 2011) with a total of 18 adults (age < 70 years) with a biopsy-confirmed diagnosis of CD and a further diagnosis of refractory coeliac disease were included in this review. All participants had no response to 1 or 2 prior courses of cladribine for 5 consecutive days. Of the 18 participants, only 13 went through autologous stem cell transplantation (ASCT); 2 had unsuccessful leukapheresis and the remaining 3 progressed to enteropathy associated T-cell lymphoma (EATL).

6.4.4 Health economic evidence

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that examined the cost effectiveness of autologous stem cell transplants in people with refractory coeliac disease.

The search identified 62 references. The references were screened on their titles and abstracts and none of the studies met the inclusion criteria.

No cost–utility or cost-effectiveness analyses were found to address selection criteria.

6.4.5 Evidence statements

There was very limited inconclusive evidence from one very low quality case study on the effectiveness of autologous stem cell transplant for people with refractory coeliac disease.

6.4.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed and agreed that a person's quality of life, resolution of gastrointestinal and non-gastrointestinal symptoms, and mortality (as a complication of coeliac disease e.g. development of T-cell lymphoma) are the critical outcomes of concern. However, the only included study (2 published papers) only reported 1 of the 3 critical outcomes which was mortality/survival from a very small study sample (13 participants).
Trade-off between benefits and harms	Due the very limited and very low quality data reported in the only included study, and the fact that autologous stem cell transplant services are very rare in the UK, the GDG felt that they were unable have a meaningful discussion about the benefits and harms of autologous stem cell transplant for people with refractory coeliac disease.
Economic considerations	<p>No published cost–utility or cost-effectiveness analyses were found from the systematic searches that addressed the inclusion criteria.</p> <p>The GDG further discussed that currently there are only approximately 3 services across the whole UK that could deliver autologous stem cell transplant, and that the cost impact of establishing more autologous stem cell transplant services would be very high. The GDG had made an assumption that based on the current available very limited low quality evidence and the high cost of autologous stem cell transplant services, autologous stem cell transplant would not be cost effective for people with refractory coeliac disease.</p>
Quality of evidence	<p>After the discussion of the only included study (2 published papers), the GDG agreed that the included study was of very low quality case series and they have a lot of uncertainties about the effect estimates reported in the study because i) very small and narrow-defined sample size (only 13 patients with specific type II RCD) and a proportion of the participants already had enteropathy associated T-cell lymphoma; ii) the data reported was non-comparative; iii) the outcomes reported were unclear.</p> <p>Hence, the GDG agreed that this limited inconclusive evidence cannot be generalised to the overall population of people with refractory coeliac disease, and therefore the GDG was unable to make any recommendation regarding autologous stem cell transplant for people with refractory coeliac disease.</p>

6.4.7 Recommendations & research recommendations

No recommendations were made.

Research recommendation:

6. What is the clinical and cost-effectiveness of autologous stem cell transplant for the treatment of people with refractory coeliac disease?

Why this is important

Refractory celiac disease (RCD) is often very severe and requires additional therapeutic intervention besides a gluten-free diet (GFD). RCD type 2 is particularly associated with poor prognosis despite conventional therapeutic interventions (GFD and/or pharmacological treatments) with 5-year survival rates of 40–58%. Poor prognosis is largely explained by the much more frequent progression to overt enteropathy-associated T-cell lymphoma (EATL) in patients with RCD type 2. Due to the poor prognosis of RCD, the aim of this research recommendation is to determine, other than GFD and pharmacological treatments, how effective it is to treat refractory coeliac disease with chemotherapy followed by transplantation of autologous stem cells.

7 Evidence for information and support related to coeliac disease

7.1 At diagnosis

7.1.1 Review question:

- a) What information do people need to help them decide whether to undergo initial testing for coeliac disease?
- b) If people are to undergo initial testing, what dietary information do they need before testing to ensure that test results are as accurate as possible?

This review question sought to investigate the information that people who are considering testing for CD should be provided with in order to help them decide whether to undergo serological testing. This is particularly relevant for people who may be informed by their healthcare professional that they are at risk of developing the condition and offered serological testing, such as first degree family members or those with certain comorbid conditions, as identified in section 4.2. Identifying the information needs of these populations will enable those deciding whether to undergo serological testing to make a more informed decision. Furthermore, it is not currently known what information should be given to people prior to testing in relation to the consumption of gluten. This chapter sought to investigate information provision around the amount of gluten that needs to be consumed prior to serological testing in order to optimize the accuracy of the result.

7.1.2 Methods

The aim of this review was to establish what information is needed by people to:

- Help them decide whether to be tested for coeliac disease
- Manage their diet before being tested

A systematic search was conducted (see Appendix C) which identified 1234 references. These references were screened on their titles and abstracts and full text papers of 5 references were obtained and reviewed against the exclusion and inclusion criteria in the review protocol (see Appendix C).

Four studies met the inclusion criteria. One study was excluded for not being a primary study.

No a priori outcomes were identified in the protocol for this question. The GDG felt that it would be difficult to find relevant evidence for this question and did not want to restrict the analyses to any particular outcome in order to avoid the potential for unnecessarily excluding studies which may be useful.

Outcomes of interest identified in the literature for the first component of this analysis include the following:

- Patient experience of diagnosis and management
- Carer perspective of diagnosis and management
- Health related quality of life pre and post diagnosis

Qualitative studies in which a structured thematic interview was utilised were considered the highest quality in a modified GRADE framework to address the information needs of people considering undergoing testing for coeliac disease. . Survey-style questionnaires were considered less informative than personalised interviews and were thus graded as moderate quality within a modified GRADE framework for the same specific outcomes.

No studies were identified that addressed question (b) which examined the dietary advice that people with coeliac disease should be made aware of prior to testing in order to ensure maximum accuracy of the serological test.

