

# **Coeliac disease: recognition and assessment of coeliac disease**

## **Full guideline**

**Draft for consultation, January 2009**

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

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Appendices are available as separate files.

## Disclaimer

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances

of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

## Foreword

*[To be added after the consultation]*

### ***Patient-centred care***

This guideline offers best practice advice on the care of adults and children with symptoms and/or signs suggestive of coeliac disease.

Treatment and care 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 about their care and treatment, 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](http://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](http://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](http://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. 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 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](http://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 *List of all recommendations*

### Recognition and assessment of coeliac disease

#### *Symptoms and Signs*

1.1.1 Serological testing for coeliac disease is recommended for children or adults with any of the following symptoms and signs:

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

1.1.2 Consider offering serological testing for coeliac disease to children or adults with:

- persistent or unexplained constipation
- epilepsy
- unexplained alopecia
- reduced bone mineral density
- other forms of metabolic bone disease (such as rickets or osteomalacia)
- low trauma fracture
- persistently raised liver enzymes of unknown cause
- liver conditions (for example primary biliary cirrhosis)
- aphthous stomatitis
- amenorrhoea/recurrent abortion

- unexplained infertility
- lymphoma
- autoimmune myocarditis
- Sjögren's syndrome
- depression or bipolar disorder
- chronic thrombocytopenia purpura
- sarcoidosis
- polyneuropathy
- Down's syndrome
- Turner syndrome.

*Coexisting conditions*

1.1.3 Serological testing for coeliac disease is recommended for children or adults if they have:

- type 1 diabetes
- autoimmune thyroid disease
- dermatitis herpetiformis
- irritable bowel syndrome
- first-degree relatives (parents, siblings, children) with coeliac disease.

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

**Dietary considerations prior to testing for coeliac disease**

1.1.5 Inform individuals and parents/carers that any testing for coeliac disease is only accurate if a gluten-containing diet is continued.

1.1.6 Recommend that people do 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 When a normal diet (containing gluten) is being followed, recommend that some gluten (for example, bread, chapattis, pasta, biscuits, or cakes) should be eaten in at least one meal every day

for a minimum of 6 weeks, although it is not possible to say exactly how much gluten should be eaten.

- 1.1.8 Refer to a gastrointestinal specialist people who are reluctant or unable to reintroduce gluten into their diet, and inform them that a diagnosis of coeliac disease may be difficult to confirm on intestinal biopsy. Healthcare professionals should inform patients that this may have implications for their ability to access prescribed gluten-free foods.

### **Information needs prior to serological testing**

- 1.1.9 Inform individuals and parents/carers who are considering or have undertaken self-testing for coeliac disease that any result from self-testing would need to be discussed with a healthcare professional and confirmed by laboratory-based tests.
- 1.1.10 Self-test and point-of-care tests for coeliac disease are not currently recommended within the NHS as a substitute for laboratory-based testing.
- 1.1.11 Before seeking and obtaining consent to take blood for serological tests, explain to individuals and parents/carers:
- what coeliac disease is
  - the role of serological tests (that is, they do not diagnose coeliac disease, but are a marker for further testing)
  - 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 this does not preclude it arising in the future).
- 1.1.12 Inform individuals and parents/carers that a delayed diagnosis of coeliac disease, or undiagnosed coeliac disease, can result in:
- continuing ill health

- a risk of long term complications, including osteoporosis and fracture risk, unfavourable pregnancy outcomes and an increased risk of rare intestinal malignancy
- in children, growth failure, pubertal delay and dental complications.

### **Serological tests for adults and children**

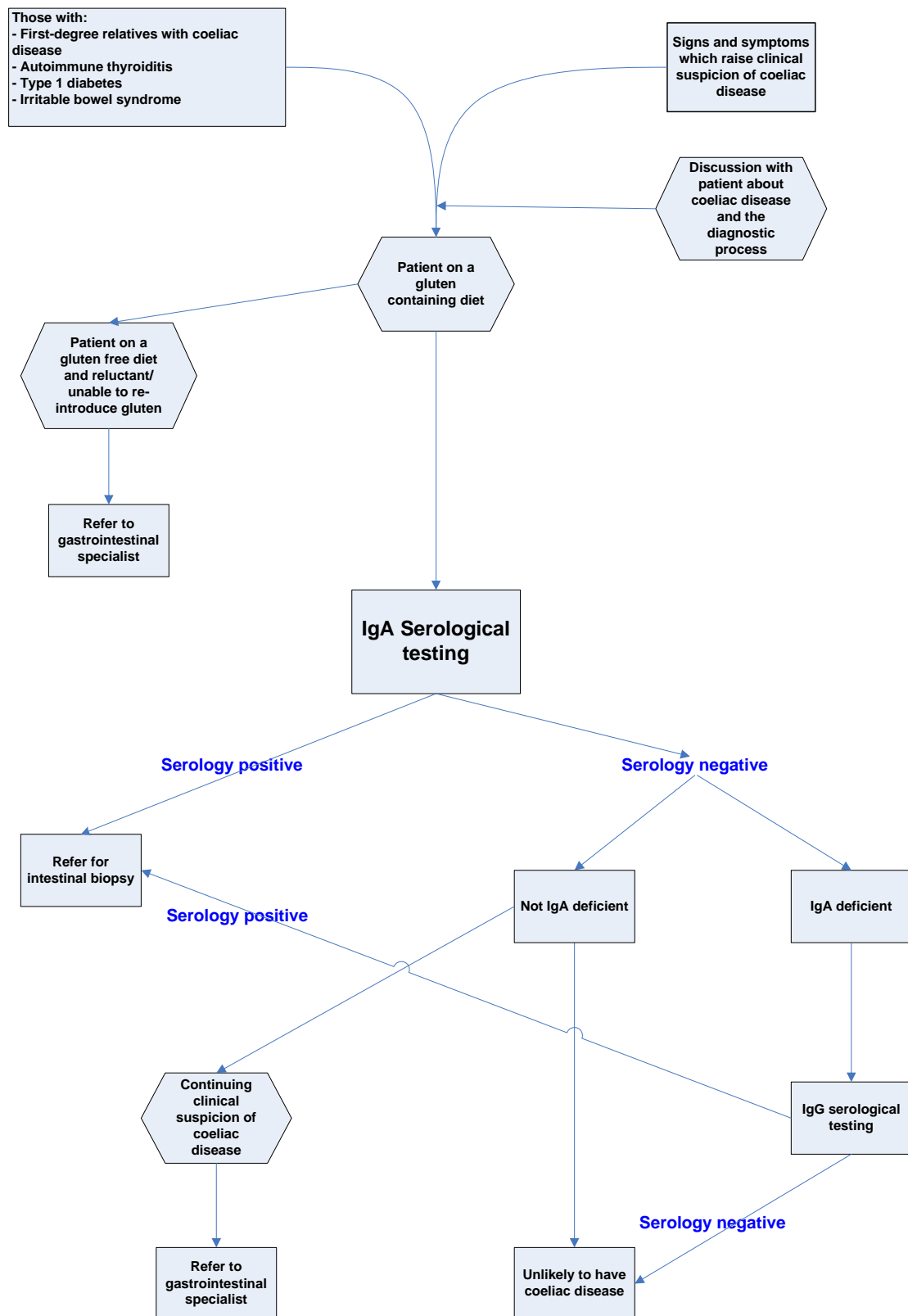
- 1.1.13 IgG and IgA AGA (immunoglobulin A and immunoglobulin anti gliadin antibodies) tests should not be used in the diagnostic process for coeliac disease.
- 1.1.14 Combination testing (IgA tTGA and IgA EMA, IgA anti-tissue transglutaminase antibodies and IgA anti endomysial antibodies) should be used as the first choice test in the diagnostic process for coeliac disease. In the event of negative serology laboratories should check for IgA deficiency (preferably on the same sample).
- 1.1.15 If combination testing is unavailable both IgA tTGA and/or IgA EMA individual serological tests are suitable for use in the diagnostic process for coeliac disease.
- 1.1.16 For those with confirmed IgA deficiency IgG tTGA and IgG EMA should be used in the diagnostic process for coeliac disease.
- 1.1.17 HLA (Human Leukocyte Antigen) DQ2/DQ8 testing should not be used in the initial diagnostic process for coeliac disease, but its high negative predictive value may be of use to gastrointestinal specialists in secondary care in specific clinical situations.
- 1.1.18 All tests should be undertaken in CPA (clinical pathology accreditation) accredited laboratories.

