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Coeliac disease

**Recognition and assessment of coeliac
disease**

NICE clinical guideline 86
Coeliac disease: recognition and assessment of coeliac disease

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Foreword

Coeliac disease is believed to be present in up to 1 in 100 of the population although only about 10–15% of people with the condition are clinically diagnosed. Many of the remainder may be well, but a significant minority will have chronic problems such as lethargy, gastrointestinal symptoms, or the effects of anaemia. These result in chronic ill health and often extensive medical investigation without a definite diagnosis.

Because coeliac disease can be very effectively treated with a gluten-free diet it is important to identify people with the undiagnosed disease so as to provide satisfactory individual treatment and also to improve the overall health of the community.

To improve the recognition of coeliac disease and to increase the number of people diagnosed with the condition, the Department of Health asked NICE to produce a short clinical guideline about how the disease should be recognised and which people should be assessed for the disease.

The Guideline Development Group (GDG) comprised experts in both adult and paediatric gastroenterology from primary and secondary care, dietitians, patient members and a clinical immunologist. It was supported by the NICE Short Clinical Guidelines Technical Team.

The GDG considered systematically identified and reviewed evidence concerning the recognition of coeliac disease. A new health economic model was also developed to consider the cost effectiveness of serological tests for coeliac disease.

The guideline gives recommendations about the clinical signs, symptoms and types of presentation or conditions that should alert practitioners to consider the presence of coeliac disease, and suggests a scheme of investigation to follow when making the diagnosis. It is expected that implementation of the guideline recommendations will lead to many new cases being diagnosed and much ill health being alleviated.

The GDG hopes that this guideline will be sufficiently clear and non-contentious that its implementation will be routine both in secondary care and in primary care, where most patients with coeliac disease will present.

Professor Peter D Howdle

Chair, Guideline Development Group

Patient-centred care

This guideline offers best practice advice on the recognition and assessment of coeliac disease and the care of children and adults who are undergoing the diagnostic process for coeliac disease.

This diagnostic process should take into account patients' needs and preferences. People with symptoms and/or signs suggestive of coeliac disease should have the opportunity to make informed decisions, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health (2001) guidelines – 'Reference guide to consent for examination or treatment' (available from www.dh.gov.uk). Healthcare professionals should also follow a code of practice accompanying the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

If the patient is under 16, healthcare professionals should follow guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Diagnosis, treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about diagnosis, treatment and care.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance

described in 'Transition: getting it right for young people' (available from www.dh.gov.uk).

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.

1 Summary

1.1 *Recommendations*

When to offer testing

1.1.1 Offer serological testing for coeliac disease to children and adults with any of the following signs and symptoms:

- chronic or intermittent diarrhoea
- failure to thrive or faltering growth (in children)
- persistent or unexplained gastrointestinal symptoms including nausea and vomiting
- prolonged fatigue ('tired all the time')
- recurrent abdominal pain, cramping or distension
- sudden or unexpected weight loss
- unexplained iron-deficiency anaemia, or other unspecified anaemia.

1.1.2 Offer serological testing for coeliac disease to children and adults with:

- any of the following conditions:
 - autoimmune thyroid disease
 - dermatitis herpetiformis
 - irritable bowel syndrome
 - type 1 diabetes

or

- first-degree relatives (parents, siblings or children) with coeliac disease.

1.1.3 Consider offering serological testing for coeliac disease to children and adults with any of the following:

- Addison's disease
- amenorrhoea
- aphthous stomatitis (mouth ulcers)
- autoimmune liver conditions
- autoimmune myocarditis
- chronic thrombocytopenia purpura
- dental enamel defects
- depression or bipolar disorder
- Down's syndrome
- epilepsy
- low-trauma fracture
- lymphoma
- metabolic bone disease (such as rickets or osteomalacia)
- microscopic colitis
- persistent or unexplained constipation
- persistently raised liver enzymes with unknown cause
- polyneuropathy
- recurrent miscarriage
- reduced bone mineral density
- sarcoidosis
- Sjögren's syndrome
- Turner syndrome
- unexplained alopecia
- unexplained subfertility.

Dietary considerations before testing for coeliac disease

1.1.4 Do not use serological testing for coeliac disease in infants before gluten has been introduced to the diet.

1.1.5 Inform people (and their parents or carers, as appropriate) that any testing for coeliac disease is accurate only if the person continues

to follow a gluten-containing diet during the diagnostic process (serological tests and biopsy if required).

- 1.1.6 Inform people that they should not start a gluten-free diet until diagnosis is confirmed by intestinal biopsy, even if a self-test or other serological test is positive.
- 1.1.7 Inform people that when they are following a normal diet (containing gluten) they should eat some gluten (for example, bread, chapattis, pasta, biscuits, or cakes) in more than one meal every day for a minimum of 6 weeks before testing; however, it is not possible to say exactly how much gluten they should eat.
- 1.1.8 If a person is reluctant or unable to reintroduce gluten into their diet before testing:
- refer them to a gastrointestinal specialist and
 - inform them that it may be difficult to confirm a diagnosis of coeliac disease on intestinal biopsy, and that this may have implications for the prescribing of gluten-free foods.

Other information before serological testing

- 1.1.9 Inform people who are considering, or have undertaken, self-testing for coeliac disease (and their parents or carers) that any result from self-testing needs to be discussed with a healthcare professional and confirmed by laboratory-based tests.
- 1.1.10 Before seeking consent to take blood for serological tests, explain:
- what coeliac disease is
 - that serological tests do not diagnose coeliac disease, but indicate whether further testing is needed
 - the implications of a positive test (including referral for intestinal biopsy and implications for other family members)
 - the implications of a negative test (that coeliac disease is unlikely but it could be present or could arise in the future).

1.1.11 Inform people and their parents or carers that a delayed diagnosis of coeliac disease, or undiagnosed coeliac disease, can result in:

- continuing ill health
- long-term complications, including osteoporosis and increased fracture risk, unfavourable pregnancy outcomes and a modest increased risk of intestinal malignancy
- growth failure, delayed puberty and dental problems (in children).

Serological tests

1.1.12 All tests should be undertaken in laboratories with clinical pathology accreditation (CPA).

1.1.13 Do not use immunoglobulin G (IgG) or immunoglobulin A (IgA) anti-gliadin antibody (AGA) tests in the diagnosis of coeliac disease.

1.1.14 Do not use of self-tests and/or point-of-care tests for coeliac disease as a substitute for laboratory-based testing.

1.1.15 When clinicians request serology, laboratories should:

- use IgA tissue transglutaminase (tTGA) as the first choice test
- use IgA endomysial antibodies (EMA) testing if the result of the tTGA test is equivocal
- check for IgA deficiency if the serology is negative¹
- use IgG tTGA and/or IgG EMA serological tests for people with confirmed IgA deficiency
- communicate the results clearly in terms of values, interpretation and recommended action.

1.1.16 Do not use human leukocyte antigen (HLA) DQ2/DQ8 testing in the initial diagnosis of coeliac disease. (However, its high negative

¹ Investigation for IgA deficiency should be done if the laboratory detects a low or very low optical density on IgA tTGA test or low background on IgA EMA test.

predictive value may be of use to gastrointestinal specialists in specific clinical situations.)

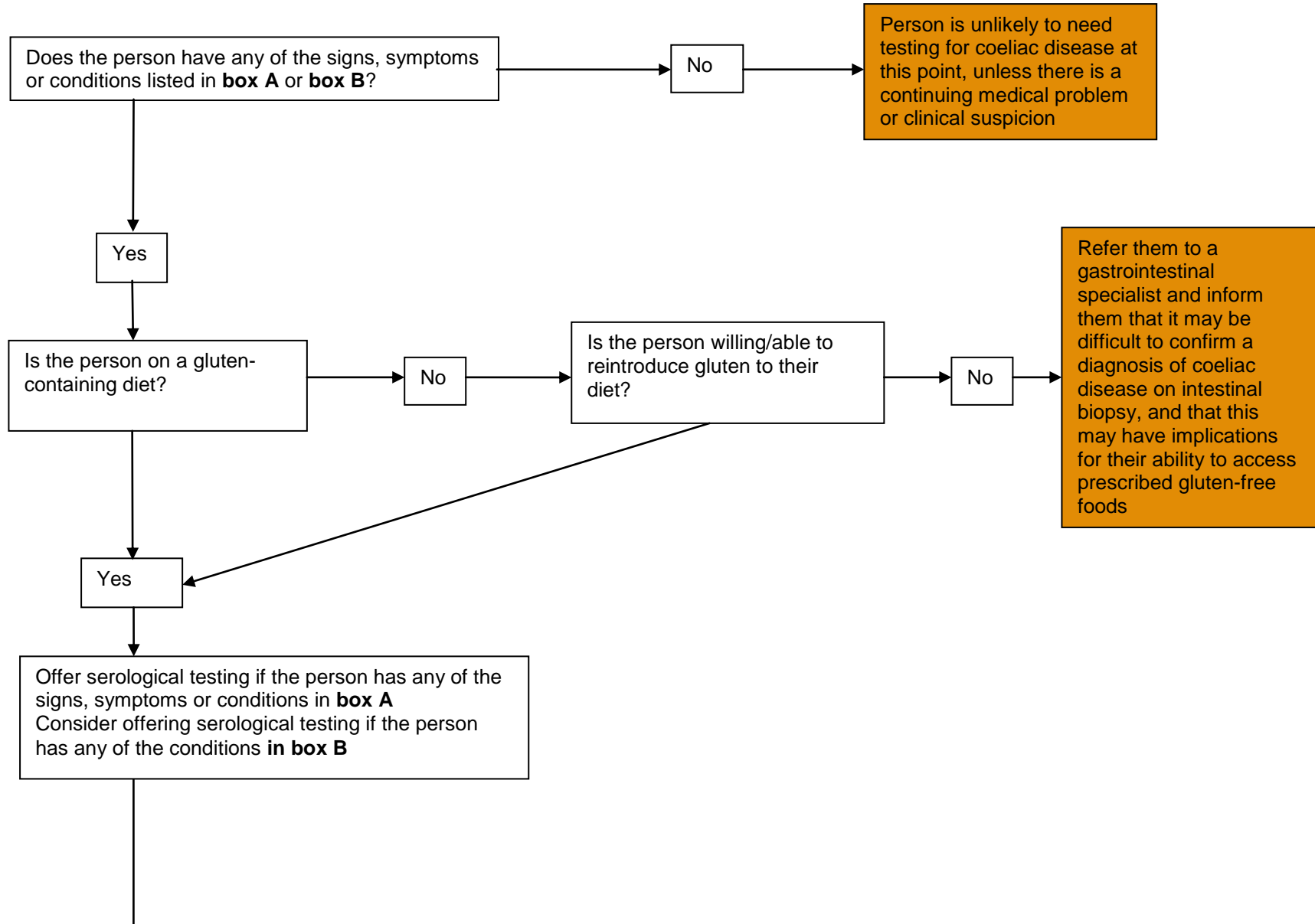
After serological testing

- 1.1.17 Offer referral to a gastrointestinal specialist for intestinal biopsy to confirm or exclude coeliac disease to people with positive serological results from any tTGA or EMA test.

- 1.1.18 If serology tests are negative but coeliac disease is still clinically suspected, offer referral to a gastrointestinal specialist for further assessment.