7.1.3 Evidence review

7.1.3.1 Carers experience of diagnosis

Two studies (Cederborg et al., 2011; Rosen et al., 2011) with a total of 165 children with a biopsy-confirmed diagnosis of CD explored the carer's experience of diagnosis for their child using structured interviews. Primary areas of focus within the interviews included understanding the diagnosis, and the impact of transforming to a GFD.

7.1.3.2 Adolescents experience of diagnosis

One study (Rosen et al., 2011) of 145 adolescents with a biopsy-confirmed diagnosis of CD and their parents explored the patient's perspective of understanding the initial CD diagnosis and in transforming to a GFD using structured interviews.

7.1.3.3 Health-related quality of life post diagnosis in symptomatic adolescents

One cohort study (Nordyke et al., 2011) of 586 Swedish school children (mean age 13 years; CD, n =103; controls, n=483) administered EQ5D questionnaires to children who had participated in a mass serological screening for CD at the time of testing, and at 1 year post screening to explore the effect of diagnosis of CD on health-related quality of life.

7.1.3.4 Histological recovery, gastrointestinal symptoms, and quality of life

One randomised controlled trial (Kurppa et al., 2014) of 40 EMA seropositive adults (mean age 42 years; gluten, n =20; GFD, n=20) examined the histological, symptomatic, and quality of life benefits of adhering to a GFD in asymptomatic people with serological markers of coeliac disease. Participants who met the inclusion criteria were randomised to either follow a gluten-free diet, or continue on a normal gluten-containing diet for a period of 12 months.

7.1.4 Health economic evidence

A search of economic literature was not conducted for this question as an economic evaluation was not deemed to be able to provide any evidence of use when recommending information that people undergoing testing for coeliac disease may find useful.

7.1.5 Evidence statements

7.1.5.1 Carers experience of getting a diagnosis of CD

High quality evidence from a single study (Cederborg et al., 2011) of 20 adults whose child had been diagnosed with CD described the difficulty of obtaining a diagnosis and a curiosity about the disease as primary concerns of carers when obtaining a diagnosis for their child.

High quality evidence from a single study (Rosen et al., 2011) of 145 adults whose child had been diagnosed with CD described that a lack of knowledge about CD fostered anxiety in carers, and that carers felt a great sense of relief when the final diagnosis was made.

7.1.5.2 Adolescent's experience of getting a diagnosis

High quality evidence from a single study (Rosen et al., 2011) of 145 adolescents who had been diagnosed with CD during a mass population screening described resentment in the

adolescents who had not been involved in the decision to undergo serological testing and that their parents had made this decision for them. The same study also described a feeling of anger upon receiving the diagnosis, and this was especially so when no symptoms had been experienced.

7.1.5.3 Carers experience of transforming to a GFD

High quality evidence from a single study (Cederborg et al., 2011) of 20 adults whose child had been diagnosed with CD described that carers felt panicked about feeding their child and learning about the gluten content of different foods, and worried about the social impact following a gluten-free diet would have on their child.

7.1.5.4 Adolescent's perspective of transforming to a GFD

High quality evidence from a single study (Rosen et al., 2011) of 145 adolescents who had been diagnosed with CD during a mass population screening described that adolescents felt that adhering to a gluten-free diet was a personal choice of great importance.

7.1.5.5 Health-related quality of life post CD diagnosis

Moderate quality evidence from a single study (Nurdyke et al., 2011) of 586 adolescents that were screened for CD as part of a mass population screening reported no change between cases and controls post diagnosis in self-reported health-related quality of life measures of mobility, activity, anxiety and depression, or immediate general health, presented in table 2. A small significant difference between cases and controls was reported in the dimension of pain, whereby control males experienced more pain between baseline and follow-up than did the cases.

7.1.5.6 Dietary advice prior to serological testing

No studies were identified that addressed the necessary dietary advice patients should be made aware of prior to testing in order to ensure maximum accuracy of the serological test.

7.1.5.7 Gastrointestinal symptoms and health-related quality of life in those following a GFD compared to gluten-containing diet in asymptomatic seropositive adults

High quality evidence from a single study of 40 seropositive adults reported an important reduction in the total gastrointestinal symptom rating score (GSRS) in those following a GFD compared to those on a gluten containing diet (MD =-0.4; 95% CI: -0.7 to -0.1).

7.1.5.8 Histological recovery in those following a GFD compared to gluten-containing diet in asymptomatic seropositive adults

Moderate quality evidence from a single study of 40 seropositive adults reported a potentially meaningful improvement in the expression of CD3+ intraepithelial lymphocytes in the duodenal biopsy samples of those following a gluten-free diet compared to those on a gluten containing diet, however this was not statistically supported (MD =-12.5; 95% CI: -39.5 to 14.4).

7.1.6 Evidence to recommendations

Relative value of different outcomes

The group discussed the evidence presented and felt that it was an accurate representation of what is observed within a clinical setting.

It was agreed that carer's find many aspects of diagnosis and GFD management difficult and that information needs to be provided to