### **Following serological testing in adults and children**

- 1.1.19 Refer those with positive serological results from any tTGA or EMA test to a gastrointestinal specialist for intestinal biopsy to confirm or exclude coeliac disease.

- 1.1.20 Where serology tests are negative and a clinical suspicion that coeliac disease remains refer to a gastrointestinal specialist for further assessment.
- 1.1.21 Repeat testing is not recommended where serological test results are negative and there is no further reason to suspect coeliac disease.

## 1.2 Care pathway



## **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 individuals. Gluten is a dietary protein which is present in wheat, barley and rye. Historically coeliac disease was believed to be relatively uncommon; however, population-based studies have identified a prevalence of coeliac disease which is higher than previously expected. Coeliac disease has traditionally been associated with mainly gastrointestinal symptoms (such as diarrhoea, abdominal pain, bloating, constipation, indigestion) as 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 with many of those with coeliac disease presenting with these features. Others with coeliac disease may have no obvious symptoms. Coeliac disease has also been identified as having a higher prevalence in those with other autoimmune conditions such as type 1 diabetes, or autoimmune thyroid disease. A high prevalence has also been identified in first-degree relatives of those with coeliac disease. Coeliac disease can be diagnosed at any age after the introduction of gluten containing foods to the infant weaning diet, presenting in both children and adults.

With the disparate nature of the signs and symptoms of coeliac disease alongside the historical belief that coeliac disease is relatively uncommon there has been concern that coeliac disease is not recognised and consequently is underdiagnosed. This may lead to a delay in diagnosis and the presentation with a variety of signs and symptoms to both primary and secondary care on many occasions prior to diagnosis. This delay in diagnosis is a concern owing to the ongoing signs and symptoms of coeliac disease which remain untreated and also for the possible long-term effects of undiagnosed coeliac disease. There is also some uncertainty as to which serological tests are most appropriate for use in the diagnostic process for coeliac disease.

Intestinal biopsy is used as the reference standard for the diagnosis of coeliac disease.

This short clinical guideline aims to improve the care of those with currently undiagnosed coeliac disease by making evidence-based recommendations on its recognition and assessment and the use of selected serological tests to direct referral for definitive diagnosis by intestinal biopsy.

This guideline uses the best available clinical and cost effectiveness evidence, which is considered and discussed by the Guideline Development Group for this guideline, to develop recommendations on how to recognise and assess children and adults who may have coeliac disease. This includes consideration of the signs and symptoms and the co-existing conditions of coeliac disease, the role of serological testing in the diagnostic process up to the point of referral for the reference standard of 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 of coeliac disease' (NICE clinical guideline ) is a NICE short clinical guideline. For a full explanation of the process, see 'The guidelines manual' (2009) by NICE (available from [www.nice.org.uk](http://www.nice.org.uk)).

### **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 suggestive of coeliac disease.

This is the full version of the guideline. It is available from [www.nice.org.uk/CGXX](http://www.nice.org.uk/CGXX). 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/CGXX](http://www.nice.org.uk/CGXX) **[Applies to the final version of the guideline after publication]**

### **1.3.4 Using recommendations and supporting evidence**

The Guideline Development Group (GDG) reviewed the evidence. For each clinical question the GDG was presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG was able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying evidence to recommendations sections.

## **2 Evidence review and recommendations**

The clinical and cost effectiveness evidence related to the recognition and assessment of coeliac disease in children and adults that was presented to and discussed by the Guideline Development Group (GDG) in the development of this guideline is summarised in this section. Further details about the clinical evidence can be found in the evidence tables (appendix 6.6) and for the cost effectiveness, including details of the economic model in appendix 6.5.

The aim of this guideline is to improve guidance on the recognition and assessment of coeliac disease in children and adults and considers the diagnostic pathway up to the point of referral for intestinal biopsy. Intestinal biopsy has been considered as the reference standard throughout this guideline and therefore the studies included are those where coeliac disease has been confirmed by intestinal biopsy. The Agency for Healthcare Research and Quality completed an evidence report/technology assessment on coeliac disease which was published in 2004. This report included a series of systematic reviews using clearly defined methods; therefore these reviews have been included throughout where appropriate to the scope of this guideline, this report is level ++ evidence (full details can be found 'The guidelines manual' (2009) by NICE (available from [www.nice.org.uk](http://www.nice.org.uk)). Other studies included in this guideline have been mainly cohort based studies notably for the evidence for the serological test accuracy. Case control studies have also been included where appropriate. Both the cohort and case control studies have limitations due to study design and as such all are regarded as

level + evidence (full details can be found 'The guidelines manual' (2009) by NICE (available from [www.nice.org.uk](http://www.nice.org.uk)). Case series, case reports and studies including small numbers of participants have not been included.