1.2 Care pathway

Important: Do not use serological testing for coeliac disease in infants before gluten has been introduced to the diet



Dietary considerations before serological testing

Inform people (and their parents or carers as appropriate) that:

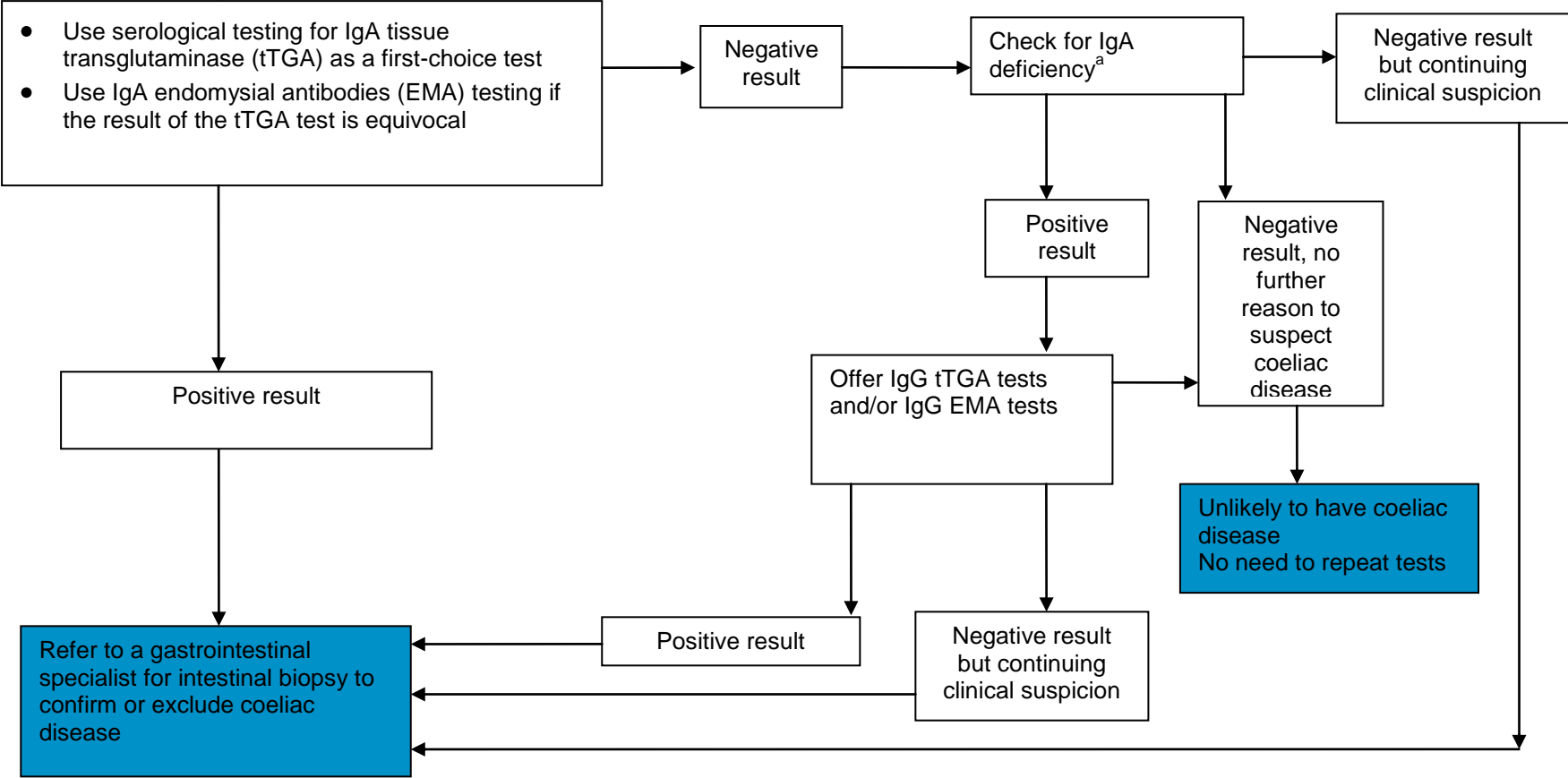
- testing (serology and biopsy if required) is accurate only if they follow a gluten-containing diet
- when following a gluten-containing diet they should eat some gluten in more than one meal every day for at least 6 weeks before testing
- they should not start a gluten-free diet until diagnosis is confirmed by intestinal biopsy (even if a self-test or other serological test is positive)

Other information before serological testing

- Inform people who are considering, or who have undertaken, self-testing for coeliac disease that any result from self-testing needs to be discussed with a healthcare professional and confirmed by laboratory-based tests.
- Before seeking consent to take blood for serological tests, explain:
 - what coeliac disease is
 - that serological tests do not diagnose coeliac disease, but indicate whether further testing is needed
 - the implications of a positive test (including referral for intestinal biopsy and implications for other family members)
 - the implications of a negative test (that coeliac disease is unlikely but it could be present or arise in the future).
- Inform people (and their parents or carers as appropriate) that a delayed diagnosis of coeliac disease, or undiagnosed coeliac disease, can result in:
 - continuing ill health
 - long-term complications, including osteoporosis and increased fracture risk, unfavourable pregnancy outcomes and a modest increased risk of intestinal malignancy
 - growth failure, delayed puberty and dental problems (in children).

Important:

- All tests should be undertaken in laboratories with clinical pathology accreditation (CPA)
- Do not use IgA or IgG anti-gliadin antibody (AGA) tests in the diagnosis of coeliac disease
- Do not use HLA DQ2/DQ8 testing in the initial diagnosis of coeliac disease (However, its high negative predictive value may be of use to gastrointestinal specialists in specific clinical situations)
- Do not use self-tests and/or point of care tests for coeliac disease as a substitute for laboratory-based testing



^a Investigation for IgA deficiency should be done if the laboratory detects a low or very low optical density on IgA tTGA test or low background on IgA EMA test.

Signs, symptoms and conditions associated with coeliac disease

Box A. Offer serological testing to children and adults with any of the following signs, symptoms and conditions

Signs and symptoms	Conditions
<ul style="list-style-type: none"> • Chronic or intermittent diarrhoea • Failure to thrive or faltering growth (in children) • Persistent or unexplained gastrointestinal symptoms including nausea and vomiting • Prolonged fatigue ('tired all the time') • Recurrent abdominal pain, cramping or distension • Sudden or unexpected weight loss • Unexplained iron-deficiency anaemia, or other unspecified anaemia 	<ul style="list-style-type: none"> • Autoimmune thyroid disease • Dermatitis herpetiformis • Irritable bowel syndrome • Type 1 diabetes • First-degree relatives (parents, siblings or children) with coeliac disease

Box B. Consider offering serological testing to children and adults with any of the following

<ul style="list-style-type: none"> • Addison's disease • amenorrhoea • aphthous stomatitis (mouth ulcers) • autoimmune liver conditions • autoimmune myocarditis • chronic thrombocytopenia purpura • dental enamel defects • depression or bipolar disorder • Down's syndrome • epilepsy • low-trauma fracture • lymphoma • metabolic bone disease (such as rickets or osteomalacia) 	<ul style="list-style-type: none"> • microscopic colitis • persistent or unexplained constipation • persistently raised liver enzymes with unknown cause • polyneuropathy • recurrent miscarriage • reduced bone mineral density • sarcoidosis • Sjögren's syndrome • Turner syndrome • unexplained alopecia • unexplained subfertility.
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1.3 Overview

1.3.1 Coeliac disease: recognition and assessment

Coeliac disease is a state of heightened immunological response to ingested gluten in genetically susceptible people. Gluten is a protein that is present in wheat, barley and rye. Historically, coeliac disease was believed to be uncommon; however, population-based studies have identified that it is more common than previously thought.

Coeliac disease has traditionally been associated with mainly gastrointestinal symptoms (such as diarrhoea, abdominal pain, bloating, constipation and indigestion), because chronic inflammation of the small intestine is a feature of the immune response to gluten. However, non-gastrointestinal features of coeliac disease have been increasingly recognised in people presenting with the disease. Some people with coeliac disease have no obvious symptoms.

Coeliac disease is considered to be more prevalent in people with autoimmune conditions such as type 1 diabetes or autoimmune thyroid disease, and in first-degree relatives of people with coeliac disease.

Coeliac disease can be diagnosed at any age (after the introduction of gluten-containing foods to the infant weaning diet), and presents in both children and adults.

Because of the disparate nature of its signs and symptoms, and the historical belief that it is not a common disease, there is concern that coeliac disease often goes unrecognised and consequently is underdiagnosed. As a result, people may present to primary and secondary care on many occasions and with a range of symptoms before diagnosis. Delayed diagnosis is a concern because the symptoms of coeliac disease remain untreated and because of the possible long-term effects of undiagnosed coeliac disease.

There is also some uncertainty about which of the serological tests are most suitable for use in the diagnostic process for coeliac disease. Small intestinal biopsy is used as the reference standard for the diagnosis of coeliac disease.

Although there is ongoing debate about the possibility of diagnosis without the need for an intestinal biopsy, it is accepted that currently it is needed for a definitive diagnosis.

This short clinical guideline aims to improve the care of children and adults with undiagnosed coeliac disease by making evidence-based recommendations about its recognition, and about using serological testing to direct referral for definitive diagnosis by intestinal biopsy.

This guideline uses the best available clinical-effectiveness and cost-effectiveness evidence, which is analysed and discussed by the GDG to develop recommendations. The GDG considered the signs and symptoms, conditions likely to coexist with coeliac disease, the role of serological testing in the diagnostic process up to referral for small intestinal biopsy, and the information needs of patients and carers throughout this process.

1.3.2 The NICE short clinical guideline programme

'Coeliac disease: recognition and assessment' (NICE clinical guideline 86) is a NICE short clinical guideline. For a full explanation of the NICE guideline development process, see 'The guidelines manual' (2009) (available from www.nice.org.uk/guidelinesmanual).

1.3.3 Using this guideline

This document is intended to be relevant to healthcare professionals in primary and secondary care. The target population is adults and children with symptoms and/or signs that suggest coeliac disease.

This is the full version of the guideline. It is available from www.nice.org.uk/CG86. Printed summary versions of this guideline are available: 'Understanding NICE guidance' (a version for patients and carers) and a quick reference guide (for healthcare professionals). These are also available from www.nice.org.uk/CG86.

1.3.4 Using recommendations and supporting evidence

For each clinical question the GDG was presented with a summary of the clinical evidence, and economic evidence if appropriate, derived from the studies reviewed and appraised. The GDG based the guideline recommendations on this information. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the 'Evidence to recommendations' sections (2.2.3, 2.3.4 and 2.4.5).

2 Evidence review

2.1 Introduction

The clinical-effectiveness and cost-effectiveness evidence that was used in the development of this guideline is summarised in this section. Further details about the cost-effectiveness evidence, including details of the economic model, are given in appendix 6.5; details about the clinical evidence are given in the tables in appendix 6.6.

The aim of this guideline is to improve the recognition and assessment of coeliac disease in children and adults; it considers the diagnostic pathway up to referral for intestinal biopsy. Small intestinal biopsy is the reference standard used throughout this guideline; the studies included are those in which coeliac disease was confirmed by intestinal biopsy. In 2004 the Agency for Healthcare Research and Quality (AHRQ) published an evidence report/technology assessment on coeliac disease. The report included a series of systematic reviews using clearly defined methods; these reviews have been included when appropriate to the scope of this guideline. The AHRQ report, assessed as a well-conducted systematic review, is considered as high-quality evidence (details of the evidence grading system can be found in 'The guidelines manual' [2009], available from www.nice.org.uk). Other studies included in this guideline have been mainly cohort-based studies, notably for the evidence of serological test accuracy. Case-control studies have also been included when appropriate. Both the cohort and case-control studies have limitations resulting from study design, and as such are regarded as level + evidence. Case series, case reports and studies with small

numbers (less than 50 participants) have not been included. When both signs and symptoms and coexisting conditions have been listed in this guideline they have been listed alphabetically.

2.2 *Prevalence of coeliac disease*

2.2.1 Evidence review

The prevalence of coeliac disease has historically been difficult to determine because in many cases people with coeliac disease do not have specific signs and symptoms. Difficulties in recognising coeliac disease have resulted in its prevalence being considerably underestimated.

A search was carried out to identify large population-based studies giving data on the prevalence of coeliac disease; these are reviewed below.

Overall prevalence of coeliac disease

The AHRQ report (2004) includes studies that considered the prevalence of coeliac disease in north America and western Europe up to and including 2003. The evidence below includes the AHRQ report with additional relevant large population-based studies in north America and western Europe from 2003 onwards and studies in other geographical areas from 1990. The AHRQ report found a prevalence of coeliac disease in children by biopsy of 0.5 to 1.6% (six studies) and by serology of 0.3 to 1.9% (eight studies); in adults the prevalence by biopsy was 0.07 to 1.9% (15 studies) and by serology was 0.2 to 2.7% (22 studies). The three UK-based studies in the AHRQ report are all of adults, and identify a prevalence of coeliac disease by biopsy of 1.0% and by serology of 0.8 to 1.9%.

The Avon Longitudinal Study of Parents and Children (a population-based cohort study) used IgA EMA to investigate children aged 7.5 years and reported that 1% (54 out of 5470) were serologically positive for coeliac disease. This study also showed that IgA EMA positive rates were higher in girls than in boys, odds ratio (OR) 2.12 (95% confidence interval [CI] 1.20 to 3.75) (Bingley et al. 2004).

Additional international studies in adults used data which was available from large samples such as people donating blood (Bdioui et al. 2006; Melo et al. 2006; Oliveria et al. 2007; Pereira et al. 2006; Shahbazkha et al. 2003) and people attending for pre-nuptial medical checks (Gomez et al. 2001). A further study used random sampling from a national register (Roka et al. 2007). These studies found a prevalence of coeliac disease in adults of 0.14 to 0.86%.