	<p>support them through this. Adolescents who receive a diagnosis of CD also struggle significantly in terms of management of their condition and this is adequately reflected by the evidence presented.</p> <p>Information about CD and the importance of the GFD to manage the condition should be provided to all persons considering serological testing for CD. The most important information that should be provided to people with CD is that gluten needs to be ingested at each meal of the day in order for both the serological test, and if necessary, the subsequent biopsy, to be accurate.</p>
Trade-off between benefits and harms	<p>Information about dietary advice prior to testing</p> <p>The group discussed that the most important thing that any GP needs to discuss with a person who is to undergo serological testing for coeliac disease is whether they are eating gluten. This can present a challenge as many people do not know what gluten is.</p> <p>Those that present for serological testing because they have an affected first-degree relative may be on a gluten-free or gluten-light diet because of their family dietary adjustment. This may pose a challenge in terms of serological screening whereby sufficient amounts of gluten are not being ingested.</p> <p>The group felt it was important that gluten should be eaten in more than one meal a day, for a minimum of 6 weeks in order to maximise accuracy of serological testing. The GDG felt that the benefit of eating this much gluten in order to maximise serological testing accuracy outweighs the potential detriment of not ingesting enough gluten, which could potentially cause a false negative test. The group also discussed the importance of gluten ingestion in the context of serological testing in infants, whom may not yet have had gluten introduced into their diet. This population is similarly at risk of a false-negative serological test result because without the introduction of gluten into the diet, any potential coeliac-associated inflammatory response would not yet have occurred. It was therefore agreed by the group that infants should not be tested until gluten-containing products have been sufficiently incorporated into their daily diet.</p> <p>Information to consider before deciding to undergo testing</p> <p>The group discussed that this was particularly important to first-degree relatives of those with coeliac disease, who would be classified as 'at risk'. This may also be relevant to those with conditions that predispose them to a higher likelihood of CD such as those with type 1 diabetes. In these circumstances, people within these populations may have a discussion with their GP about their increased likelihood of having CD and whether they would like to be tested for this. The GDG felt that it was important that it was explained in detail to people in this situation that the potential social and personal harm of avoiding eating gluten was far outweighed by the benefits for their general health and in order to avoid very serious long-term complications. The GDG discussed the potential for serious long-term complications such as reduced bone mineral density, malabsorption of key vitamins and minerals, dental enamel defects, and in extreme circumstances, increased risk of cancer such as enteropathy associated T-Cell lymphoma. The risk of these serious potential long-term complications</p>

	are greatly reduced if coeliac disease is diagnosed and the person follows a strict gluten-free diet, highlighting the great importance of deciding to undergo testing in order to make an informed decision to manage these risks.
Economic considerations	Economic evidence was not considered as part of this question.
Quality of evidence	The overall quality of evidence for this question ranged from high to medium in a modified GRADE framework. The GDG was happy with the quality of evidence available and felt it of satisfactory quality on which to base recommendations.
Other considerations	In the opinion of the GDG, It is uncommon for a person to present to their GP and request serological testing for coeliac disease. Most present with generic gastrointestinal complaints or fatigue and may be tested for coeliac disease as part of a battery of investigative tests. The groups discussed the variability of time delay between serological testing and endoscopic intestinal biopsy in different areas. Those who test serologically positive for CD are required to continue a gluten-containing diet until the biopsy is carried out, and this can take up to 4 months or longer in some instances. This is particularly distressing for people when they are aware that there is a high chance that gluten is making them ill.

7.1.7 Recommendations & research recommendations

Dietary considerations prior to testing for coeliac disease

23. Do not offer serological testing for coeliac disease in infants before gluten has been introduced into the diet.

24. For people undergoing investigations for coeliac disease:

- explain that any test is accurate only if a gluten-containing diet is eaten during the diagnostic process **and**
- advise the person not to start a gluten-free diet until diagnosis is confirmed by a specialist, even if the results of a serological test are positive.

25. Advise people who are following a normal diet (containing gluten) to eat some gluten in more than 1 meal every day for at least 6 weeks before testing.

26. If people who have restricted their gluten intake or excluded gluten from their diet are reluctant or unable to re-introduce gluten into their diet before testing:

- refer the person to a gastrointestinal specialist **and**
- explain that it may be difficult to confirm their diagnosis by intestinal biopsy.

Other information before serological testing

- 27. Explain to people who are thought to be at risk of coeliac disease that a delayed diagnosis, or undiagnosed coeliac disease, can result in continuing ill health and serious long-term complications.**

7.2 Evidence to improve adherence to a gluten-free diet

7.2.1 Review questions

- a) What information, education, and support do people with coeliac disease (and their family members or carers) need to improve adherence to a gluten-free diet and self-management of their condition?
- b) What is the patient perspective of self-management and how to improve adherence, including what information is required, different monitoring strategies, and with whom they are followed up?

Many individuals with coeliac disease find it difficult both to understand the nature of gluten and the products that it is found in, and to completely avoid gluten containing products and exclude all gluten from their daily diet. This chapter sought to investigate the efficacy of information, education, or support strategies to improve adherence, as well as the patient perspective on how people with coeliac disease manage their daily gluten-free diet and what information they feel that they require to adhere to and maintain a gluten-free diet.

7.2.2 Methods

The aim of this review was to establish what information, education, and support is needed by people with coeliac disease to help them follow a gluten-free diet and manage their own condition. The second component of this question was designed to examine the preferences of people with coeliac disease to improve their self-management and adherence, including information, different monitoring strategies, and with whom they are followed-up.

Studies were only included if the population examined included people who were diagnosed with coeliac disease and who were being monitored while on a gluten-free diet. Outcomes of interest were as follows: resolution of gastrointestinal and non-gastrointestinal symptoms; participant experience; complications of coeliac disease; resource use and cost; adherence; health-related quality of life; impact on carers.

For full details of the review protocol please see Appendix C.

A systematic search was conducted (see Appendix C) which identified 1234 references. The references were screened on their titles and abstracts and full papers of 30 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see Appendix C).

Twenty one studies were excluded as they did not meet the eligibility criteria such as not being a primary study, or not reporting on the predefined outcomes of interest. A detailed list of excluded studies and reasons for their exclusion is provided in Appendix F.

Nine papers met the review criteria and were included. Data were extracted into detailed evidence tables (see Appendix D).

Randomised controlled trials were considered to be the highest quality evidence available to answer question 7.2.1 (a), and were graded as high within a GRADE framework. There were no restrictions as to study design to answer the second question 7.2.1 (b), except for case reports, which were excluded. Structured thematic interviews were considered the highest quality qualitative study designs within a modified GRADE framework. Survey-style questionnaires were considered less informative than personalised interviews and were thus graded as moderate quality within a modified GRADE framework. The quality for each outcome could be downgraded due to risk of bias in terms of study design, methods, inconsistency between studies, indirectness in terms of population, tests and outcomes used, or imprecision of outcomes.