## **2.1 Prevalence of coeliac disease**

### **2.1.1 Evidence review**

The prevalence of coeliac disease has historically been difficult to determine as in many cases it is a condition without specific signs and symptoms. It has been assumed that the difficulties with the recognition of coeliac disease have meant that the prevalence of it has been considerably underestimated.

The search completed on the prevalence of coeliac disease aimed to consider the current available data on the prevalence of coeliac disease with the identification and review of large population-based studies.

#### **Overall prevalence of coeliac disease**

The Agency for Healthcare Research and Quality (AHRQ) 2004 report included studies which considered the prevalence of coeliac disease in North America and Western Europe up to 2003. Relevant large population-based studies in North America/Western Europe from 2003 onwards were included alongside studies in other geographical areas from 1990 onwards. The AHRQ report found a prevalence of coeliac disease in children by biopsy of 0.5% to 1.6% (6 studies) and by serology of 0.3% to 1.9% (8 studies) and in adults by biopsy of 0.07% to 1.9% (15 studies) and by serology of 0.2% to 2.7% (22 studies). The three UK based studies in the AHRQ report were all in adults and identified a prevalence of coeliac disease by biopsy of 1.0% and by serology of 0.8% to 1.2%.

The Avon Longitudinal Study of Parents and Children a population-based cohort considered children aged 7.5 years using IgA EMA positive serology and found 1% (n = 54/5470) positive for coeliac disease. This study also identified that IgA EMA positive rates were more common 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 papers, in adults, used data from large available samples such as those donating blood (Bdioui et al 2006, Melo et al 2006, Oliveria et al 2007, Pereira et al 2006, Shahbazkha et al 2003) and those attending for pre-nuptial medical checks (Gomez et al 2001), alongside one study which used random sampling from a national register (Roka et al 2007). These studies identified the prevalence of coeliac disease in adults of 0.14% to 0.86%.

Additional international papers, in children, considered newborns from normal deliveries (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 the 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 where coeliac disease was suspected. These studies were mainly situated within referral centres and the prevalence of coeliac disease varied widely; children (1.1% to 4.0% with EMA serology; 4.6% to 17.0% with biopsy), adults (1.5% with EMA serology; 11.6% to 50.0% with biopsy).

### **Prevalence in first-degree relatives**

The AHRQ report (2004) included studies which considered the prevalence of coeliac disease in the first-degree relatives of those who were known to have 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 included those who had biopsies and had a prevalence in first-degree relatives of 5.6% to 22.5%.

An additional three studies were identified (Fraser et al 2006, Biagi et al 2008, Szaflaraka-Sczepanik et al 2001) with a prevalence of coeliac disease in first-degree relatives of 2% to 17.7%. One of these studies was in the UK and had a prevalence of 5.5% (Fraser et al 2006).

## **2.1.2 Evidence statements**

*Within UK based national studies prevalence rates of coeliac disease range between 0.8% and 1.9%. This is broadly similar to other international studies.*

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

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

## **2.2 The possible long-term consequences of undiagnosed coeliac disease**

### **2.2.1 Evidence review**

This review considered only any possible long-term consequences of undiagnosed coeliac disease and did not include any studies which considered those with diagnosed coeliac disease; as such the included studies considered those with undiagnosed coeliac disease or those where conditions were present at the point of diagnosis. It should be noted that this is not considered to provide evidence of a causal relationship. For all of the included studies coeliac disease had been confirmed by biopsy, with the exception of one study which had pregnant women as participants and where intestinal biopsy was not considered ethical in those near to delivery (Greco et al 2004). Evidence was available in three areas: pregnancy outcomes, fracture risk and malignancy.

#### **Pregnancy outcomes**

An Italian study where 5055 participants who had been admitted to obstetric and gynaecological wards were included (Greco et al 2004). It identified no pregnancy outcomes where there was a significant difference in those with coeliac disease and those without coeliac disease (outcomes included: risk of spontaneous abortion, premature delivery, small birth weight, intrauterine growth retardation [IUGR]).

A Swedish study used analysis of those with a hospital based discharge of coeliac disease from a Swedish national inpatient register and considered 929 women with undiagnosed coeliac disease at the time of birth and 2,822,805 without coeliac disease (Ludvigsson et al 2005). Significant differences were identified between those with undiagnosed coeliac disease at the time of infant birth compared without coeliac disease in IUGR 5.5% vs. 3.1% (adjusted<sup>1</sup> OR 1.62, 95% CI, 1.22 to 2.15,  $p = 0.001$ ), low birth weight; 7.0% vs. 3.4% (adjusted OR 2.13, 95% CI, 1.66 to 2.75,  $p < 0.001$ ), very low birth weight; 1.2% vs. 0.5% (adjusted OR 2.45, 95% CI, 1.35 to 4.43,  $p = 0.003$ ), preterm birth; 8.0% vs. 5.0% (adjusted OR 1.71, 95% CI, 1.35 to 2.17,  $p < 0.001$ ) and for caesarean section rate; 3.4% vs. 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 (< 30 weeks) and for low Apgar score (< 7).

### **Fracture risk**

A second Swedish study using the national inpatient register considered hip fractures (14187 with coeliac disease and 68852 without coeliac disease) and any fractures (13724 with coeliac disease and 65627 without coeliac disease) (Ludvigsson et al 2007). The estimated association of coeliac disease and prior fractures showed an increased risk of 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 those with undiagnosed coeliac disease compared to those with coeliac disease, this increased risk was found throughout the time period from 10 years to 0.01 years up to diagnosis.

A Danish study used the national patient discharge register to consider the fracture risk in those 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 for osteoporosis.

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<sup>1</sup> Adjusted for maternal age, parity, nationality, calendar period and infant sex.