Additional international studies in children used data on children younger than 3 years (Castano et al. 2004), samples from an existing public health register (Korponay-Szabo et al. 1999) and random sampling of school children (Ben Hariz et al. 2007; Ertekin et al. 2005). These studies identified a prevalence of coeliac disease in children of 0.64 to 1.17%.

The AHRQ report (2004) also included studies on the prevalence of coeliac disease in both children and adults in whom coeliac disease was suspected. These studies were mainly situated in referral centres and the prevalence of coeliac disease varied widely: in children it was 1.1 to 4.0% with EMA serology, 4.6 to 17.0% with biopsy; in adults it was 1.5% with EMA serology, 11.6 to 50.0% with biopsy.

Prevalence in first-degree relatives

The AHRQ report (2004) included studies that considered the prevalence of coeliac disease in first-degree relatives of people who had had a diagnosis of coeliac disease. These studies showed a prevalence of 2.8 to 17.2% with serology (five studies) and 5.6 to 44.1% with biopsy (12 studies). The three studies completed in the UK all reported a prevalence found using biopsy, and reported a prevalence in first-degree relatives of 5.6 to 22.5%.

Three additional studies were included (Fraser et al. 2006; Biagi et al. 2008; Szaflaraka-Sczapanik et al. 2001). These reported a prevalence of coeliac disease in first-degree relatives of 2 to 17.7%. The study by Fraser et al. was in the UK and reported a prevalence of 5.5%.

2.2.2 Evidence statements

In national studies in the UK, the prevalence of coeliac disease ranges between 0.8% and 1.9%. This is broadly similar to other international studies.

Among first-degree relatives of people with coeliac disease, the majority of studies report a prevalence of coeliac disease between 4.5% and 12%.

There is limited evidence that the prevalence of coeliac disease is twice as high in females as in males.

2.3 The possible long-term consequences of undiagnosed coeliac disease

2.3.1 Evidence review

The review considered only the possible long-term consequences of undiagnosed coeliac disease, and therefore did not include any studies that considered people with diagnosed coeliac disease. It did not include consideration of any long-term consequences of coeliac disease that may affect coexisting conditions such as type 1 diabetes. The included studies looked at undiagnosed coeliac disease or where other possible long-term consequences had been noted as present at the point of diagnosis. It should be noted that these possible long-term consequences are associations and the studies are not considered to provide evidence of a causal relationship. In all but one of the included studies coeliac disease had been confirmed by biopsy; the other study included pregnant women and intestinal biopsy was not considered ethical in those near to delivery (Greco et al. 2004). Overall evidence was identified in three areas: pregnancy outcomes, fracture risk and malignancy.

Pregnancy outcomes

An Italian study of 5055 women admitted to obstetric and gynaecological wards (Greco et al. 2004) identified no pregnancy outcomes for which there was a significant difference between women with and without coeliac disease. Outcomes included risk of spontaneous abortion, premature delivery, low birth weight and intrauterine growth retardation (IUGR).

A Swedish study analysed data on people from a national inpatient register who had a hospital-based discharge record of coeliac disease (Ludvigsson et al. 2005). It included 929 women whose coeliac disease had not been diagnosed when they gave birth, and 2,822,805 women without coeliac disease. There were significant differences between outcomes in the two groups of women. IUGR was reported in 5.5% of mothers with undiagnosed coeliac disease, and in 3.1% of mothers without coeliac disease (adjusted odds ratio [OR] 1.62, 95% confidence interval [CI] 1.22 to 2.15, $p = 0.001$). The equivalent figures for low-birth-weight were 7.0% and 3.4% (adjusted OR 2.13, 95% CI 1.66 to 2.75, $p < 0.001$); for very-low-birth-weight 1.2% and 0.5% (adjusted OR 2.45, 95% CI 1.35 to 4.43, $p = 0.003$); for preterm birth 8.0% and 5.0% (adjusted OR 1.71, 95% CI 1.35 to 2.17, $p < 0.001$); and for caesarean section 3.4% and 2.3% (adjusted OR 1.82, 95% CI 1.27 to 2.60, $p = 0.001$). No significant difference was found between the groups for very preterm birth (before 30 weeks) or for babies with low Apgar scores (less than 7).

Fracture risk

A second Swedish study using the national inpatient register (Ludvigsson et al. 2007) considered hip fractures (14,187 in patients with coeliac disease; 68,852 in patients without coeliac disease) and any fractures (13,724 in patients with coeliac disease; 65,627 in patients without coeliac disease). The estimated association of coeliac disease and prior fractures showed an increased risk of diagnosis with coeliac disease after hip fracture (OR 2.0, 95% CI 1.6 to 2.5, $p < 0.001$) and after any fracture (OR 1.6, 95% CI 1.5 to 1.8, $p < 0.001$). This study also identified significantly higher rates of hip fractures in people with undiagnosed coeliac disease compared with those with diagnosed coeliac disease. This increased risk was seen throughout the time period from 10 years to 0.01 years before diagnosis of coeliac disease.

A Danish study used the national patient discharge register to consider fracture risk in people with coeliac disease (Vestergaard et al. 2002). This study identified no increase in fracture risk before diagnosis of coeliac disease compared with matched controls for skull and jaw fractures, spine, rib and

pelvis fractures, upper arm fractures, forearm fractures, Colles' fractures, hand and finger fractures, hip and femur fractures, fractured neck of femur, lower leg fractures, foot fractures and osteoporosis.

Malignancy

A US study considered the standardised mortality ratio (SMR) of observed to expected rates for cancers that were diagnosed before or simultaneously with coeliac disease diagnosis (Green et al. 2003). Although numbers were small, this study identified significant SMRs for non-Hodgkin's lymphoma (4 observed cases compared with 0.7 expected, SMR 5.3, 95% CI 2.3 to 13, $p < 0.001$), small bowel cancer (3 vs. 0.1, SMR 45, 95% CI 34 to 61, $p < 0.001$), oesophageal cancer (3 vs. 0.2, SMR 16, 95% CI 9.7 to 26, $p < 0.001$) and melanoma (4 vs. 0.8, SMR 5, 95% CI 2.1 to 12, $p < 0.001$). It did not identify a significant difference SMR for colon cancer, breast cancer and total cancers.

An Italian study considered the impact of delayed diagnosis of coeliac disease on cancer risk using a standardised incidence ratio (SIR) of observed compared with expected cases in 1968 adults with diagnosed coeliac disease (Silano et al. 2007). In this study 55 people were diagnosed with cancer before or simultaneously with coeliac disease diagnosis, compared with 42.1 expected cases (SIR 1.3, 95% CI 1.0 to 1.7). Although numbers involved were small, this study identified 20 observed cases compared with 4.2 expected of non-Hodgkin's lymphoma (SIR 4.7, 95% CI 2.9 to 7.3), for colon cancer 7 compared with 6.2 (SIR 1.1, 95%CI 0.68 to 1.56), for small bowel cancer 5 compared with 0.19 (SIR 25, 95% CI 8.5 to 51.4) and for Hodgkin's lymphoma 4 compared with 0.4 (SIR 10, 95% CI 2.7 to 25). A lower risk was identified for breast cancer in people with newly diagnosed coeliac disease (3 vs. 14, SIR 0.2, 95% CI 0.04 to 0.62).

2.3.2 Evidence statements

There is evidence that undiagnosed maternal coeliac disease has a negative effect on intrauterine growth and birth weight, and is associated with increased preterm birth and caesarean section rates.

Evidence suggests an association between undiagnosed coeliac disease and an increased risk of fractures.

Undiagnosed coeliac disease is associated with an increased risk of non-Hodgkin's and Hodgkin's lymphoma and small bowel cancer, but overall rates are low.

2.3.3 Linking evidence to recommendations

The GDG discussed the evidence, agreed the evidence statements relating to the possible effects of long-term undiagnosed coeliac disease, and developed recommendations. This discussion is summarised here:

- The GDG agreed the need to include information about the risk of long-term complications of undiagnosed coeliac disease. It noted that although there is an increased risk of the specific cancers with undiagnosed coeliac disease, the overall risk of developing these cancers is low.
- The GDG discussed the different possible long-term effects in children and adults and agreed an additional recommendation for children specifying growth failure, delayed puberty and dental complications.

2.4 *Signs and symptoms of coeliac disease and coexisting conditions with coeliac disease*

2.4.1 Evidence review – signs and symptoms

Recognition and assessment of coeliac disease can be difficult because of the variety of presenting signs and symptoms.

The AHRQ report considered the prevalence of coeliac disease in adults with iron-deficiency anaemia and in adults with low bone-mineral density. Eight studies from the AHRQ report with 50 or more participants were included; these were all in adults with biopsy-proven coeliac disease. The prevalence of coeliac disease in people with iron-deficiency anaemia ranged from 2.3 to 15%. Four studies from the AHRQ report considered people with low bone mineral density; these studies identified a prevalence of coeliac disease ranging from 0 to 3%.

Further papers included in this review considered people with coeliac disease at the point of it being diagnosed and the features that they presented with. (Those reported in table 1 are where 5% or more of participants had the presenting feature.)

Table 1 Presenting features of people with coeliac disease

Feature	People with the feature	Adults/children	Studies
Iron-deficiency anaemia	39.3%	adults and children	Bottaro 1999
	25%	adults	Brandimarte 2002
	11.7%	adults and children	Emami 2008
Other or unspecified anaemia	16%	adults and children	Dickey 1997
	3 to 19%	children	Gampazzi 2007
	3.0 to 12.7%	adults	Rampertab 2006
	23.3%	older adults	Vilppula 2008
Anorexia	7.8 %	adults and children	Bottaro 1999
	25.6 to 35.1%	children	Bottaro 1993
Weight loss	43.6 to 59.6%	children	Bottaro 1993
	6%	adults and children	Dickey 1997
	15.6%	adults	Hopper 2008
	16.7%	older adults	Vilppula 2008
Abdominal distension/bloating	28.4 to 35.8%	children	Bottaro 1993
	10%	adults and children	Emami 2008
	20 to 39%	children	Gampazzi 2007
Abdominal pain	12%	adults and children	Dickey 1997
	8.2%	adults and children	Emami 2008
	11 to 21%	children	Gampazzi 2007
Abdominal pain/distension/flatulence	31.7%	older adults	Vilppula 2008
Vomiting	26.1 to 32.5%	children	Bottaro 1993
Flatulence	5.4%	adults and children	Emami 2008
Diarrhoea	70.2 to 75.2%	children	Bottaro 1993
	51%	adults and children	Dickey 1997
	13.1%	adults and children	Emami 2008
	12 to 60%	children	Gampazzi 2007
	42.9%	adults	Hopper 2008
	37.2 to 91.3%	adults	Rampertab 2006
	25%	older adults	Vilppula 2008
Short stature/growth failure	19.2%	adults and children	Bottaro 1999
	20.2 to 30.8%	children	Bottaro 1993
Irritability	10.3 to 13.9%	children	Bottaro 1993
Alopecia	10%	adults	Brandimarte 2002

Feature	People with the feature	Adults/children	Studies
Osteoporosis	6%	adults	Brandimarte 2002
Recurrent aphthous stomatitis	6%	adults	Brandimarte 2002
Amenorrhoea/ recurrent abortion	6%	adults	Brandimarte 2002
Hypertransaminase-aemia	6%	adults	Brandimarte 2002
Abnormal liver biochemistry	5%	adults and children	Dickey 1997
Chronic fatigue	7% 8.3%	adults and children older adults	Dickey 1997 Vilppula 2008
Failure to thrive	48 to 89%	children	Garampazzi 2007
Constipation	4 to 12%	children	Garampazzi 2007
Irregular bowel habits	4 to 12%	children	Garampazzi 2007

Three further studies considered a specific symptom or presentation and the percentage of those presenting with it who also had coeliac disease:

- Karnam et al. (2004) considered adults who were undergoing endoscopy for iron-deficiency anaemia and found 3 of 105 people (2.9%) had coeliac disease.
- Imanzadeh et al. (2005) considered children with small bowel type chronic diarrhoea and found that 54 of 825 people (8.96%) had coeliac disease.
- Sanders et al. (2005) considered adults with acute abdominal pain and found that 9 of 300 people (3%) had coeliac disease. In people with non-specific abdominal pain 10.5% had coeliac disease.