7.2.3 Evidence review

7.2.3.1 Specialised education intervention to resolve gastrointestinal symptoms

One study (Jacobssen et al., 2007) randomised a total of 106 Swedish women with a biopsy-confirmed diagnosis of CD to take part in a patient education program to improve CD-associated gastrointestinal symptoms (n=51) or a control group (n=52). The control participants were sent a total of 5 separate written information sheets concerning diagnosis, symptoms, and treatment of CD. The intervention group participated in 10 sessions of 'coeliac school' where they were educated about coeliac disease and the GFD. Both groups were assessed at the termination of treatment at 10 weeks, and at a 6 month follow-up. Gastrointestinal symptoms were assessed using a gastrointestinal symptom rating scale (GSRs). All participants had followed a GFD for a minimum of 5 years.

7.2.3.2 Specialised education, behavioural modification, and cognitive behavioural therapy intervention to improve GFD adherence

One study (Sainsbury et al., 2012) of 1 total of 189 adults with a biopsy-confirmed diagnosis of CD were randomised to an interactive online multicomponent education and cognitive behavioural therapy intervention (n=101), or a wait-list control group (n=88). Both groups were assessed at the termination of treatment at 6 weeks, and at 6 months follow-up. Dietary adherence to the GFD was assessed using a standardised coeliac dietary adherence questionnaire (CDAQ). The risk ratio presented here was calculated using the number of event data presented in the paper. All participants had been following a GFD for >3 months.

7.2.3.3 Specialised psychological support counselling to improve GFD adherence

One study (Addolorato e al., 2004) of a total of 66 adults with a recent biopsy-confirmed diagnosis of CD, state of anxiety, and current depression were randomised to psychological support (n=33), or a wait-list control group (n=33). Psychological support was commenced at the beginning of the GFD and focused on counselling to improve social problems that related to restrictions imposed by following a GFD. Wait-list controls were free of psychological support and underwent standard health checks at each assessment. GFD adherence was evaluated through participant's self-report and family member interview, by clinical symptoms and histological and serological recovery. The risk ratio presented here was calculated using the number of event data presented in the paper. Both groups were followed every 2 weeks for 6 months.

7.2.3.4 Useful sources of information about coeliac disease and the GFD

Two studies (Zarkadas et al., 2012; Leffler et al., 2008) of a total of 6066 participants with biopsy-confirmed CD utilised structured surveys to assess participant's preferences for useful information about CD and the GFD. All participants had been diagnosed with CD and were following a GFD for > three months.

7.2.3.5 Patient experience of the GFD

A total of 5 studies (Rashid et al., 2005; Olsson et al., 2008; Leffler et al., 2008; Erichiello et al., 2010; Zarkadas et al., 2012) with 6281 biopsy-confirmed CD participants contributed to this analyses. Study designs were a mix of structured interviews and questionnaires which explored participant experience on the GFD. All participants had been following a GFD for a minimum of three months.

7.2.3.6 Patient experience of factors that positively influence adherence

A total of 3 studies (Leffler et al., 2008; Erichiello et al., 2010; Zarkadas et al., 2012) with 6270 biopsy-confirmed CD participants contributed to this analyses. Study designs were a mix of structured questionnaire or interview, which explored participant experience of CD and the GFD. All participants had been following a GFD for a minimum of three months.

7.2.3.7 Patient experience of strategies to improve adherence

A total of 2 studies (Olsson et al., 2008; Zarkadas et al., 2012) with 5959 biopsy-confirmed CD participants contributed to this analyses. Study designs were structured questionnaires which explored participant experience of CD and the GFD. All participants had been following a GFD for a minimum of three months.

7.2.4 Health economic evidence

A search of economic literature was not conducted for this question as an economic evaluation was not deemed to be able to provide any evidence of use when recommending information that people may need to improve their adherence to a gluten-free diet or to improve their self-management of their condition.

7.2.5 Evidence statements

7.2.5.1 Resolution of gastrointestinal symptoms

Low quality evidence form a single study (Jacobssen et al., 2007) of 106 women with CD reported that a specialised education intervention program had no significant impact (MD= -0.19, 95% CI: -0.21 to -0.17) upon the presence of gastrointestinal symptoms compared to a provision of information sheets alone after 10 weeks of treatment.

7.2.5.2 Improving adherence: Education, behavioural, and psychological intervention

Low quality evidence from a single study (Sainsbury et al., 2012) of 189 adults with CD reported that a specialised online multicomponent intervention program did not significantly increase adherence to a GFD compared to wait-list control participants at post-intervention follow-up (RR = 1.7, 95% CI:0.81 to 2.77).

Moderate quality evidence form a single study (Addolorato et al., 2004) of 66 adults with CD, anxiety, and depression, reported that a specialised psychological intervention program commenced at the beginning of the GFD significantly improved diet adherence compared to a wait-list control group (RR = 0.23, 95% CI: 0.07 to 0.734).

7.2.5.3 Patients experience of the GFD: useful sources of information

Moderate quality evidence from 2 studies (Leffler et al., 2008; Zarkadas et al., 2012) with a total of 6066 participants with CD reported that participants considered the following as useful sources of information about CD: the Coeliac society (88% to 90%); another person with CD (67%); their GP (25% to 36); their gastroenterologist (43% to 57%); their dietitian (52% to 63%); specialist cook books (62%); the internet (52%).