## **Malignancy**

An American study considered the standardised mortality ratio (SMR) of the observed to expected rates for cancers which were diagnosed before or simultaneously with the diagnosis of coeliac disease (Green et al 2003). Though numbers were small this study identified SMRs which were significant for non-Hodgkin's lymphoma, SMR 5.3, 95%CI 2.3 to 13,  $p < 0.001$  ( $n = 4$  observed cases vs.  $n = 0.7$  expected), small bowel cancer SMR 45, 95% CI 34 to 61,  $p < 0.001$  ( $n = 3$  vs.  $n = 0.1$ ), oesophageal cancer SMR 16, 95% CI 9.7 to 26,  $p < 0.001$  ( $n = 3$  vs.  $n = 0.2$ ) and melanoma, SMR 5, 95% CI 2.1 to 12,  $p < 0.001$  ( $n = 4$  vs.  $n = 0.8$ ), with no significant difference identified in SMR with colon cancer, breast cancer and total cancers<sup>2</sup>.

An Italian study also 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  $n = 1968$  adults who were diagnosed with coeliac disease (Silano et al 2007). This study identified that  $n = 55/1968$  who were diagnosed with cancer before or simultaneously with coeliac disease diagnosis vs. 42.1 expected cases, SIR 1.3 (95%CI 1.0 to 1.7,  $p = 0.001$ ). For individual cancers (though again numbers involved were small) non-Hodgkin's lymphoma SIR 4.7, 95% CI, 2.9 to 7.3,  $p < 0.001$  (observed  $n = 20$  vs. expected  $n = 4.2$ ), colon cancer SIR 1.1, 95%CI, 0.68 to 1.56,  $p < 0.001$  ( $n = 7$  vs.  $n = 6.2$ ), small bowel cancer SIR 25, 95%CI, 8.5 to 51.4,  $p < 0.001$  ( $n = 5$  vs.  $n = 0.19$ ) and Hodgkin's lymphoma SIR 10, 95% CI, 2.7 to 25,  $p = 0.01$  ( $n = 4$  vs.  $n = 0.4$ ). A lower risk was identified for breast cancer in those with newly diagnosed coeliac disease SIR 0.2, 95% CI, 0.04 to 0.62,  $p < 0.001$ , ( $n = 3$  vs.  $n = 14$ ).

### **2.2.2 Evidence statements**

*There is evidence that undiagnosed maternal coeliac disease impacts negatively on intrauterine growth and birth weight and is associated with increased preterm birth and caesarean section rates.*

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<sup>2</sup> Included chronic lymphocytic leukaemia, ovarian cancer, cervical cancer, liver cancer, prostate cancer, bladder cancer, endometrial cancer, thyroid cancer and Hodgkin's disease.

*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.*

### **2.2.3 Linking evidence to recommendations**

The Guideline Development Group (GDG) discussed the evidence and 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 discussed the evidence and agreed the need to include information about the risk of long-term complications of undiagnosed coeliac disease. Within this the GDG noted that although there is an increased risk of the specified cancers with undiagnosed coeliac disease the overall risk of developing these cancers is low.
- The GDG further discussed that these possible long-term effects are different in children and adults and agreed an additional recommendation for children specifying growth failure, delayed puberty and dental complications.

## **2.3 *Signs and symptoms of coeliac disease and co-existing conditions with coeliac disease***

### **2.3.1 Evidence review – signs and symptoms**

There is a lack of any specific defining features for coeliac disease and the variety of methods of presentation which bring those with coeliac disease to the point of serological testing or biopsy and thus the recognition and assessment of coeliac disease can be challenging.

The AHRQ report considered the prevalence of coeliac disease in adults in those with iron-deficiency anaemia and low bone mineral density. Eight of the studies from the AHRQ report in adult patients with biopsy proven coeliac

disease and with 50 or more participants were included. The percentage of coeliac disease in those with iron-deficiency anaemia ranged from 2.3% to 15%. There were four studies included from the AHRQ report and these identified the prevalence of coeliac disease in those with low bone mineral density from 0% to 3%.

Further papers included in this review considered those with coeliac disease at the point of diagnosis and the features that they presented with (reported here for those where 5% or more of participants had the presenting feature).

**Table 1 Presenting features of coeliac disease**

<b>Feature</b>	<b>% with the feature</b>	<b>Adults/Children</b>	<b>Studies</b>
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	Garmpaz 2007
	3.0 to 12.7%	adults	Rampertab 2006
	23.3%	older adults	Vippula 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
	28.4 to 35.8%	children	Bottaro 1993
Abdominal distension/bloating	10%	adults and children	Emami 2008
	20 to 39%	children	Garmpaz 2007
Abdominal pain	12%	adults and children	Dickey 1997
	8.2%	adults and children	Emami 2008
	11 to 21%	children	Garmpaz 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	Garmpaz 2007
	42.9%	adults	Hopper 2008

<b>Feature</b>	<b>% with the feature</b>	<b>Adults/Children</b>	<b>Studies</b>
	37.2 to 91.3%	adults	Rampertab 2006
	25%	older adults	Vippula 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
Osteoporosis	6%	Adults	Brandimarte 2002
Recurrent aphthous stomatitis	6%	Adults	Brandimarte 2002
Amenorrhoea/recurrent abortion	6%	Adults	Brandimarte 2002
Hypertransaminasaemia	6%	adults	Brandimarte 2002
Abnormal liver biochemistry	5%	adults and children	Dickey 1997
Chronic fatigue	7%	adults and children	Dickey 1997
	8.3%	older adults	Vilppula 2008
Failure to thrive	48 to 89%	children	Garampaz 2007
Constipation	4 to 12%	children	Garampaz 2007
Irregular bowel habits	4 to 12%	children	Garampaz 2007
Dyspepsia	17.3%	Adults	Hopper 2008
Reflux	13.8%	Adults	Hopper 2008
Dysphagia	7.2%	Adults	Hopper 2008

There were an additional three studies which had considered a specific symptom and investigated the rate of coeliac disease in those presenting with it.

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

There were also some conditions identified in the studies in table 1 which were present 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)
- rheumatologic 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).

### **2.3.2 Evidence review – co-existing conditions**

The studies included for this review considered co-existing conditions associated with coeliac disease up to and including the point of diagnosis. Therefore studies which considered subsequent development of conditions in those who had been previously diagnosed with coeliac disease were excluded. The relationship between the co-existing conditions and coeliac disease here is not considered causal but aims to examine whether those with certain conditions have a higher rate of coeliac disease than would be expected in the general population. There was a possibility that results could be biased where those with positive serology have not all had a biopsy, therefore any papers where there was a substantial discrepancy between those who had serological tests and those who had biopsies were excluded.