Some people presenting with the features of coeliac disease in the studies summarised in table 1 had a coexisting condition at the point of diagnosis of coeliac disease:

- dermatitis herpetiformis – 10%, Brandimarte 2002 (adults); 1%, Dickey 1997 (adults and children)
- irritable bowel syndrome – 20.2%, Emami 2008 (adults and children)
- liver disorder – 0.85%, Emami 2008 (adults and children)
- rheumatological disorder – 0.28%, Emami 2008 (adults and children)

- Crohn's disease – 0.57%, Emami 2008 (adults and children)
- bone disease – 0 to 15%, Rampertab 2006 (adults)
- malignancy – 5 to 21.7%, Rampertab 2006 (adults).

2.4.2 Evidence review – coexisting conditions

The studies included for this review considered coexisting conditions associated with coeliac disease up to and including the point of it being diagnosed. Studies that considered subsequent development of conditions in people who had been diagnosed with coeliac disease were excluded. The relationship between the coexisting conditions and coeliac disease here is not considered to be causal; the aim was to examine whether people with certain conditions have a higher rate of coeliac disease than the general population. Papers in which there was a substantial discrepancy between numbers of people who had serological tests and numbers of people who had biopsies were excluded, because of the possibility that results could be biased if not all those with positive serology had a biopsy.

Type 1 diabetes

The AHRQ report included papers on the prevalence of coeliac disease in people with type 1 diabetes; 21 of these studies (people with coeliac disease proven by biopsy; each had 50 or more participants) were included here. These studies identified a prevalence of coeliac disease in people with type 1 diabetes of 1.4 to 8.2% in children, 0.3 to 11.3% in adults and 1.7 to 5.7% in combined child and adult studies. Two additional papers also considered people with type 1 diabetes: one in children reported that 6.6% had coeliac disease (Salardi et al. 2008) and one in adults reported that 6.4% had coeliac disease (Picarelli et al. 2005).

Other conditions

Papers were included that considered cohorts of people with specified other conditions who were tested for coeliac disease (see table 2).

Table 2 Coexisting conditions and coeliac disease

Condition	Study participants	Participants with coeliac disease	Study author and year
Arthritis	160 adults with rheumatoid arthritis	0.63%	Francis 2002
	62 children with juvenile chronic arthritis	1.5%	George 1996
	119 children with juvenile chronic arthritis	2.5%	Lepore 1996
Autoimmune thyroid	136 adults with autoimmune thyroiditis	2.9%	Guliter 2007
	152 adults with autoimmune thyroid disease	3.29%	Sategna-Guidetti 1998
Down syndrome	1453 children and adults	4 (0.3%), adjusted risk ratio 4.7 (95% CI 1.3 to 12.2)	Goldacre 2004
	1110 children, 92 adults	55 (4.6%)	Bonamico 2001
Epilepsy	255 children and adults	2 (0.8%)	Pratesi 2003
	177 adults	1:44 (2.3%)	Cronin 1998
Inflammatory bowel disease	354 adults (173 Crohn's disease, 154 ulcerative colitis, 27 other conditions)	0.85%	Leeds 2007
Irritable bowel syndrome	300 adults	OR 7 (95% CI 1.7 to 28.0)	Sanders 2001
Liver disease	624 adults with chronic hepatitis C	0%	Thevenot 2007
	738 children and adults with chronic liver disease	1:185 (0.45%)	Germenis 2005
	57 adults with primary biliary cirrhosis	7%	Dickey 1997
Lymphoid malignancy	298 adults	0.67%	Farre 2004
Myocarditis	187 adults with autoimmune myocarditis	4.4% (p < 0.003 vs. control group)	Frustaci 2002
Sjögren's syndrome	111 adults	4.54%	Szodoray 2004
Subfertility	99 women	3.03% (p = 0.037 unexplained infertility vs. control group)	Meloni 1999
	150 women	2.7% all unexplained infertility (p = 0.06 vs. control group)	Collin 1996
Turner syndrome	389 children and adults	25 (6.4%)	Bonamico 2002

One study was also included that identified the existing conditions of people at the point of diagnosis of coeliac disease (Collin et al. 1994). Also included were studies in which logistical regression had been used to investigate coeliac disease that developed following a prior history of a coexisting condition (see table 3).

Table 3 Coexisting conditions and coeliac disease

Study group: people with newly diagnosed coeliac disease	Coexisting conditions
335 adults (335 control group) (figures are given for study group first, control group second) (Collin 1994)	Endocrine disorders: 12% (study group) vs. 4.2% (control group), p = 0.0003 <ul style="list-style-type: none"> insulin dependent diabetes 18 (5.4%) vs. 5 (1.5%), p = 0.0094 autoimmune thyroid 18 (5.4%) vs. 9 (2.7%) Connective tissue disorder: 7.2% vs. 2.7%, p = 0.011 <ul style="list-style-type: none"> Sjögren's syndrome 11 (3.3%) vs. 1 (0.3%), p = 0.0059 rheumatoid arthritis 6 (1.8%) vs. 7 (2.1%) Pulmonary disorders: <ul style="list-style-type: none"> asthma 9 vs. 12 sarcoidosis 5 vs. 0 Neurological disorders: <ul style="list-style-type: none"> epileptic seizures 5 vs. 3 dementia 5 vs. 1 Liver diseases: 4 vs. 0
14,349 adults and children (69,998 control) (Ludvigsson 2007a)	Increased risk of coeliac disease in those with prior sarcoidosis OR 3.58, 95% CI 1.98 to 6.45, p < 0.001
14,371 adults and children (70,096 control) (Ludvigsson 2007b)	Increased risk of coeliac disease in those with prior polyneuropathy OR 5.4, 95% CI 3.6 to 8.2, p < 0.001 Other neurological diseases were not associated with subsequent coeliac disease
13,776 adults and children (66,815 control) (Ludvigsson 2007c)	Increased risk of coeliac disease in those with history of mood disorder: <ul style="list-style-type: none"> prior depression OR 2.3, 95% CI 2.0 to 2.8, p < 0.001 prior bipolar disorder OR 1.7, 95% CI 1.2 to 2.3, p = 0.001

Study group: people with newly diagnosed coeliac disease	Coexisting conditions
13,818 adults and children (66,584 control) (Ludvigsson 2007d)	<p>Increased risk of coeliac disease in those with history of liver disorder:</p> <ul style="list-style-type: none"> • acute hepatitis OR 4.98, 95% CI 1.59 to 12.06, p = 0.004 • chronic hepatitis OR 5.79, 95% CI 3.13 to 10.70, p < 0.001 • primary sclerosing cholangitis OR 4.42, 95% CI 2.38 to 8.24, p < 0.001 • fatty liver OR 5.83, 95% CI 1.96 to 17.36, p < 0.002 • ascites OR 5.00, 95% CI 2.08 to 12.01, p < 0.001 • liver failure, extended OR 5.88, 95% CI 4.05 to 8.54, p < 0.001 • liver failure, restricted OR 8.33, 95% CI 1.99 to 34.87, p < 0.004 • liver cirrhosis/fibrosis OR 5.83, 95% CI 3.86 to 8.81, p < 0.001 • primary biliary cirrhosis OR 15.00, 95 %CI 4.84 to 46.51, p < 0.001 • hepatomegaly OR 2.00 (95% CI 0.39 to 10.31) not significant
14,335 children and adults (69,888 control) (Ludvigsson 2007e)	<p>Increased risk of coeliac disease in those with prior tuberculosis: OR 2.5, 95% CI 1.75 to 3.55, p < 0.001</p>
15,533 children and adults (14,491 inpatient reference controls) (Ludvigsson 2008)	<p>Increased risk of coeliac disease in those with prior sepsis OR 2.2, 95% CI 1.7 to 3.0, p < 0.001</p>
14,366 children and adults (70,095 control) (Elfström 2007)	<p>Increased risk of coeliac disease in those with prior Addison's disease OR 8.6, 95% CI 3.4 to 21.8</p>
14,347 adults and children (69,967 control) (Olen 2008)	<p>Increased risk of coeliac disease in those with history of thrombocytopenia purpura OR 2.96, 95% CI 1.60 to 5.50, p = 0.001; and those with prior chronic thrombocytopenia purpura OR 6.00, 95% CI 1.83 to 19.66, p = 0.003</p>

2.4.3 Evidence statements

In children and adults, coeliac disease can present with a broad range of signs and symptoms. The most frequent are:

- abdominal pain, cramping or distension
- chronic or intermittent diarrhoea

- failure to thrive or faltering growth in children
- fatigue
- iron-deficiency anaemia
- nausea or vomiting
- weight loss.

The following findings may also be present when coeliac disease is diagnosed:

- abnormal liver biochemistry
- alopecia
- amenorrhoea
- aphthous stomatitis (mouth ulcers)
- constipation
- dermatitis herpetiformis
- epilepsy
- microscopic colitis
- osteoporosis
- recurrent abortion
- type 1 diabetes.

There is good evidence that coeliac disease has an increased prevalence in people with:

- autoimmune thyroid disease (up to 7%)
- irritable bowel syndrome (up to 7%)
- type 1 diabetes (2–10%).

There is some evidence that coeliac disease has an increased prevalence in people with:

- autoimmune myocarditis
- chronic thrombocytopenic purpura
- depression/bipolar disorder
- Down's syndrome

- epilepsy
- liver conditions
- lymphoid malignancy
- polyneuropathy
- Sjögren's syndrome
- sarcoidosis
- Turner syndrome
- unexplained subfertility.

2.4.4 Linking evidence to recommendations

The GDG discussed the evidence and agreed the evidence statements relating to the signs and symptoms of coeliac disease and the coexisting conditions, and developed recommendations. This discussion is summarised here:

- The GDG agreed that there were certain signs and symptoms and coexisting conditions (as well as the known risk factor of being a first-degree relative of a person with coeliac disease) that are sufficiently associated with coeliac disease that people with them should be offered serological testing, and developed recommendations to reflect this. The GDG discussed the historic division of symptoms into gastrointestinal and non-gastrointestinal and concluded that it would be more beneficial to identify the overall signs and symptoms for which testing would be recommended. 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 coeliac disease are identified.
- 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 coeliac disease should be considered.
- The GDG discussed weight loss as a feature of coeliac disease and noted that, although weight loss can be a symptom of coeliac disease, the traditional view of a patient with coeliac disease being underweight is no

longer true and that patients may present underweight, at a normal weight or overweight.

Recommendation 1.1.1

Offer serological testing for coeliac disease to children and adults with any of the following signs and symptoms:

- chronic or intermittent diarrhoea
- failure to thrive or faltering growth (in children)
- persistent or unexplained gastrointestinal symptoms including nausea and vomiting
- prolonged fatigue ('tired all the time')
- recurrent abdominal pain, cramping or distension
- sudden or unexpected weight loss
- unexplained iron-deficiency anaemia, or other unspecified anaemia.

Recommendation 1.1.2

Offer serological testing for coeliac disease to children and adults with:

- any of the following conditions:
 - autoimmune thyroid disease
 - dermatitis herpetiformis
 - irritable bowel syndrome
 - type 1 diabetes
- or
- first-degree relatives (parents, siblings or children) with coeliac disease.

Recommendation 1.1.3

Consider offering serological testing for coeliac disease to children and adults with any of the following:

- Addison's disease
- amenorrhoea
- aphthous stomatitis (mouth ulcers)
- autoimmune liver conditions
- autoimmune myocarditis
- chronic thrombocytopenia purpura
- dental enamel defects
- depression or bipolar disorder
- Down's syndrome
- epilepsy
- low-trauma fracture
- lymphoma
- metabolic bone disease (such as rickets or osteomalacia)
- microscopic colitis
- persistent or unexplained constipation
- persistently raised liver enzymes with unknown cause
- polyneuropathy
- recurrent miscarriage
- reduced bone mineral density
- sarcoidosis
- Sjögren's syndrome
- Turner syndrome
- unexplained alopecia
- unexplained subfertility.

Recommendation 1.1.4

Do not use serological testing for coeliac disease in infants before gluten has been introduced to the diet.

2.5 Serological tests in the diagnostic process for coeliac disease

2.5.1 Evidence review – information for patients before testing

The search strategy was designed to identify any studies that relate specifically to the information needs and support of patients and parents or carers before the diagnosis of coeliac disease. No studies were identified.