7.2.5.4 Patients experience of the GFD: social and emotional factors that influence adherence

Moderate quality evidence from 5 studies (Rashid et al., 2005; Olsson et al., 2008; Leffler et al., 2008; Erichiello et al., 2010; Zarkadas et al., 2012) with a total of 6281 participants with CD examined the participant perspective of adhering to a GFD and reported a number of social and emotional factors that influenced adherence, including: embarrassment of eating GF foods in a social environment, feeling a burden to friends and family; the limited

availability and palatability of GF foods, difficulty finding appropriate food options at restaurants; and feeling left out of social activities.

7.2.5.5 Patients experience of the GFD: Other factors that positively influence adherence

Moderate quality evidence from 3 studies (Leffler et al., 2008; Erichiello et al., 2010; Zarkadas et al., 2012) with a total of 6270 participants with CD examined the participant perspective of adhering to a GFD and reported a number of factors that positively influence GFD adherence, including: good knowledge of CD and the GFD; longer time spent following the GFD; good social and school integration; membership of a CD specialist organisation; and motivation to avoid symptoms and long-term health complications.

7.2.5.6 Strategies for improving adherence

Moderate quality evidence from 2 studies (Olsson et al., 2008; Zarkadas et al., 2012) with a total of 5959 participants with CD examined the participant perspective of adhering to a GFD and reported a number of adaptive behavioural strategies that positively influence GFD adherence, including; bringing GF foods to social occasions; avoiding sensory exposure to non-GF foods; reading all ingredients on food labels; labelling and storing GF foods separately to non-GF foods; enquiring about the gluten content of food at restaurants; talking to other CD patients about the GFD; and reminding hosts of the GFD if a social event involves food.

7.2.6 Evidence to recommendations

<p>Relative value of different outcomes</p>	<p>The group discussed and agreed that educating people about coeliac disease and the gluten-free diet was the most important thing that could be done in order to help them manage their condition adequately by: improving adherence, resolving any gastrointestinal or non-gastrointestinal symptoms, and improving general patient experience of the condition and health-related quality of life.</p> <p>As the only treatment for coeliac disease is a specialist diet, the group agreed that a dietitian with specialist knowledge of coeliac disease is the best person to deliver such specific individually-tailored dietary advice.</p> <p>Complications of CD were discussed by the GDG, and in particular the social consequences for teenagers. It was recognised by the group that teenagers often find it the most difficult to adhere to a gluten-free diet due to various social reasons and not wanting to be excluded or feel different from their peers. In these circumstances, dietetic input and psychological support counselling can be particularly useful.</p> <p>Self-care testing was discussed at length by the group, who felt that a recommendation should be made about these kinds of tests, as many people conduct them at home and need to know what they should do following a positive result.</p>
<p>Trade-off between benefits and harms</p>	<p>The group agreed that there is little quantitative evidence that shows the benefit of dietetic involvement in coeliac disease, although it is recognised by both healthcare professionals and the people with coeliac disease themselves to be very useful in order to improve adherence and resolve any outstanding symptoms of CD.</p> <p>The group discussed the utility of psychological support for people</p>

	<p>with coeliac disease in order to improve health-related quality of life and the patient experience of the condition. It was discussed whether this should be given by someone with specialist coeliac knowledge, or a general clinical psychologist or counsellor. It was agreed that depression and anxiety are always treated within the context in which they have arisen, and that specialist knowledge of coeliac is not necessary to resolve these problems. A dietitian can also provide useful input in terms of solutions to different social situations that may cause difficulty or embarrassments in relation to the gluten-free diet.</p>
Economic considerations	<p>Economic evidence was not considered as part of this question.</p>
Quality of evidence	<p>The evidence for this question ranged from low quality RCT's to high quality qualitative studies within a modified GRADE framework.</p> <p>The group agreed that the evidence from the RCT's on educational and psychological interventions was insufficient to base recommendations on, as it was inconclusive and mostly of poor quality.</p> <p>The qualitative evidence from both interview and survey study designs was agreed to provide useful evidence to inform the patient-perspective of self-management, which formed the basis of the recommendations made for this question.</p>
Other considerations	<p>The group raised the importance of gluten free meal provisions in schools and pre-schools in helping children and adolescents to adhere to the gluten-free diet. Making sure that people with coeliac disease and their family and carers were aware of gluten free food prescriptions was also raised by the group as an important consideration.</p> <p>Self-care testing was discussed at length by the group, who felt that it was difficult to interpret and act on results from these. People who received a positive result through self-care testing will often exclude gluten from their diet, which means that both further serological testing in an NHS setting and endoscopic intestinal biopsy to confirm diagnosis will be inaccurate unless gluten is reintroduced. The group also discussed the dangers of people obtaining false-negative results when using self-testing kits and the serious long-term health consequences that could arise from this.</p>

7.2.7 Recommendations & research recommendations

28. **Give people with coeliac disease (and their family members or carers, where appropriate) sources of information on the disease, including national and local specialist coeliac groups and dietitians with a specialist knowledge in coeliac disease.**
29. **A healthcare professional with a specialist knowledge of coeliac disease should 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 give them information to help them follow it. This should include:

- information on which types of food contain gluten and suitable alternatives, including gluten-free substitutes
- explanations of food labelling
- information sources about gluten-free diets, recipe ideas and cookbooks
- how to manage social situations, eating out and travelling away from home, including travel abroad
- avoiding cross contamination in the home and minimising the risk of accidental gluten intake when eating out
- the role of national and local coeliac support groups.

30. Be aware that people with coeliac disease may experience anxiety and depression. Diagnose and manage these issues in line with the following NICE guidelines:

- [Depression in adults with a chronic physical health problem](#)
- [Depression in children and young people](#)
- [Generalised anxiety disorder and panic disorder \(with or without agoraphobia\) in adults.](#)
- [Social anxiety disorder](#)

7.3 Evidence for advice on dietary management

7.3.1 Review question

- a) What dietary management strategy/advice should be given to people with coeliac disease?
- b) Should the advice include avoiding gluten-free oats as part of the exclusion diet?