#### **Type 1 diabetes**

The AHRQ report included papers on the prevalence of coeliac disease in those with type 1 diabetes; 21 of these studies (those with biopsy proven coeliac disease and > 50 participants) were included here. These studies identified a prevalence of coeliac disease in those with type 1 diabetes which ranged from 1.4% to 8.2% in children, 0.3% to 11.3% in adults and 1.7% to 5.7% in children/adult studies. Two additional papers also considered those with type 1 diabetes; one in children found 6.6% of those with type 1 diabetes

had coeliac disease (Salardi et al 2008) and one in adults found 6.4% of those with type 1 diabetes had coeliac disease (Picarelli et al 2005).

### Other conditions

Papers were included which included cohorts of those with the chosen condition who were tested for coeliac disease.

**Table 2 Co-existing conditions with coeliac disease**

Condition	Study
Down's syndrome	<ul style="list-style-type: none"> <li>• n = 55 (n = 48/1110 children, n = 7/92 adults). 4.6% with coeliac disease (Bonamico 2001)</li> <li>• n = 4/1453 (0.3%) children and adults with coeliac disease (expected 0.9), adjusted risk ratio 4.7 (95% CI, 1.3 to 12.2)(Goldacre 2004)</li> </ul>
Turner's syndrome	<ul style="list-style-type: none"> <li>• n = 25/389 children and adults, 6.4% with coeliac disease (Bonamico 2002)</li> </ul>
Epilepsy	<ul style="list-style-type: none"> <li>• n = 177 adults, frequency of coeliac disease 1:44 (Cronin 1998)</li> <li>• n = 2/255 children and adults with coeliac disease, 1:127 (Pratesi 2003)</li> </ul>
Liver disease	<ul style="list-style-type: none"> <li>• n = 57 adults with primary biliary cirrhosis, 7% (1:14) with coeliac disease (Dickey 1997)</li> <li>• n = 738 children and adults with chronic liver disease, 0.45% (1:185) with coeliac disease (Germenis 2005)</li> <li>• n = 624 adults with chronic hepatitis C, 0% had coeliac disease (Thevenot 2007)</li> </ul>
Lymphoid malignancy	<ul style="list-style-type: none"> <li>• n = 298 adults, 0.67% with coeliac disease (Farre 2004)</li> </ul>
Arthritis	<ul style="list-style-type: none"> <li>• n = 160 adults with rheumatoid arthritis, 0.63% with previously diagnosed coeliac disease (Francis 2002)</li> <li>• n = 62 children with juvenile chronic arthritis, 1.5% with coeliac disease (George 1996)</li> <li>• n = 119 children with juvenile chronic arthritis, 2.5% with coeliac disease (Lepore 1996)</li> </ul>
Myocarditis	<ul style="list-style-type: none"> <li>• n = 187 adults, 4.4% with coeliac disease (p &lt; 0.003 compared with control group) (Frustaci 2002)</li> </ul>
Autoimmune thyroid	<ul style="list-style-type: none"> <li>• n = 136 adults with autoimmune thyroiditis, 2.9% with coeliac disease (Guliter 2007)</li> <li>• n = 152 adults with autoimmune thyroid disease, 3.29% with coeliac disease (Sategna-Guidetti 1998)</li> </ul>
Sjögren syndrome	<ul style="list-style-type: none"> <li>• n = 111 adults, 4.54% with coeliac disease (Szodoray 2004)</li> </ul>
Irritable bowel syndrome	<ul style="list-style-type: none"> <li>• n = 300 adults, compared with matched controls there was a significant association between coeliac disease and irritable bowel syndrome, OR 7.0 (95%CI, 1.7 to 28.0) (Sanders 2001)</li> </ul>
Inflammatory bowel disease	<ul style="list-style-type: none"> <li>• n = 354 adults (n = 173 Crohn's disease, n = 154 ulcerative colitis) 0.85% with coeliac disease (not significant vs. control) (Leeds 2007)</li> </ul>

- Infertility
- n = 150 women with infertility, 2.7% with coeliac disease (p = 0.06 compared with control group), all those with coeliac disease had unexplained fertility (Collin 1996)
  - n = 99 women with infertility, 3.03% with coeliac disease (those with unexplained infertility with coeliac disease vs. control group, p = 0.037)(Meloni 1999)

Studies were also included which considered co-existing conditions with coeliac disease at the point of diagnosis or considered coeliac disease which developed following a prior history of a co-existing condition (again the relationship is not considered causal).

**Table 3 Co-existing conditions and coeliac disease**

<b>Study group of those with newly diagnosed coeliac disease</b>	<b>Coeliac disease</b>
n = 335 adults with coeliac disease (n = 335 control group) (Collin 1994)	<p>Endocrine disorders: 12% (with coeliac disease) vs. 4.2%, p = 0.0003</p> <ul style="list-style-type: none"> <li>• insulin dependent diabetes; n = 18 (5.4%) vs. n = 5 (1.5%) control, p = 0.0094</li> <li>• autoimmune thyroid; n = 18 (5.4%) vs. n = 9 (2.7%)</li> <li>• Connective tissue disorder: 7.2% vs. 2.7%, p = 0.011</li> <li>• Sjögren syndrome; n = 11 (3.3%) vs. n = 1 (0.3%) control, p = 0.0059</li> <li>• rheumatoid arthritis; n = 6 (1.8%) vs. n = 7 (2.1%)</li> </ul> <p>Pulmonary disorders: asthma; n = 9 vs. n = 12; sarcoidosis; n = 5 vs. n = 0</p> <p>Neurological disorders: epileptic seizures; n = 5 vs. n = 3; dementia; n = 5 vs. n = 1</p> <p>Liver diseases; n = 4 vs. n = 0</p>
n = 14,349 adults and children (n = 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
n = 14,371 adults and children (n = 70,096 control) (Ludvigsson 2007b)	<p>Increased risk of coeliac disease in those with prior polyneuropathy; OR 5.4 (95% CI; 3.6 to 8.2), p &lt; 0.001</p> <p>Other neurological diseases were not associated with subsequent coeliac disease</p>
n = 13,776 adults and children (n = 66,815 control) (Ludvigsson 2007c)	<p>Increased risk of coeliac disease in those with prior history of mood disorder;</p> <ul style="list-style-type: none"> <li>• prior depression; OR 2.3 (95%CI; 2.0 to 2.8), p &lt; 0.001</li> <li>• prior bipolar disorder; OR 1.7 (95%CI; 1.2 to 2.3), p = 0.001</li> </ul>
n = 13,818 adults and children (n = 66,584 control) (Ludvigsson 2007d)	<p>Increased risk of coeliac disease in those with prior history of liver disorder;</p> <ul style="list-style-type: none"> <li>• acute hepatitis; OR 4.98 (95%CI; 1.59 to 12.06), p = 0.004</li> <li>• chronic hepatitis; OR 5.79 (95%CI; 3.13 to 10.70), p &lt; 0.001</li> <li>• primary sclerosing cholangitis; OR 4.42 (95%CI; 2.38 to 8.24), p &lt; 0.001</li> <li>• fatty liver; OR 5.83 (95%CI; 1.96 to 17.36), p &lt; 0.002</li> </ul>