2.5.2 Evidence review – serological tests

This review incorporated studies that included a blood sample drawn from children or adults suspected of having coeliac disease. This suspicion may have been based on clinical symptoms, an existing condition (such as type 1 diabetes) or having a first-degree relative with coeliac disease. The included studies were mainly cohort studies, which provided the best quality evidence. The data were synthesised and are presented in the form of forest plots and receiver operating characteristic (ROC) curves (see appendix 6.3). Summary statistics have not been included because the studies were not considered homogenous, the methodology for the meta-analysis of diagnostic studies is not clear and expert opinion in this area varies. Within the studies different kits and different cut-off values were used for the analysis². Further differences between studies were different or incompletely reported biopsy strategies, possible variability between laboratories or operators, the use of different samples or studies taking place in several different countries.

The serological tests considered for this review were:

- IgA AGA
- IgG AGA
- IgA EMA
- IgG EMA
- IgA tTGA
- IgG tTGA.

² If studies used different cut-off levels, the data used were that of the manufacturer's recommended cut-off levels.

Table 4 summarises the studies, total participants, test methods (enzyme-linked immunosorbent assay [ELISA] or diffusion in gel [DIG]) and substrate used for EMA (human umbilical cord [HU] or monkey oesophagus [ME]) and for tTGA (human recombinant [HR] or guinea pig [GP]) in the included studies.

Table 4 Summary of serological test studies

Serological test	Number of studies including this test	Total participants	Methods
IgA AGA	31	5600	24 used ELISA, 5 used DIG-ELISA, 1 used immunohistochemistry, 1 used immunofluorescence
IgG AGA	25	4820	20 used ELISA, 3 used DIG-ELISA, 1 used immunohistochemistry, 1 used immunofluorescence
IgA EMA ME	21	5265	18 used immunofluorescence, 2 used ELISA, 1 used DIG-ELISA, 1 unknown
IgA EMA HU	3	264	3 used immunofluorescence
IgG EMA ME	1	89	1 used immunofluorescence
IgA tTGA GP	8	946	8 used ELISA
IgA tTGA HR	11	3853	9 used ELISA, 1 used radiobinding assay, 1 unknown
IgG tTGA GP	1	111	1 used ELISA
IgG tTGA HR	1	254	1 unknown

IgA deficiency

People with IgA deficiency will have a false negative result if IgA-based serological tests are used in the diagnosis of coeliac disease. It has been suggested that there has been inadequate evaluation of IgA deficiency while testing for coeliac disease, which has resulted in the underdiagnosis of both (McGowan et al. 2008). Therefore, this guideline also considered the use of IgA-deficiency testing and IgG-based serological testing in the diagnostic process for coeliac disease.

Included studies

All studies considered people with suspected coeliac disease who had one of the included serological tests and had coeliac disease confirmed by biopsy. There were 29 studies included from the AHRQ (2004) report, 18 in children

(Altuntas et al. 1998; Artan et al. 1998; Ascher et al. 1996; Bahia et al. 2001; Bode et al. 1993; Chan et al. 2001; Chartrand et al. 1997; Chirido et al. 1999; Iltanen et al. 1999; Kumar et al. 1989; Lindberg et al. 1985; Lindquist et al. 1994; Maki et al. 1991; Meini et al. 1996; Poddar et al. 2002; Rich et al. 1990; Russo et al. 1999; Wolters et al. 2002), seven in adults (Bardela et al. 2001; Bode et al. 1994; Carroccio et al. 2002; Kaukinen et al. 2000; McMillan et al. 1991; Valdimarsson et al. 1996; Vogelsang et al. 1995) and four in children and adults (Carroccio et al. 2002; Gonczi et al. 1991; Tesei et al. 2003; Troncone et al. 1999). A further 14 studies were identified from the search, four in children (Del Rosario et al. 1998; Liu et al. 2003 and 2005; Viola et al. 2004), six in adults (Abrams et al. 2006; Hopper et al. 2008; Johnston et al. 2003; Kocna et al. 2002; Niveloni et al. 2007; Reeves et al. 2006) and four in children and adults (Carroccio et al. 2006; Dickey et al. 1997; Emami et al. 2008; Rostami et al. 1999). The largest of the additional studies was based in the UK and included a cohort of 2000 adults, 77 of whom were diagnosed with coeliac disease, and included data on IgA/IgG AGA, IgA tTGA and IgA EMA with biopsy (Hopper et al. 2008).

Table 5 Sensitivity/specificity of serological tests for coeliac disease

Serological test	Studies	Sensitivity	Specificity
IgA AGA	31 studies (5600 participants) 18 child studies 10 adult studies 3 child/adult studies	Range 23 to 100% (adults 46 to 100%) (children 23 to 100%)	Range 45 to 100% (adults 45 to 100%) (children 51 to 99%)
IgG AGA	25 studies (4830 participants) 15 child studies 8 adult studies 2 child/adult studies	Range 46 to 100% (adults 22 to 100%) (children 71 to 100%)	Range 77 to 99% (adults 41 to 97%) (children 38 to 99%)
IgA EMA	23 studies (5529 participants) 10 child studies 9 adult studies 4 child/adult studies	Range 68 to 100% (adults 68 to 100%) (children 46 to 100%)	Range 89 to 100% (adults 94 to 100%) (children 77 to 100%)
IgG EMA	1 adult study (89 participants)	Sensitivity 39%	Specificity 98%
IgA tTGA	19 studies (4799 participants) 6 child studies 9 adult studies 4 child/adult studies	Range 38 to 100% (adults 71 to 100%) (children 89 to 100%)	Range 25 to 100% (adults 65 to 100%) (children 25 to 100%)
IgG tTGA	2 studies (365 participants) 1 adult study 1 child/adult study	Sensitivity 23 to 85%	Specificity 89 to 98%

The overall efficacy of the IgA AGA, IgA EMA and IgA tTGA serological tests was summarised in forest plots and ROC curves (see appendix 6.3). The ROC curves below show the overall results for the IgA AGA, tTGA and EMA tests. They show a lower level of accuracy for the IgA AGA than the other tests, with both IgA EMA and IgA tTGA identified as having high levels of both sensitivity and specificity. For AGA the IgA serological tests results appeared to show higher sensitivity and specificity than the IgG tests. For IgG tTGA and IgG EMA there were insufficient data available to draw reasonable conclusions.

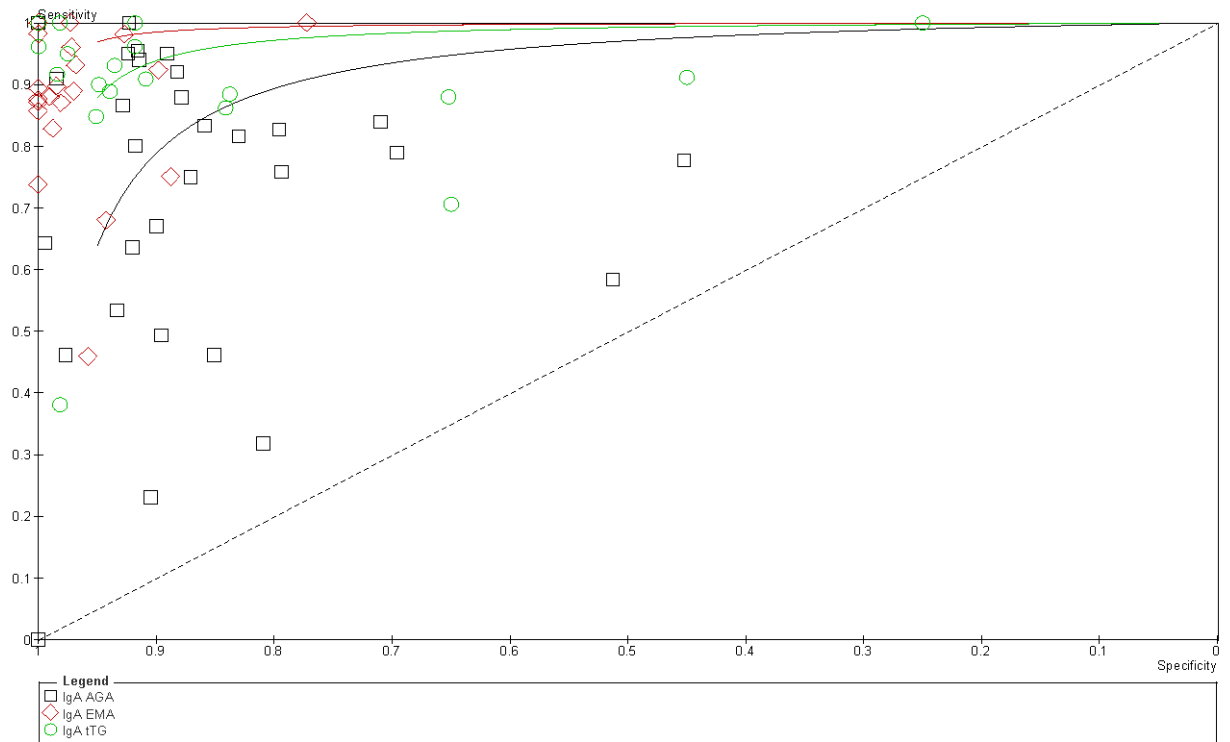


Figure 1 IgA overall results for anti-gliadin antibodies, anti-endomysial antibodies and anti tissue transglutaminase antibodies

Combined and sequence tests

A small number of papers considered the sensitivity and specificity of test combinations or sequencing of tests. One large UK study in adults (Hopper et al. 2008) considered the use of IgA tTGA and EMA. This study identified improvements in positive predictive value (PPV) and some small differences in sensitivity, specificity and negative predictive value (NPV) if both tests were used, either in a two-step process or simultaneously, compared with if tests were completed individually.

A second UK-based paper (Johnston et al. 2003), also in adults, considered the results if either IgA tTGA or EMA were positive. Positive results for either test gave a lower PPV than was found with each test individually, and a higher NPV than IgA tTGA.

A paper from the Czech Republic (Kocna et al. 2002) considered a two-step screening algorithm and identified IgA/IgG AGA to be the least accurate

first-step marker if it is followed by biopsy, with IgA EMA the most accurate first-step marker if it is followed by IgA tTGA.

Three studies in the AHRQ report considered the use of IgA/IgG AGA together or each individually; they did not find the combination results to be notably different from the individual tests.

Human leukocyte antigen tests

Coeliac disease has a genetic association with certain types of type II human leukocyte antigens (HLA); HLA DQ2 is found in 95% of people with coeliac disease and HLA DQ8 in most of the remaining 5%. No studies identified by the searches considered the sensitivity and specificity of the HLA DQ2 and DQ8 tests in coeliac disease. The AHRQ report identified papers that considered the prevalence of HLA DQ2 and DQ8 in a population of people with coeliac disease, but these studies were not designed to determine the diagnostic utility of HLA DQ2 or DQ8. Three studies in the AHRQ report were completed in people with biopsy-proven coeliac disease; these had sensitivity results of 87 to 90% and specificity of 70 to 81%.

Age

ROC curve analysis categorising studies into those with child participants, those with adult participants and those with mixed (child and adult) participants reflected the overall analysis, with both IgA EMA and IgA tTGA (there is insufficient evidence for IgG in either test to plot on the curves) showing considerably higher levels of sensitivity and specificity than IgA or IgG AGA.

One study (Viola 2004) also considered IgA AGA, IgA EMA and IgA tTGA results in children 2 years and younger and those older than 2 years. It found similar results in both age categories for IgA tTGA and for IgA EMA.

Subgroups

The search for this question was 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. The only areas in which studies were identified were liver disease and IgA deficiency.

- Liver disease: one study of 105 participants who had primary biliary cirrhosis reported a specificity range for IgA tTGA of 82.5 to 97.1% and 95.1 to 100% for IgG tTGA (Bizzaro et al. 2006). The authors noted that with almost all the antibody concentrations IgA tTGA was close to the cut-off level, and that positive results were inconsistent between the test kits. They identified a concern about the false-positive rate with IgA tTGA testing in people with primary biliary cirrhosis, although only six participants had biopsies.
- IgA deficiency: one paper was identified that considered the use of IgG AGA and IgG tTGA tests in 126 children with IgA deficiency (Lenhardt et al. 2004). Eleven were diagnosed with coeliac disease: all were IgG tTGA positive and five were also IgG AGA positive, this suggests that IgG tTGA is more accurate than IgG AGA in children with IgA deficiency.

Newer tests

Deamidated gliadin

Two papers were included that considered the use of deamidated gliadin peptide (DGP)-based assays as a diagnostic tool for coeliac disease. The first paper considered the use of IgA and IgG antibodies to synthetic DGP and tTGA in 176 children (Agardh et al. 2007) and found 119 (68%) with coeliac disease.