While oats do not contain any gluten, they do contain the protein avenin, which may cause symptoms in a small minority of individuals with coeliac disease. Oats are however, often processed in the same environment as gluten-containing products such as wheat, barley, and rye, which means that they may be at risk of contamination by these other products. Gluten free oats ensure that the oats were produced in an environment that does not manufacture any gluten-containing products, excluding any contamination risk.

The aim of this review question was to determine which dietary management strategy/advice, other than gluten-free diet (GFD), should be given to people with coeliac disease. The first part of this question was designed to investigate the clinical efficacy dietary management or strategies, including the use of nutritional supplements as additional (adjunctive) dietary intervention to the GFD. The nutritional supplements included in the review protocol (agreed by the GDG) were calcium, vitamin D, vitamin B-12, iron and folic acid. The second part of the question was designed to investigate whether gluten-free oats should be part of the exclusion diet (including the thresholds/volume for oats intake) for people with coeliac disease. For full details of the review protocol see Appendix C.

7.3.2 Methods

A systematic search was conducted (see Appendix C) which identified 3274 references. After removing duplicates the references were screened on their titles and abstracts and full papers of 79 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (Appendix C).

Sixty nine studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (case series), not a primary study (descriptive narrative, opinions, etc.) or studies that simply looked at prevalence of nutritional deficiencies (but not the benefits of taking nutritional supplements). A detailed list of excluded studies and reasons for their exclusion is provided in Appendix G.

The 10 remaining published papers did meet the eligibility criteria and were included. Data was extracted into detailed evidence tables (see Appendix D) and are summarised below. These ten publications contributed to a total of 4 separate RCT's.

The overall quality of the evidence from these RCTs (10 publications) was of low to very low quality due methodological issues such as methods of randomisation not reported and no intention-to-treat analysis. Overall, most trials only had 12-month follow up period and there was also a lack of evidence on quality of life outcomes or GI symptoms outcomes as most included studies only reported serological or histological outcomes.

As all of the serological and histological outcomes were reported using different measurements or metrics with different length of follow-up periods, meta-analyses on individual outcomes were not appropriate. However, the evidence was synthesised using the GRADE methodology. For dichotomous outcomes where relative risk and 95% confidence intervals were available, the default MIDs of 0.75 and 1.25 were used to assess imprecision.

For continuous outcomes, the optimal information size (> 400 participants) was used to assess imprecision (as currently there is no guidance on default MIDIs for various continuous measure e.g. mean change from baseline, median with range, etc.). For the full GRADE profiles please see Appendix E.

7.3.3 Evidence review

7.3.3.1 The benefits and harms of including nutritional supplements as adjuvant therapy to the GFD in adults

One RCT (65 adults; intervention n=33; comparator n=32; age range 45 - 64 years) investigated the use of nutritional supplements where the trial compared a daily dose of 0.8 mg folic acid, 0.5 mg cyanocobalamin (vitamin B-12) and 3 mg pyridoxine (vitamin B-6) for 6 months (with GFD) to placebo tablets (with GFD). All participants had been following a GFD for > 8 years.

7.3.3.2 The benefits and harms of including gluten free oats in the GFD in children

Three published papers from 1 RCT investigated the benefits and harms of gluten-free oats in children (total n = 116; intervention n=57; comparator n=59; mean age 6.5 years). This RCT with multiple publications (at different time points) compared GFD with oats (a daily oat intake of 25–50g) to GFD only. There was also one additional RCT (N=171; intervention =75; comparator n=96; mean age 9 years) that compared 6 months on a gluten-free diet with the addition of purified oats or placebo. In this crossover trial, all participants experienced both diets (with or without the addition of oats) with a 3 month washout period in between trials.

7.3.3.3 The benefits and harms of including gluten free oats in the GFD in adults

Four published papers from 1 RCT investigated the benefits and harms of gluten-free oats in adults (total n = 63 intervention n=35; comparator n=28; mean age 45 years). This RCT with multiple publications (at different time points) compared GFD with oats (a daily oat intake of 50–70g) to GFD only. There was also 1 additional separate RCT (N = 39 adults; intervention n=23; comparator n=16; mean age 47 years) that compared GFD with oats (a daily oat intake of 50g) to GFD only.

7.3.4 Health economic evidence

An economic evaluations filter was applied to the search protocol for this research question with the aim of finding economic evaluations that examined the cost effectiveness of different dietary management strategies (including the inclusion or exclusion of oats) in people with refractory coeliac disease.

The search identified 113 references. The references were screened on their titles and abstracts and none of the studies met the inclusion criteria.

No cost–utility or cost-effectiveness analyses were found to address selection criteria.

7.3.5 Evidence statements

7.3.5.1 The benefits and harms of gluten-free oats in children

7.3.5.1.1 Serological outcomes:

Low quality evidence from a single study with small sample size on newly diagnosed children with CD suggested that, there were no statistical significant differences in the number of children who were tested IgA EMA positive and TGA positive, and who reached nitric oxide (NO) metabolites threshold of 1406 µM, between the GFD-oats group and the standard GFD

group at 12-month. The same RCT also suggested that there were no statistical significant differences in the median IgA and IgG anti-avenin antibodies at 12-months.

Subgroup analyses also suggested that there were no statistical significant differences between the newly diagnosed children with CD in the GFD-oats group (consumed GF-oats ≥ 8 g daily) and those in the standard GFD group in the number of children who tested IgA EMA positive and TGA positive at 12-months.

7.3.5.1.2 *Histological outcomes:*

Low quality evidence from a single studies with small sample size suggested that there were no difference in mean IEL count (per 100 enterocytes) at 12-months between newly diagnosed children with CD in the GFD-oats and those in the standard GFD group at 12-month.