- 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
- n = 14,335 children and adults (n = 69,888 control) (Ludvigsson 2007e) Increased risk of coeliac disease in those with prior tuberculosis; OR 2.5 (95% CI; 1.75 to 3.55),  $p < 0.001$
- n = 15,533 children and adults (n = 14,491 inpatient reference controls) (Ludvigsson 2008) Increased risk of coeliac disease in those with prior sepsis; OR 2.2 (95% CI; 1.7 to 3.0),  $p < 0.001$
- n = 14,347 adults and children (n = 69,967 control) (Olen 2008) Increased risk of coeliac disease in those with prior history of thrombocytopenia purpura; OR 2.96 (95% CI; 1.60 to 5.50),  $p = 0.001$ , and with prior chronic thrombocytopenia purpura; OR 6.00 (95% CI; 1.83 to 19.66),  $p = 0.003$

### 2.3.3 Evidence statements

*In children and adults, coeliac disease can present with a broad range of signs and symptoms, the most common are:*

- *iron-deficiency anaemia*
- *fatigue*
- *chronic or intermittent diarrhoea*
- *abdominal pain/cramping/distension*
- *weight loss*
- *failure to thrive/faltering growth in children*
- *nausea/vomiting.*

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

- *constipation*
- *epilepsy*
- *type 1 diabetes*
- *dermatitis herpetiformis*
- *alopecia*
- *osteoporosis*

- *abnormal liver biochemistry*
- *aphthous stomatitis*
- *amenorrhoea/recurrent abortion*
- *microscopic colitis.*

*There is good evidence that coeliac disease has an increased prevalence in the following common conditions:*

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

*There is some evidence that coeliac disease has an increased prevalence in the following conditions:*

- *epilepsy*
- *liver conditions*
- *lymphoid malignancy*
- *autoimmune myocarditis*
- *Sjögren's syndrome*
- *depression/bipolar disorder*
- *chronic thrombocytopenic purpura*
- *sarcoidosis*
- *polyneuropathy*
- *Down's syndrome*
- *Turner syndrome*
- *unexplained infertility.*

#### **2.3.4 Linking evidence to recommendations**

The Guideline Development Group (GDG) discussed the evidence and agreed the evidence statements relating to the signs and symptoms of coeliac disease and the co-existing conditions with coeliac disease and developed recommendations. This discussion is summarised here.

- The GDG discussed the evidence and agreed that those with key signs and symptoms should be tested for coeliac disease. The GDG further discussed the historic division of symptoms into gastrointestinal and non-gastrointestinal and concluded that it would be more beneficial to identify the key signs and symptoms where testing would be recommended.
- The GDG discussed weight loss as a feature of coeliac disease and noted that while weight loss is a symptom the traditional view of a patient with coeliac disease being underweight is no longer true and that many patients present at a normal weight or overweight.
- The GDG further discussed the non-specific nature of many of the signs and symptoms of coeliac disease and consequently added unexplained and chronic to some of the key signs and symptoms to ensure that those who may have coeliac disease are appropriately identified.
- The GDG agreed a list of further signs and symptoms where they wanted to raise awareness that coeliac disease is also linked with these signs and symptoms though less clearly than with the key signs and symptoms.
- The GDG discussed the co-existing conditions in which coeliac disease has a prevalence of around 5% to 10% and therefore the GDG developed a recommendation on testing for coeliac disease in those with these conditions. The GDG also agreed from previous prevalence evidence that first-degree relatives of those with coeliac disease should also be included in this recommendation.
- The GDG discussed the evidence and the additional expert opinion of the GDG and identified a further list of co-existing conditions where there is some evidence that coeliac disease is more prevalent than in the general population. The GDG also developed a recommendation to raise the awareness of the possibility of coeliac disease in those with these conditions with the need to consider testing for coeliac disease in those with the specified conditions.

## **2.4      *The use of serological tests in the diagnostic process for coeliac disease***

### **2.4.1      The information needs of patients prior to undergoing testing for coeliac disease**

#### **Evidence review – information needs**

The search strategy was designed to identify any studies which related specifically to the information needs of patients and parents/carers prior to the diagnosis of coeliac disease. No studies were identified.

### **2.4.2      The use of serological tests in the diagnostic process for coeliac disease**

#### **Evidence review – serological tests**

This review incorporated those studies which included a blood sample that was drawn from children or adults who were suspected of having coeliac disease. This suspicion may be based on clinical symptoms, an existing condition (e.g. type 1 diabetes), or having a first-degree relative with coeliac disease. The included studies were mainly cohort studies as these provided the best quality available evidence. The data was synthesised and has been graphically pooled and presented in the form of forest plots and ROC (receiver operating characteristic) curves. Summary statistics have not been included as the studies were not considered homogenous and the methodology for the meta-analysis of diagnostic studies is debated. Within the studies there were different kits and different cut-off values used for the analysis<sup>3</sup>. Furthermore different or incompletely reported biopsy strategies, possible inter-lab or operator variability, the use of different samples and studies being undertaken in several different countries were also areas of heterogeneity between studies.

The serological tests considered for this review were:

- immunoglobulin A anti gliadin antibodies (IgA AGA)
- immunoglobulin G anti gliadin antibodies (IgG AGA)

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<sup>3</sup> Where studies used different cut-off levels, the data used was that of the manufacturer's recommended cut-off levels.