Table 6 Sensitivity and specificity results for deamidated gliadin (Agardh et al. 2007)

Antibody	Sensitivity	Specificity	PPV	NPV
IgA/G DGP/tTGA	100%	94.7%	97.5%	100%
IgA/G DGP	97.5%	98.2%	99.1%	94.9%
IgA DGP	90.8%	94.7%	97.3%	83.1%
IgG DGP	95.0%	98.2%	99.1%	90.3%
IgA tTGA	96.6%	100%	100%	93.4%
IgG tTGA	12.6%	100%	100%	35.4%

The second study considered 141 adults and used IgA tTGA and IgA/IgG DGP; 60 were diagnosed with coeliac disease (Niveloni et al. 2007).

Table 7 Sensitivity and specificity results for deamidated gliadin (Niveloni et al. 2007)

Antibody	Sensitivity	Specificity	PPV	NPV
IgA DGP	98.3%	93.8%	92.2%	98.7%
IgG DGP	96.7%	100%	100%	97.6%
IgA + IgG DGP	98.3%	98.8%	98.3%	79.6%
IgA tTGA	95.0%	97.5%	96.6%	96.3%
IgA DGP + tTGA	100%	97.5%	96.7%	100%
IgG DGP + IgA tTGA	100%	97.5%	96.7%	100%
IgA+IgG DGP + tTGA	100%	96.3%	95.2%	100%

Results for both of these studies using deamidated gliadin peptide showed sensitivity and specificity values similar to those found with tTGA.

Immunochromatographic sticks

One paper was included that considered the use of immunochromatographic sticks³ for tissue transglutaminase and antigliadin antibody screening in 286 children and 49 adults (Ferre-Lopez et al. 2004); 142 (51%) children and 30 (61%) adults were diagnosed with coeliac disease. Sensitivity and specificity results for immunochromatographic sticks were broadly similar to those from the ELISA method:

- IgA/G tTGA (tTG stick): children sensitivity 97%, specificity 98%; adults sensitivity 83%, specificity 100%
- IgA tTGA (tTG-AGA stick): children sensitivity 96%, specificity 98%; adults sensitivity 80%, specificity 100%
- IgA AGA (tTG-AGA stick): children sensitivity 89%, specificity 96%; adults sensitivity 83%, specificity 100%
- IgA tTGA + AGA (stick, one test): children sensitivity 99%, specificity 95%; adults sensitivity 86%, specificity 100%.

2.5.3 Evidence statements

The IgA tTGA and IgA EMA serological tests show high levels of sensitivity and specificity in the diagnostic process for coeliac disease.

Gliadin antibody serological tests show lower levels of sensitivity and specificity than tTGA and EMA.

Based on limited clinical evidence, combination testing with IgA tTGA and IgA EMA does not appear to substantially to improve accuracy in the diagnostic process.

There is limited evidence that IgA tTGA yields more false positive results in people with liver disease than in the general population.

Serological tests have comparable accuracy in children and in adults.

Newer tests for deamidated gliadin may be useful but require further evaluation.

³ Can be used for self-test or point of care testing.

Limited evidence suggests that point-of-care tests and self tests may be accurate but require further evaluation.

HLA DQ2 or DQ8 is present in approximately 25% of the UK population so a positive test has no predictive value, but a negative test can exclude a diagnosis of coeliac disease.

2.5.4 Health economics

Published health economics material

A literature review was conducted to identify evidence on the cost-effectiveness of serological tests for coeliac disease.

Several potentially useful studies were identified (Atkinson et al. 1997; Dretzke et al. 2004; Dorn et al. 2007; Harewood and Murray 2001; Hopper et al. 2008; Mein and Ladabaum et al. 2004; Shamir et al. 2006; Spiegel et al. 2004; Swigonski et al. 2008; Yagil et al. 2005). The studies by Atkinson et al. (1997) and Harewood and Murray (2001) were cost-minimisation studies that compared serological test strategies with biopsy for diagnosing coeliac disease. Dorn et al. (2007), Hopper et al. (2008) and Yagil et al. (2005) used cost-effectiveness analysis to examine the costs and diagnostic accuracy of serological tests for coeliac disease. Dorn et al. (2007) also examined the cost effectiveness of HLA testing. Mein and Ladabaum (2004) and Spiegel et al. (2004) examined the cost effectiveness of testing people with irritable bowel syndrome for coeliac disease. Shamir et al. (2006) examined a population screening approach in the adult population and Swigonski et al. (2008) examined the cost effectiveness of screening for coeliac disease in children with Down's syndrome, with the specific aim of preventing lymphoma.

None of the 10 papers examining the cost effectiveness of serological tests for coeliac disease was considered directly applicable to this guideline. However, one UK study (Dretzke et al. 2004) examined serological tests and used quality-adjusted life-years (QALYs) as an outcome measure, so was reviewed in detail for this guideline. The remaining papers were used to explore previous approaches to modelling serological test strategies and to inform the structure of the model but were not quality-assessed or reviewed in detail for

this guideline because they did not include health-related quality-of-life outcomes and/or were not based in the UK.

A full data extraction form for Dretzke et al. (2004) is available in appendix 6.5 and the techniques from that study (2004) have been examined alongside careful consideration of the modelling methods used by the other studies identified in the review.

Summary of Dretzke et al. (2004)

Dretzke et al. (2004) is a full health technology assessment (HTA) of autoantibody testing in children with newly diagnosed type 1 diabetes. It includes an economic model to quantify the costs and benefits of screening for coeliac disease at the time of diagnosis of diabetes. The assessment took place because of the variation in practice of screening for autoantibodies associated with coeliac disease in this population.

Six possible screening strategies were compared:

- no screening
- biopsy of all children
- single autoantibody test confirmed by biopsy in those testing positive
- combination of autoantibody tests confirmed by biopsy in those testing positive
- single autoantibody test without confirmatory biopsy
- combination of autoantibody tests without confirmatory biopsy.

The authors were clear that not all of these strategies are used in current clinical practice, although all strategies were included for completeness. The analysis took an NHS perspective, with costs and outcomes modelled over a lifetime.

The prevalence of undiagnosed coeliac disease in children with diabetes was estimated from the literature. The effectiveness estimates for the serological tests were taken from the authors' systematic review outlined in the report. The tests considered were IgA AGA, IgG AGA, IgA EMA, IgA ARA and IgA tTGA. Other tests were excluded because too few studies were found. The

values used in the model were taken from the summary ROC curves presented in the clinical section of Dretzke et al. (2004) for each test at the point at which sensitivity and specificity were equal. This is called the Q point. For combination tests the authors assumed that the results of the tests were independent and clearly set out the method of calculating sensitivity and specificity for combination strategies. Adherence to a gluten-free diet was included in the model, as was the proportion of patients who would have received a later diagnosis through normal clinical routes if they had not been previously picked up by screening. The delay to diagnosis for these patients was included, with associated costs and utilities for undiagnosed coeliac disease. The authors assumed that the delay to diagnosis was 5 years in the base case.

Utility estimates (quality of life weights) and assumptions were informed by existing literature. Studies on quality of life of treated and untreated coeliac disease were searched and reviewed. Utilities could not be derived directly from the studies identified. Estimates of the utility of treated and untreated coeliac disease, and of the disutility of endoscopy, biopsy and gluten-free diet were derived from the literature and assumptions.

Costs were estimated for serological tests, endoscopy and biopsy, and gluten-free diet. Personal communication was used to evaluate the costs of the serological tests; this is likely to be because of the absence of a national tariff for diagnostic tests (such as the British National Formulary for drug prices).

All strategies were compared with a no-screening strategy. The lowest cost per QALY gained was for a positive IgA EMA with confirmatory biopsy, with an incremental cost-effectiveness ratio of £12,250 per QALY gained compared with no screening. The least cost-effective strategies were those using IgG AGA tests alone or in combination with other autoantibody tests. The authors reported that the results were sensitive to the disutility of being on a gluten-free diet, the cost of gluten-free diet, the differences in utilities between health states and the reduction in life expectancy as a result of coeliac disease.

An important limitation of this study is that the authors do not present the costs and QALYs separately in the results section. This makes it difficult to determine whether costs or QALYs have the most influence on the incremental cost-effectiveness ratio. Limitations of the individual input parameters are discussed throughout the methods section, but the discussion does not address limitations of the overall model.

De novo economic model

In summary, there is evidence on the cost effectiveness of serological tests for various patient populations and country settings; however, there is a lack of evidence for the cost effectiveness of serological tests for the patient population of direct relevance to this guideline.

Because of the lack of published economic evidence that fully addresses the cost effectiveness of serological testing in the decision-making context of this guideline, the GDG requested the development of a de novo model. Any cost-effectiveness analysis carried out should also examine the costs and consequences of the outcomes of diagnosis. Although it is outside the scope of this guideline to make recommendations on the treatment or management of coeliac disease, the economic evaluation considers the costs and benefits of current standard practice after diagnosis of coeliac disease. This allows us to include the long-term consequences of testing, along with the costs and consequences of incorrect diagnosis.

A model was developed to estimate the cost effectiveness of serological test strategies for detecting coeliac disease in patients presenting with signs and symptoms. The model was built and analysed using TreeAge Pro 2007 Suite (TreeAge software) and adopted a lifetime horizon. Several test strategies were examined and compared with a no-test strategy (see table 8). The structure of the decision tree was agreed with the GDG and was also informed by previous cost-effectiveness studies. Patients accrued costs and utilities depending on their pathway through the model. At the end of the decision tree, patients entered a Markov model with states reflecting their eventual diagnosis (that is, diagnosed as having coeliac disease, no diagnosis of

coeliac disease or undiagnosed coeliac disease) and picked up costs and utilities linked with these states until death.

Serological tests examined in the model were the IgA tTGA and the IgA EMA tests. These were analysed alone and in combination. In all cases, tests were followed by biopsy to confirm positive results. Strategies with separate IgA deficiency testing were also included. For completeness a no-test strategy and a biopsy-only strategy were included.

Table 8 List of strategies in the model

Strategy number	Description
1	IgA tTGA test, followed by biopsy in the case of a positive result
2	IgA EMA test, followed by biopsy in the case of a positive result
3	IgA tTGA then IgA EMA in a two-step strategy, followed by a biopsy if IgA tTGA was positive then IgA EMA was positive
4	IgA tTGA and IgA EMA in combination, followed by a biopsy if both tests were positive
5	IgA tTGA and IgA EMA in combination, followed by a biopsy if either test was positive
6	IgA tTGA test followed by IgA deficiency test, and biopsy in the case of a positive result or IgA deficiency
7	IgA EMA test followed by IgA deficiency test, and biopsy in the case of a positive result or IgA deficiency
8	Biopsy all patients
9	No test for any patients

The clinical systematic review identified several studies on the sensitivity and specificity of serological tests for coeliac disease. There was no evidence synthesis for these studies, for reasons explained in appendix 6.4. Therefore data on sensitivity and specificity were taken from a UK-based, good quality study (Hopper et al. 2008). This evaluated the sensitivity and specificity of several serological test strategies in 2000 patients who had been referred for biopsy. The results of the study were confirmed by biopsy. This study was considered to provide the best available evidence on diagnostic accuracy to inform the base-case economic model.

The model takes into account the effect on quality of life of having an endoscopy and biopsy, having coeliac disease, having undiagnosed coeliac disease and of being on a gluten-free diet, all based on the literature review of quality of life evidence. It also takes into account any possible increased mortality resulting from undiagnosed coeliac disease, taken from a review of the literature on mortality and coeliac disease. Adherence to a gluten-free diet was taken into account in the model.

The model included the following costs: serological tests, endoscopy and biopsy, gluten-free diet and follow-up to the NHS, and delayed diagnosis. Costs were based on national-level costs from published sources, calculations and data provided by laboratories. Costs were considered from an NHS and personal social services (PSS) perspective as stated in the guideline scope. The cost of serological testing is difficult to estimate because there is no national tariff available. Cost of serological tests can vary greatly depending on who orders the tests and how they are carried out. Economies of scale are also realised when using diagnostic equipment, so the cost may differ depending on the volume of tests carried out by the laboratory. For the present analysis, the costs of serological tests have been estimated from data provided by two laboratories in the UK following communication with a GDG member. It is important to note that the methods laboratories use when charging for serological tests means that the cost of two tests or combination testing is often only marginally more expensive than a single test. This is because most laboratories charge a fixed fee for coeliac disease testing, based on an average of all tests for coeliac disease including the cost for tTGA plus any additional tests needed.

Given this potential uncertainty on how laboratories charge, extensive sensitivity analysis was carried out on this variable.

Full details of the model, including results and sensitivity analysis, are presented in appendix 6.5.