7.3.5.2 The benefits and harms of gluten-free oats in adults

7.3.5.2.1 *Gastrointestinal symptoms:*

Low quality evidence form a single study with small sample size suggested that there was no significant difference in the mean change scores (cluster of flatulence, abdominal pain and distention, general wellbeing) from baseline at 6-month between the GFD-oats group and the standard GFD group in adults with CD (in remission). One low quality RCT (with small sample size) suggested that there were no significant differences in the mean scores of indigestion, constipation and reflux at 12-months between the GFD-oats group and the standard GFD group in adults with CD (in remission). However, the trial suggested that the GFD-oats group had significant higher mean score of diarrhoea compared to the standard GFD group. One further RCT showed no significant change between children ingesting GFD-oats and those on a standard GFD in symptom severity based on the gastrointestinal symptom rating scale (GSRS).

7.3.5.2.2 *Histological outcomes:*

Low quality evidence from a single study with small sample size suggested that there were no significant differences in villous atrophy and IEL count between the GFD-oats group and the standard GFD group (both newly diagnosed or in remission adults with CD) at 6-, 12-month and 5-year follow-up.

7.3.5.2.3 *Serological outcomes:*

Low quality evidence from a single study with small sample size suggested that there were no significant differences in Anti-gliadin IgA, Anti-gliadin IgG and Anti-reticulin IgA between the GFD-oats group and the standard GFD group (both newly diagnosed or in remission adults with CD) at 6- and 12-month follow-up.

7.3.5.3 Nutritional supplements in adults with CD:

One very low quality RCT with small sample size suggested that there were no significant difference in the median score of the psychological general wellbeing (PGWB) scale between the nutritional supplements (folic acid, B-6 and B-12) group and the placebo group (adults with CD in remission) at 6-months. However, the study suggested that the nutritional supplements group had significant lower median P-tHcy ($\mu\text{mol/L}$) level at 6-month.

7.3.6 Evidence to recommendations

Relative value of different

The GDG discussed and agreed that currently there was very limited evidence on the critical outcomes such quality of life measures and

outcomes	<p>growth for children. The GDG further discussed that GI symptoms, serological outcomes and histological outcomes may not necessarily be associated with each other for example, people with villous atrophy could be symptom free or vice versa.</p> <p>Nutritional supplements</p> <p>The GDG agreed that the psychological general wellbeing (PGWB) scale reported in the 1 RCT was the critical outcome. However, the other reported outcome in the study, the B-vitamin marker P-tHcy ($\mu\text{mol/l}$) was of limited utility as the marker could not distinguish which vitamin B was associated with the effect estimates. Also, the GDG pointed out that the trial had very short follow-up (6-months) considering coeliac disease is a long-term condition.</p> <p>The benefits and harms of gluten-free oats</p> <p>In the absence of high quality evidence on the critical outcomes (QoL measures and growth for children), the GDG agreed that all 3 other important outcomes (GI symptoms, serological outcomes and histological outcomes) should be given equal weight as they do not necessarily correlate to each other. The GDG also pointed out, out of the 3 RCTs on gluten-free oats, only 1 trial had follow-up of up to 5-years (in adults); the other was only up to 12-month or less.</p>
Trade-off between benefits and harms	<p>Nutritional supplements</p> <p>As there was only one trial with very small sample size, and the critical outcome (PGWB scale) suggested no significant difference between the two groups, the GDG felt that they could not make a positive recommendation on the use of nutritional supplements on top of gluten-free diet (GFD).</p> <p>The GDG also further discussed the potential harms of overdosing on over-the-counter vitamin-D, calcium and iron if inappropriate information was given to people with coeliac disease. Hence, the GDG agreed that healthcare professionals should advise people with coeliac disease not to self-medicate with over-the-counter vitamins or minerals supplements without first having a discussion with a member of their healthcare team. Nevertheless, the GDG acknowledged that some people with coeliac disease may need additional nutritional supplements alongside their normal diet, particular during the early stages following diagnosis. However, the GDG agreed that this should be identified through appropriate ongoing monitoring based on individuals' need and supplementations should not be initiated without a full assessment from the healthcare professional team including the dietitian.</p> <p>The benefits and harms of oats</p> <p>The GDG discussed the evidence and agreed that all the evidence did not suggest any significant harms from consuming gluten-free oats in the vast majority of adults (newly diagnosed or in remission) and children (newly diagnosed) with coeliac disease. The group discussed that while oats do not contain any gluten, they do contain the protein avenin, which may cause symptoms in a small minority of individuals</p>

	<p>with coeliac disease. Gluten free oats ensure that the oats were produced in an environment that does not manufacture any gluten-containing products; excluding any contamination risk. The evidence suggested that there were no significant differences on GI symptoms, serological and histological outcomes between the GFD with oats group and the standard GFD group.</p> <p>Based on the GDG's experiences and knowledge, the GDG also noted the potential benefits of including gluten-free oats in the standard GFD, such as, to improve adherence (due to improved variety and palatability of food) as well as to improve daily essential nutrients intake through diet. Hence, the GDG agreed that gluten-free oats can be included at any stage of the person's dietary plan depending on the person's preferences.</p> <p>Nevertheless, the GDG acknowledged that out of the 4 included RCTs, only 1 trial had follow-up data up to 5 years while the other trials were only up to 12 months or less. Due to this reason, the GDG agreed that ongoing monitoring of immunological, clinical or histological responses of people who chose to consume gluten-free oats was crucial, and that advice on whether they should continue their consumption of gluten-free oats on a long-term basis or not should be based on the immunological, clinical or histological responses that are regularly monitored by the healthcare professionals.</p>
Economic considerations	No economic evidence was found to address this question.
Quality of evidence	<p>The GDG discussed and agreed that the evidence were of low to very low quality due methodological issues such as methods of randomisation not reported, small sample size and no intention-to-treat analysis. However, the GDG agreed that the evidence on gluten-free oats did consistently suggest the same direction of effects estimates.</p> <p>Nevertheless, the GDG felt it was important to have further longer follow-up research with bigger sample sizes, particularly on the use of nutritional supplements as an additional intervention to GFD.</p>

7.3.7 Recommendations & research recommendations

7.3.7.1 Recommendations

31. Advise people with coeliac disease (and their family members or carers, where appropriate) to seek advice from a member of their healthcare team if they are thinking about taking over-the-counter vitamin or mineral supplements.
32. Explain to people with coeliac disease (and their family members or carers, where appropriate) that they may need to take specific supplements such as calcium or vitamin D if their dietary intake is insufficient.
33. Explain to people with coeliac disease (and their family or carers, where appropriate) that:
 - they 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.