- immunoglobulin A anti endomysial antibodies (IgA EMA)
- immunoglobulin G anti endomysial antibodies (IgG EMA)
- immunoglobulin A anti-tissue transglutaminase antibodies (IgA tTGA)
- immunoglobulin G anti-tissue transglutaminase antibodies (IgG tTGA).

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

**Table 4 Summary of serological test studies**

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

### **IgA deficiency**

Individuals who have IgA deficiency will have a false negative result when IgA based serological tests are used in the diagnostic process for 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 the use of IgG based serological tests in the diagnostic process for coeliac disease.

### Included studies

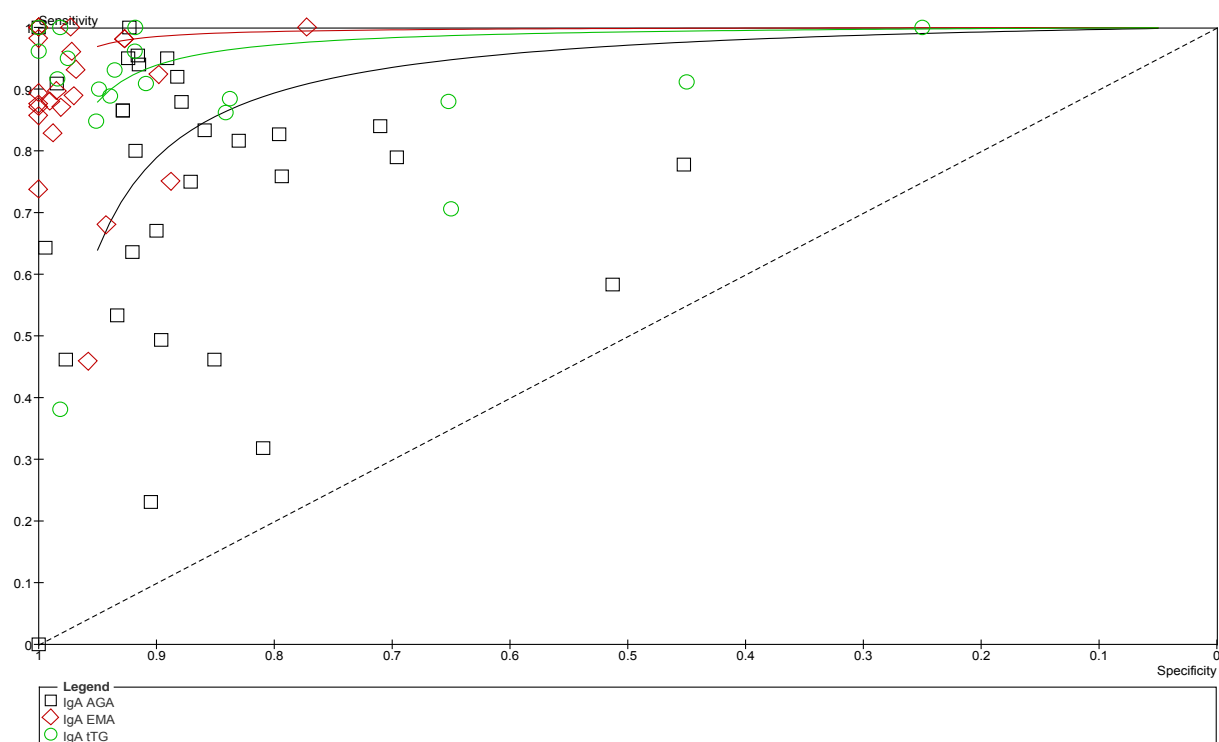
All studies considered those with a suspicion of coeliac disease who had one of the included serological tests and had coeliac disease confirmed by biopsy. There were 29 studies included from the AHRQ (2004) report, 18 in children (Altuntas et al 1998, Artan et al 1998, Ascher et al 1996, Bahia et al 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, Valdimarss et al 1996, Vogelsang et al 1995) and four in children/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, Lui et al 2003, Lui et al 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/adults (Carroccio et al 2006, Dickey et al 1997, Emami et al 2008, Rostami et al 1999). The largest additional paper 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**

<b>Serological test</b>	<b>Studies</b>	<b>Sensitivity</b>	<b>Specificity</b>
IgA AGA	31 studies (n = 5600 participants) 18 children studies 10 adult studies 3 children/adult studies	Range: 23% to 100% (adults: 46-100%) (children: 23-100%)	Range: 45% to 100% (adults: 45-100%) (children: 51-99%)
IgG AGA	25 studies (n = 4830 participants)	Range: 22% to 100%	Range: 38% to 99% (adults: 41-97%)

<b>Serological test</b>	<b>Studies</b>	<b>Sensitivity</b>	<b>Specificity</b>
	15 children studies 8 adult studies 2 children/adult studies	(adults: 22-100%) (children: 71-100%)	(children: 38-99%)
IgA EMA	23 studies (n = 5529 participants) 10 children studies 9 adult studies 4 children/adult studies	Range: 68% to 100% (adults: 68-100%) (children: 46-100%)	Range: 89% to 100% (adults: 94-100%) (children: 77-100%)
IgG EMA	1 adult study (n = 89 participants)	Sensitivity: 39%	Specificity: 98%
IgA tTGA	19 studies (n = 4799 participants) 6 children studies 9 adult studies 4 children/adult studies	Range: 38% to 100% (adults: 71-100%) (children: 89-100%)	Range: 25% to 100% (adults: 65-100%) (children: 25-100%)
IgG tTGA	2 studies (n = 365 participants) 1 adult study 1 children/adult study	Sensitivity: 23% to 85%	Specificity: 89% to 98%

The overall efficacy of the IgA AGA, IgA EMA and IgA tTGA serological tests were summarised in the forest plots and ROC curves (forest plots and other ROC curves analysis from this data available in the appendices). The ROC curves below show the results for the IgA AGA, tTGA and EMA tests overall results. These 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 results the IgA serological tests results appeared to show higher sensitivity and specificity than the IgG tests. For IgG tTGA and IgG EMA there was insufficient data available to draw reasonable conclusions.



**Figure 1: IgA overall results anti gliadin antibodies /anti endomysial antibodies/anti-tissue transglutaminase antibodies**

### Combined/sequence tests

There was a small number of papers available which considered the sensitivity/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/negative predictive value (NPV) where both tests were used either in a 2-step process or where both tests were completed simultaneously, compared with where tests were completed individually.