The model suggests that the no-test strategy is both the least effective strategy (that is, produces the least number of QALYs) and the least costly

strategy. Although no testing costs are involved, people who have undiagnosed coeliac disease also have a lower quality of life and increased costs resulting from undiagnosed coeliac disease.

Moving from no testing to any of the testing strategies examined appears to be cost effective. Comparing the incremental costs and benefits of the testing strategies with a common comparator (no testing), the model indicates that there is very little difference between the strategies in terms of cost effectiveness or clinical effectiveness. This is because of the similarity in the diagnostic accuracy of these strategies and in the cost of the tests. These small differences mean that an incremental analysis of the strategies would not give meaningful results. The test strategies all have incremental cost-effectiveness ratios between £4000 to £5300 per QALY gained compared with no testing, which is well within acceptable levels of cost-effectiveness thresholds for approval by NICE.

Because all the testing strategies have similar sensitivity and specificity, the incremental differences in QALYs between them are very small. However, the biopsy-only strategy is the most expensive, costing about £380 more than the next most expensive strategy. Therefore, although a biopsy-only strategy may be preferable to a no-test strategy those strategies that include serological tests before confirmatory biopsy for positive results are still more cost effective than the biopsy-only strategy

Combinations of EMA and tTGA tests had sensitivity and specificity similar to the individual test strategies. The method of costing the test strategies did not significantly affect the results. Therefore carrying out any of the test strategies remains cost effective compared to no testing. Sensitivity analysis was carried out to evaluate the effect of charging separately for these tests at high cost. Even when additive fees are considered, the cost effectiveness is still similar between the strategies because the costs of the tests are relatively low compared with the cost and disutility of undiagnosed coeliac disease.

In sensitivity analysis, results were shown to be affected by the increase in quality of life for treated coeliac disease compared with untreated coeliac

disease. However, even in the extreme case that the utility of treated and untreated coeliac disease are equal, serological testing remains cost effective compared with no testing. This is because there is still a difference between the utility of having coeliac disease (whether treated or untreated) compared with the utility of not having coeliac disease.

The model is also sensitive to the cost of delayed diagnosis. A threshold analysis was carried out on this parameter because of the uncertainty around the additional resources used by people who have coeliac disease but have not yet been diagnosed. When the cost is relatively low, testing for coeliac disease is a cost-effective intervention; as the cost of this parameter increases, testing becomes even more cost effective and specifically, when the cost of undiagnosed coeliac disease becomes as high as £260 per person per year, the testing strategies become cost saving.

One-way sensitivity analysis on the most uncertain parameters in the model showed that the model seems robust to variations in most of the parameter inputs.

Probabilistic sensitivity analysis was also carried out. Distributions were added to the sensitivity and specificity of each of the test strategies, the prevalence of coeliac disease in the population of interest and the cost of delayed diagnosis. At a threshold of £20,000 per QALY gained (the lower end of the threshold considered acceptable by NICE), the probability of the test strategies being cost effective was 100%. At around £6000 per QALY gained, the probability of each of the strategies becoming cost effective approached 100%.

Full details of the model including results, and all sensitivity analyses, are presented in appendix 6.5.

2.5.5 Linking evidence to recommendations

The GDG discussed the evidence and agreed the evidence statements relating to the information needs and use of serological tests in the diagnostic

process for coeliac disease and developed recommendations. This discussion is summarised here:

- The GDG discussed the importance of stressing the need to continue a gluten-containing diet until coeliac disease is diagnosed or excluded using intestinal biopsy. The need to provide clear information relating to what coeliac disease is and the place of serological tests in this process was also identified and recommendations developed. The GDG noted the importance of clear information to everyone, but also highlighted the additional support that may be needed by people who have a coexisting condition, such as type 1 diabetes.
- The GDG debated the lack of evidence about the amount of gluten needed in the gluten-containing diet to maximise the diagnostic potential of the serological tests and intestinal biopsy. The GDG agreed that this amount was not known, so it developed a recommendation that acknowledged the lack of evidence and used the GDG experience and expertise to give a guide to the amount of gluten to be eaten.
- The GDG also considered that people with suspected coeliac disease who had already begun to exclude gluten from their diet may be reluctant or unable to re-commence a gluten-containing diet. The GDG considered that the support and expertise of a gastrointestinal specialist should be recommended in these situations.
- The GDG discussed the pooled results and studies included in the serological tests review and agreed that the gliadin-based tests had both lower sensitivity and lower specificity. It therefore agreed to recommend that gliadin-based tests are not used.
- The GDG considered from the clinical evidence and the economic model that the serological test of choice is IgA tTGA as a first test, and where the results are equivocal then IgA EMA testing should be used. Both the individual tests and combination testing are clinically effective and cost effective compared with no testing. The GDG considered that IgA tTGA should also be recommended as first choice for ease of use and quality assurance factors.

- The GDG recognised that the deamidated gliadin tests and point-of-care tests or self tests may be of use in the future, but noted that they cannot be recommended yet because the evidence for them is limited. The GDG also discussed the need for a recommendation that advises people who may have used self tests to discuss the results with healthcare professionals, and that if coeliac disease is suspected patients should have laboratory-based serological tests.
- The GDG discussed the evidence relating to the use of IgA tTGA in people with liver disease. It agreed that, although the available evidence was limited, the possibility of false positive results in people with liver disease may be a concern.
- The GDG discussed the use of HLA DQ2 and DQ8 testing and noted that because DQ2 or DQ8 is present in around one quarter of the UK population, a positive test for it is of limited value in the diagnosis of coeliac disease. However, it noted the potential use of a negative result in a specialist setting where serology and biopsy have proven inconclusive.
- The GDG noted the need for all serological testing to be undertaken at an accredited laboratory, and developed a recommendation to reflect this.
- The GDG noted the lack of evidence regarding the possibility of repeat serological testing for coeliac disease, specifically in people with coexisting conditions for whom serological testing has been recommended (including type 1 diabetes and autoimmune thyroid disease). It was felt, with the lack of evidence and without expert consensus, that a recommendation on repeat testing could not be made. A research recommendation in this area was developed.

Recommendation 1.1.5

Inform people (and their parents or carers, as appropriate) that any testing for coeliac disease is accurate only if the person continues to follow a gluten-containing diet during the diagnostic process (serological tests and biopsy if required).

Recommendation 1.1.6

Inform people that they should not start a gluten-free diet until diagnosis is confirmed by intestinal biopsy, even if a self-test or other serological test is positive.

Recommendation 1.1.7

Inform people that when they are following a normal diet (containing gluten) they should eat some gluten (for example, bread, chapattis, pasta, biscuits, or cakes) in more than one meal every day for a minimum of 6 weeks before testing; however, it is not possible to say exactly how much gluten they should eat.

Recommendation 1.1.8

If a person is reluctant or unable to reintroduce gluten into their diet before testing:

- refer them to a gastrointestinal specialist and
- inform them that it may be difficult to confirm a diagnosis of coeliac disease on intestinal biopsy, and that this may have implications for the prescribing of gluten-free foods.

Recommendation 1.1.9

Inform people who are considering, or have undertaken, self-testing for coeliac disease (and their parents or carers) that any result from self-testing needs to be discussed with a healthcare professional and confirmed by laboratory-based tests.

Recommendation 1.1.10

Before seeking consent to take blood for serological tests, explain:

- what coeliac disease is
- that serological tests do not diagnose coeliac disease, but indicate whether further testing is needed
- the implications of a positive test (including referral for intestinal biopsy and implications for other family members)
- the implications of a negative test (that coeliac disease is unlikely but it could be present or could arise in the future).

Recommendation 1.1.11

Inform people and their parents or carers that a delayed diagnosis of coeliac disease, or undiagnosed coeliac disease, can result in:

- continuing ill health
- long-term complications, including osteoporosis and increased fracture risk, unfavourable pregnancy outcomes and a modest increased risk of intestinal malignancy
- growth failure, delayed puberty and dental problems (in children).

Recommendation 1.1.12

All tests should be undertaken in laboratories with clinical pathology accreditation (CPA).

Recommendation 1.1.13

Do not use immunoglobulin G (IgG) or immunoglobulin A (IgA) anti-gliadin antibody (AGA) tests in the diagnosis of coeliac disease.

Recommendation 1.1.14

Do not use of self-tests and/or point-of-care tests for coeliac disease as a substitute for laboratory-based testing.

Recommendation 1.1.15

When clinicians request serology, laboratories should:

- use IgA tissue transglutaminase (tTGA) as the first choice test
- use IgA endomysial antibodies (EMA) testing if the result of the tTGA test is equivocal
- check for IgA deficiency if the serology is negative⁴
- use IgG tTGA and/or IgG EMA serological tests for people with confirmed IgA deficiency
- communicate the results clearly in terms of values, interpretation and recommended action.

Recommendation 1.1.16

Do not use human leukocyte antigen (HLA) DQ2/DQ8 testing in the initial diagnosis of coeliac disease. (However, its high negative predictive value may be of use to gastrointestinal specialists in specific clinical situations.)

Recommendation 1.1.17

Offer referral to a gastrointestinal specialist for intestinal biopsy to confirm or exclude coeliac disease to people with positive serological results from any tTGA or EMA test.

Recommendation 1.1.18

If serology tests are negative but coeliac disease is still clinically suspected, offer referral to a gastrointestinal specialist for further assessment.

⁴ Investigation for IgA deficiency should be done when the laboratory detects a low optical density (OD) on IgA tTGA test, very low IgA tTGA results or low background on IgA EMA test.

2.6 *Research recommendations*

- Dietary assessment of gluten content of diet before serological testing: what is the minimum gluten dietary content necessary for the optimal accuracy of serological tests and intestinal biopsy for the diagnosis of coeliac disease?
 - There is no robust evidence on how much gluten people should include in their diet when undergoing testing for coeliac disease. Different definitions are used, based on a single study and expert opinion, and this can lead to confusion among patients and clinicians. Although it is evident that a gluten-containing diet for a sustained period is necessary to ensure that serological test results are as accurate as possible and that intestinal biopsy results are as clear as possible, the amount of gluten and the period of intake needed are unknown. Research is needed on how serological tests and intestinal biopsy accuracies are associated with gluten intake in order to define the minimum level of gluten and period of intake for adults and children with suspected coeliac disease.
- How many people with undiagnosed coeliac disease are misdiagnosed as having other conditions, and what are the clinical and cost implications of this?
 - People with coeliac disease often have significant health problems that resolve with correct diagnosis and treatment. If coeliac disease is undiagnosed, or misdiagnosed as another condition, health problems continue, resulting in the use of inappropriate interventions and resources, such as visits to GPs or outpatient clinics. Misdiagnosis can also limit further investigation (and thus correct diagnosis) and the health problems continue or increase, with a corresponding effect on the person's quality of life. There are no reliable data on the extent to which coeliac disease is misdiagnosed in adults and children; high-quality population-based studies are needed to assess the associated clinical outcomes and costs in adults and children with undiagnosed coeliac disease.

- Should repeat serological testing for coeliac disease be performed, and if so, how often?
 - Currently, serological tests (tTGA and EMA) for coeliac disease are both relatively sensitive and specific, with low rates of false-negative results. It is not clear whether coeliac disease develops over time (that is, an individual can be tested for coeliac disease at one point in time and be true-negative and then tested at a later point in time, and be true-positive). There is a lack of evidence on the need for repeat testing. Studies are needed to determine whether serological tests should be repeated if the initial results are negative and there is no high clinical suspicion of coeliac disease, and if so, when and how often they should be repeated.
- Does adherence to a gluten free diet improve diabetes-related outcomes in people with coeliac disease and type 1 diabetes?
 - There is some evidence that glycaemic control is improved in people with type 1 diabetes who have coeliac disease and follow a gluten-free diet, but this evidence is not conclusive. Good quality, longitudinal cohort studies are needed to determine whether adherence to a gluten-free diet improves diabetes-related outcomes in adults and children with newly-diagnosed type 1 diabetes and coeliac disease. Such outcomes should include blood glucose control, cardiovascular risk factors (including weight), diabetic-related complications, and health-related quality of life.
- Is the prevalence of coeliac disease higher in adults and children with autism than in the general population?
 - There is no conclusive evidence on the prevalence of coeliac disease in people with autism. Anecdotally, higher rates of coeliac disease are seen in people with autism, and when diagnosed, adherence to a gluten-free diet improves both gastrointestinal symptoms and behavioural problems. Research is needed to determine the prevalence of coeliac disease in people with autism and whether any behavioural problems improve following diagnosis.
- What are the long-term effects of undiagnosed coeliac disease?