7.3.7.2 Research recommendation

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

Why this is important

People with coeliac disease are at an increased risk of malabsorption of key nutrients such as calcium and vitamin D. This is because of the role gluten plays in preventing these nutrients from being properly absorbed. It is not known how long the body takes to properly absorb these vitamins and minerals once a gluten-free diet is started. It is also not known whether the majority of people diagnosed with coeliac disease have enough calcium and vitamin D in their diet, or whether some people with coeliac disease are able to get enough of these nutrients from what they eat. Answering this research question will help healthcare professionals to understand whether calcium and vitamin D should be offered to everyone at the time of diagnosis and for how long these vitamin and mineral supplements should be taken.

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8.6 Question 5.3

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9 Glossary

2 x 2 table

A table that summarises diagnostic information (true and false positives and negatives) and allows for further interpretation of the data such as sensitivity, specificity, forest plots and ROC curves.

Case-control study

Comparative observational study in which the investigator selects people who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Cohort study

An observational study in which a defined group of people (the cohort) is followed over time. Outcomes are compared in subsets of the cohort who were exposed or not exposed (or exposed at different levels) to an intervention or other factor of interest.

Confidence interval

The range within which the 'true' values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias).

Cost-effectiveness analysis

An economic evaluation that compares alternative options for a specific patient group, looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental (or average or marginal) cost-effectiveness ratio.

Cost-utility analysis

An economic evaluation that compares alternative options for a specific patient group, looking at a single effectiveness dimension measured in a non-monetary (natural) unit that also takes quality of life into account. It expresses the result in the form of incremental cost per quality-adjusted life year (QALY) gained.

Economic evaluation

Technique developed to assess both costs and consequences of alternative health strategies and to provide a decision-making framework.

False negative

A negative result in a diagnostic test when the person being tested does possess the attribute for which the test is conducted.

False positive

A positive result in a diagnostic result when the person being tested does not possess the attribute for which the test is conducted.

Generalisability

The degree to which the results of a study or systematic review can be extrapolated to other circumstances.

Gluten-free diet

A gluten-free diet is the primary strategy of managing the symptoms and clinical features of coeliac disease. A gluten-free diet does not contain any product derived from the gluten-containing grains: wheat, barley, or rye.

Gluten challenge

The process by which people who are currently on a gluten-free diet are requested to resume eating gluten for a period of time before serological testing in order to 'challenge' their autoimmune system and ensure an accurate serological test results.

Heterogeneity

A term used to illustrate the variability or differences among studies. High heterogeneity indicates greater differences.

Marsh histological criteria (Marsh Grade III)

The current histological criteria by which a biopsy sample is graded in order to determine the presence of coeliac disease. Marsh grade III, which indicates the presence of villous atrophy, is considered to be diagnostic for coeliac disease.

Negative predictive value

The proportion of people with negative test results who do not have the disease.

Non-responsive coeliac disease

Non-responsive coeliac disease refers to the continuation of symptoms of coeliac disease, despite a patient's best efforts to follow a gluten-free diet. The most common cause of non-responsive coeliac disease is inadvertent gluten-exposure, which can be rectified with the guidance of a dietitian with a specialist interest and knowledge in coeliac disease.

Odds ratio

A measure of treatment effectiveness. The likelihood of an event happening in the intervention group, divided by the likelihood of it happening in the control group. The 'odds ratio' is the ratio of non-events to events.

Positive predictive value

The proportion of people with a positive test result who actually have the disease.

Quality-adjusted life year (QALY)

A statistical measure, representing 1 year of life, with full quality of life.

Refractory Coeliac disease

True refractory disease refers to the very rare occurrence of patients who do not respond to a gluten-free diet and continue to experience the symptoms of coeliac disease, and/or continued histological damage. Refractory coeliac disease can be diagnosed when all other potential co-morbidities have been ruled out, the certainty of the original diagnosis has been made, and the inadvertent ingestion of gluten has been ruled out. Patients with this condition require highly specialist care and management.

10 List of abbreviations

AGA	Antigliadin antibodies
CD	Coeliac disease
CI	Confidence intervals
CT	Computerised tomography
CUA	Cost–utility analysis
CVID	Common variant immunodeficiency
DBE	Double balloon enteroscopy
DGP	Deamidated gliadin peptides
DH	Dermatitis herpetiformis
EATL	Enteropathy-associated T-cell lymphoma
EMA	Endomysial antibodies
GDG	Guideline development group
GFD	Gluten-free diet
GI	Gastrointestinal
GRADE	Grading of recommendations assessment development evaluation
HLA DQ2/DQ8	Human leucocyte antigen
IBS	Irritable bowel syndrome
ICER	Incremental cost-effectiveness ratio
IEL	Intra epithelial lymphocytes
IgA	Immunoglobulin A
IgG	Immunoglobulin G
MD	Mean difference
MRI	Magnetic resonance imaging
NRCD	Non responsive coeliac disease
OR	Odds ratio
QALY	Quality-adjusted life year

RCD	Refractory coeliac disease
RCT	Randomised controlled trial
RR	Risk ratio
TCR	T-cell receptor
tTG	Tissue transglutaminase