- Undiagnosed coeliac disease is associated with several long-term complications, including osteoporosis and some malignancies. Long-term follow-up studies are needed to determine the long-term complications associated with undiagnosed coeliac disease in adults and children, and the effect of diagnosis of coeliac disease and adherence to a gluten-free diet on these complications.
- How reliable are serological tests compared with intestinal biopsy in detecting early coeliac disease?
 - Evidence of the presence of coeliac disease can be suggested by the finding of highly specific and sensitive antibodies to tissue transglutaminase and to endomysium. Confirmation of the presence of intestinal damage revealed by the histological examination of small-intestinal biopsies remains the traditional method of making the diagnosis. The sensitivity of this investigation has rarely, if ever, been formally investigated. With increased use of serological tests for coeliac disease it has become evident that some people with positive coeliac autoantibodies have apparently normal small-intestinal histology. Some such people are, nonetheless, symptomatic and have gluten-sensitive malabsorption. Early detection of coeliac disease may be important to prevent long-term complications, Therefore longitudinal studies are needed to determine whether serological markers are superior and can reliably detect early coeliac disease before intestinal damage occurs.

3 References, glossary and abbreviations

3.1 References

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3.2 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.

Heterogeneity

A term used to illustrate the variability or differences among studies. High heterogeneity indicates greater differences.

Negative predictive value

The proportion of people with negative test results who do not have the 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.

Randomised controlled trial (RCT)

A form of clinical trial to assess the effectiveness of medicines or procedures, in which participants are randomly assigned to receive a treatment or a placebo. Considered reliable because it tends not to be biased.

Reference standard

An agreed standard, for example for a test or treatment, against which other interventions can be compared.

Relative risk

Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total number of people in the group. A relative risk (RR) of 1 indicates no difference between the groups being compared.

Sensitivity (of a test)

The proportion of people classified as positive by the reference standard who are correctly identified by the study test.

Specificity (of a test)

The proportion of people classified as negative by the reference standard who are correctly identified by the study test.

True negative

A negative result in a diagnostic test, when the person **does not** possess the attribute for which the test is conducted.

True positive

A positive result in a diagnostic test, when the person **does** possess the attribute for which the test is conducted.

Utility

A measure of the strength of a person's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale of 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

Estimates of utility – ideally based on the use of standardised and validated

generic instruments such as EQ-5D – are critical in the calculation of health-related quality of life weights used in QALYs.

3.3 Abbreviations

AGA	Anti-gliadin antibodies
CI	Confidence interval
EMA	Anti-endomysial antibodies
IgA	Immunoglobulin A
IgG	Immunoglobulin G
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
tTGA	Anti tissue transglutaminase antibodies

4 Methods

4.1 Aim and scope of the guideline

4.1.1 Scope

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover (see appendix 1). The scope of this guideline is available from www.nice.org.uk/CG86

The aim of this guideline is to provide evidence-based recommendations to guide healthcare professionals in the recognition and assessment of coeliac disease in children and adults.

4.2 Development methods

This section sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the previous chapters of this guideline. The methods used to develop the

recommendations are in accordance with those set out by NICE in 'The guidelines manual' (2009; available from www.nice.org.uk).

4.2.1 Developing the guideline scope

The scope for this guideline defined the areas the guideline would and would not cover. It was prepared by the Short Clinical Guidelines Technical Team in consultation with relevant literature and following a workshop with clinical experts and patient groups. The scope was also refined following public consultation.

4.2.2 Forming and running the Short Clinical Guideline Development Group

The short clinical guideline on recognition and assessment of coeliac disease was developed by a Guideline Development Group consisting of 10 members, including healthcare professional and patient/carer members who were recruited through open advertisement, and the Short Clinical Guidelines Technical Team.

4.2.3 Developing key clinical questions

The key clinical questions were refined from the scope and formed the starting point for the subsequent evidence reviews and facilitated the development of recommendations by the Guideline Development Group. The Guideline Development Group and Short Clinical Guidelines Technical Team agreed appropriate review parameters (inclusion and exclusion criteria) for each question or topic area. The full list of key clinical questions is given in appendix 6.2.

4.2.4 Developing recommendations

For each key question, recommendations were derived from the clinical- and cost-effectiveness evidence reviews and the economic model developed for this guideline, which were presented to and discussed, alongside their expert opinion, by the Guideline Development Group.

4.2.5 Literature search

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in 'The guidelines manual' (2009). The purpose of systematically searching the literature is to attempt to comprehensively identify the published evidence to answer the key clinical questions developed by the Guideline Development Group and Short Clinical Guidelines Technical Team.

The search strategies for the key clinical questions were developed by the Information Services Team with advice from the Short Clinical Guidelines Technical Team. Structured clinical questions were developed using the PICO (population, intervention, comparison, outcome) model and were translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches.

To identify economic evaluations the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched. Search filters to identify economic evaluations and quality of life studies were used to interrogate bibliographic databases. There were no date restrictions imposed on the searches.

In addition to the systematic literature searches, the Guideline Development Group was asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between May and October 2008. Full details of the systematic search, including the sources searched and the MEDLINE strategies for each evidence review, are presented in appendix 6.4.

4.2.6 Reviewing the evidence

The aim of the clinical review was to systematically identify and synthesise relevant evidence in order to answer the key clinical questions developed from the guideline scope. The guideline recommendations were evidence based if

possible; if evidence was not available, informal consensus within the Guideline Development Group was used. Future research needs were also specified in research recommendations.

The papers chosen for inclusion were then critically appraised by the Short Clinical Guidelines Technical Team for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differed according to study type, and the level of evidence ascribed to them was based on the checklists included in 'The guidelines manual' (2009).

The data were extracted to standard evidence table templates. The findings were summarised by the Short Clinical Guidelines Technical Team into both a series of evidence statements and an accompanying narrative summary.

4.2.7 Grading the evidence

Intervention studies

Studies that meet the minimum quality criteria were ascribed a level of evidence to help the guideline developers and the eventual users of the guideline understand the type of evidence on which the recommendations have been based.

NICE uses elements of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for questions about interventions in its clinical guidelines. The GRADE working group is developing an approach for summarising the evidence for diagnostic tests and strategies. In the absence of this system a narrative summary of the quality of the evidence is used, based on the quality appraisal criteria from QUADAS (Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews). Numerical summaries and analyses are followed by short evidence statements summarising what the evidence shows (more details can be found in 'The guidelines manual' [2009]).

4.2.8 Evidence to recommendations

Recommendations were drafted after discussion of the clinical- and cost-effectiveness evidence, including consideration of the quality of the available

evidence, and using the experience of Guideline Development Group members. The 'linking evidence to recommendations' sections of the guideline aim to reflect this decision-making process and provide transparency about the development of the recommendations. The Guideline Development Group was able to agree recommendations through informal consensus.

4.2.9 Health economics

An economic evaluation aims to integrate data on the benefits (ideally in terms of quality-adjusted life years [QALYs]), harms and costs of alternative options. An economic appraisal will consider not only whether a particular course of action is clinically effective, but also whether it is cost effective (that is, value for money). If a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to redirect resources to other activities that yield greater health gain.

A systematic review of the economic literature relating to the recognition and assessment of coeliac disease was also conducted.

4.2.10 Consultation

The draft of the full guideline was available on the website for consultation from 15 January to 12 February 2009, and registered stakeholders were informed by NICE that the documents were available. Non-registered stakeholders could view the guideline on the NICE website.

4.2.11 Other national guidance

None relevant.

4.2.12 Piloting, implementation and audit

It is beyond the scope of the work to pilot the contents of this guideline or validate any approach to implementation. Implementation support tools for this guideline will be available from the Implementation Team at NICE. The guideline recommendations have been used to develop clinical audit criteria for use in practice. Audit criteria are essential implementation tools for monitoring the uptake and impact of guidelines and thus need to be clear and straightforward for organisations and professionals to use. NICE develops

audit support for all its guidance programmes as part of its implementation strategy.

4.2.13 Scheduled review of this guideline

Following the 4-week public consultation period the comments made by stakeholders, peer reviewers and the Guideline Review Panel were collated and presented anonymously for consideration by the Guideline Development Group, responses and changes to the guideline were agreed by the Short Clinical Guidelines Technical Team and the Guideline Development Group to create the final version of the guideline.

This guideline will be considered for an update following the current process (chapter 14 of 'The guidelines manual' [2009]).

5 Contributors

5.1 *The Guideline Development Group*

The Guideline Development Group is composed of relevant healthcare professionals, patient representatives and NICE technical staff.

The members of the Guideline Development Group are listed below.

David Wray (Chair of GDG 1)

Professor of Oral Medicine

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Dietitian

5.1.1 The Short Clinical Guidelines Technical Team

The Short Clinical Guidelines Technical Team is responsible for this guideline throughout its development. It is responsible for preparing information for the Guideline Development Group, for drafting the guideline and for responding to consultation comments. The following people, who are employees of NICE, make up the technical team working on this guideline.

Fergus Macbeth (Chair of GDG 2)

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5.1.2 Guideline Review Panel

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Consultant Radiologist, Royal Cornwall Hospital NHS Trust

Dr Graham Archard

General Practitioner, Dorset

Ms Karen Cowley

Practice Development Nurse, York

Dr David Gillen

Medical Director, Wyeth Pharmaceutical

Ms Catherine Arkley

Lay member

5.1.3 List of stakeholders

Addisons Disease Self-Help Group

Association for Clinical Biochemistry

Association of the British Pharmaceuticals Industry (ABPI)

Barnsley Hospital NHS Foundation Trust

Barnsley PCT

Bournemouth and Poole PCT

British Dietetic Association

British Geriatrics Society

British National Formulary (BNF)

British Nuclear Medicine Society

British Society of Gastroenterology

British Society of Gastrointestinal and Abdominal Radiology (BSGAR)

British Society of Paediatric Gastroenterology, Hepatology & Nutrition
(BSPGHAN)

BUPA

Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)

Care Quality Commission (CQC)

Cheshire PCT

Coeliac UK

College of Emergency Medicine

Commission for Social Care Inspection

Connecting for Health

Department for Communities and Local Government

Department of Health

Department of Health, Social Security and Public Safety of Northern Ireland

DHSSPSNI

Diabetes UK

Faculty of Public Health

Glutafin

Guys and St Thomas NHS Trust

Harrogate and District NHS Foundation Trust

Imperial College Healthcare NHS Trust

Infant and Dietetic Foods Association

Institute of Biomedical Science

Leeds PCT

Leeds Teaching Hospitals NHS Trust

Luton & Dunstable Hospital NHS Foundation Trust

Manchester Royal Infirmary

Medicines and Healthcare Products Regulatory Agency (MHRA)

Milton Keynes PCT

National Osteoporosis Society

National Patient Safety Agency (NPSA)

National Public Health Service – Wales

National Treatment Agency for Substance Misuse

NCCHTA

NHS Bedfordshire

NHS Clinical Knowledge Summaries Service (SCHIN)

NHS Direct

NHS Kirklees

NHS Knowsley

NHS Plus

NHS Purchasing & Supply Agency

NHS Quality Improvement Scotland

NHS Sefton

NHS Sheffield

North Yorkshire and York PCT

Nottingham University Hospitals NHS Trust

PERIGON Healthcare Ltd

Primary Care Society for Gastroenterology (PCSG)

Royal College of General Practitioners

Royal College of Nursing

Royal College of Paediatrics and Child Health

Royal College of Pathologists

Royal College of Physicians London

Royal College of Radiologists

Royal Free Hospital NHS Trust

Royal Society of Medicine

SACAR

Scottish Intercollegiate Guidelines Network (SIGN)

Sedgefield PCT

Sheffield PCT

Sheffield Teaching Hospitals NHS Foundation Trust

Shire Plc

Shrewsbury & Telford Hospital NHS Trust

Social Care Institute for Excellence (SCIE)

South Asian Health Foundation

South Devon Acute Trust

Teva UK Limited

United Kingdom Clinical Pharmacy Association (UKCPA)

University Hospital Birmingham NHS Foundation Trust

University of Oxford

Wellfoods Ltd

Welsh Assembly Government

Welsh Scientific Advisory Committee (WSAC)

Western Cheshire Primary Care Trust

Western Health and Social Care Trust

York NHS Foundation Trust

5.2 *Declarations*

5.2.1 Authorship and citation

Authorship of this full guideline document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

The guideline should be cited as:

National Institute for Health and Clinical Excellence (2009) Coeliac disease: recognition and assessment of coeliac disease. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/CG86

5.2.2 Declarations of interest

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).

Please note the appendices are available as separate files.