A second UK based paper (Johnston et al 2003), also in adults, considered the results when 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 following biopsy with IgA EMA the most accurate first step marker followed by IgA tTGA.

There were three studies in the AHRQ report which considered the use of IgA/IgG AGA together or each individually and did not find the combination results to be notably different compared with the individual tests.

### **HLA tests**

Coeliac disease has a genetic association with certain types of type II human leukocyte antigens (HLA) with HLA DQ2 found in 95% of those with coeliac disease and with most of the remaining having HLA DQ8. There were no studies identified from the searches which considered the sensitivity/specificity of the HLA DQ2 and DQ8 tests in coeliac disease. The AHRQ report identified papers which considered the prevalence of HLA DQ2/DQ8 in a coeliac disease population but these studies were not designed to determine the diagnostic utility of DQ2 or DQ8. The three studies in the AHRQ report which were completed in those with known biopsy proven coeliac disease and had sensitivity results of 87% to 90% and specificity of 70% to 81%.

### **Age**

ROC curve analysis categorising studies into those with children, those with adults and those with mixed (children/adults) 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), in children, also considered IgA AGA, IgA EMA and IgA tTG result in those who were  $\leq 2$  years and those over 2 years old, this identified that results were similar in both age categories for IgA tTG and for IgA EMA.

### **Subgroups**

The search for this question was designed to identify any studies where there was any evidence that the serological tests for coeliac disease performed in any way differently than in the general population, the only areas in which studies were identified were liver disease and IgA deficiency.

- Liver disease: one study with n = 105 participants who had primary biliary cirrhosis, and found a specificity range for IgA tTG of 82.5% to 97.1% and for IgG tTG of 95.1% to 100% (Bizzaro et al, 2006). The authors noted that with almost all of the antibody concentrations IgA tTG was close to the cut-off level and that positive results were inconsistent between the test kits and identified a concern about the false positive rate with IgA tTG testing in those with primary biliary cirrhosis, though only n = 6 participants were biopsied.
- IgA deficiency: there was one paper identified which considered the use of IgG AGA and IgG tTG in n = 126 children with IgA deficiency (Lenhardt et al, 2004). N = 11 were diagnosed with coeliac disease of these all were IgG tTG positive while n = 5 were also IgG AGA positive, suggesting IgG tTG to be more accurate in children with IgA deficiency than IgG AGA.

### Newer tests

#### *Deamidated gliadin*

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

**Table 6 Sensitivity/specificity results for deamidated gliadin <sup>4</sup>**

<b>Antibody</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV</b>
IgAG DGP/tTG	100%	94.7%	97.5%	100%
IgAG 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 tTG	96.6%	100%	100%	93.4%
IgG tTG	12.6%	100%	100%	35.4%

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

<sup>4</sup> Using the cut-off value, which was considered positive, not including those considered weakly positive.

**Table 7 Sensitivity/specificity results for deamidated gliadin**

<b>Antibody</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV</b>
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 tTG	95.0%	97.5%	96.6%	96.3%
IgA DGP+tTG	100%	97.5%	96.7%	100%
IgG DPG+IgA tTG	100%	97.5%	96.7%	100%
IgA+IgG DGP+tTG	100%	96.3%	95.2%	100%

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

#### *Immunochromatographic sticks*

One paper was included which considered the use of immunochromatographic sticks for tissue transglutaminase and antigliadin antibody screening in n = 286 children and n = 49 adults (Ferre-Lopez et al, 2004), n = 142 (51%) of children and n = 30 (61%) of adults were diagnosed with coeliac disease. Results identified sensitivity and specificity results for the use of immunochromatographic sticks which were broadly similar to those found using the ELISA methodology:

- 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 tTG+AGA (stick, 1 test): children (sensitivity 99%, specificity 95%), adults (sensitivity 86%, specificity 100%).

### **2.4.3 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 those found for tTGA and EMA.*

*Serological tests have comparable accuracy in children and in adults.*

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

*Limited evidence suggests that point of care/self tests may be accurate but these require further evaluation.*

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

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

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

#### **2.4.4 Health economics**

##### **Published health economics literature**

A literature review was conducted to identify evidence on the cost-effectiveness of serological tests for coeliac disease (see section 2.4.2 for details).

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). Atkinson et al (1997) and Harewood and Murray (2001) were cost minimisation studies examining serological test strategies compared with biopsy for the diagnosis of coeliac disease. Dorn et al (2007), Hopper et al (2008) and Yagil et al (2005) examined both the costs and the diagnostic accuracy of serological tests for diagnosing coeliac disease using cost effectiveness analysis. In addition, Dorn et al (2007) also examined

the cost effectiveness of HLA testing. Mein and Ladabaum et al (2004) and Spiegel et al (2004) examined the cost effectiveness of testing for coeliac disease in people with irritable bowel syndrome. 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 study, Dretzke et al (2004) was carried out in a UK context examining serological tests and used quality adjusted life years (QALYs) as an outcome measure and was therefore reviewed for this guideline. The remaining papers were used to inform the structure of the model and to explore previous approaches to modelling serological test strategies. These papers were not quality assessed and reviewed for this guideline as they did not include health related quality of life outcomes and/or were not UK based studies.

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

Dretzke et al (2004) is a full health technology assessment (HTA) report examining autoantibody testing in children with newly diagnosed type I diabetes mellitus. This report included an economic model to quantify the costs and benefits of screening for coeliac disease at the time of diagnosis of diabetes. This was conducted due to 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, and combination of autoantibody tests without confirmatory biopsy. The authors were clear that not all of these strategies are used in current clinical practice

but 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, EMA, IgA ARA and IgA tTGA. Other tests were excluded due to the small number of studies found. The values used in the model were taken from the SROC curves for each test where the sensitivity and specificity were equal. This is called the Q point. For combination tests the authors made the simplifying assumption 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 been diagnosed later through normal clinical suspicion if they had not been picked up earlier by screening. The delay to diagnosis for these patients was included. Costs and utilities for undiagnosed coeliac disease were included during this delay. We assumed that the delay to diagnosis was 5 years in the base case.

Utility estimates and assumptions were informed using existing literature. Studies on quality of life of treated and untreated coeliac disease were searched and reviewed. Utilities could not be directly derived from the studies identified. Estimates on the utility of treated and untreated coeliac disease, and of the disutility of endoscopy and 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, probably because of the absence of a national tariff for diagnostic tests (such as the BNF for drug prices).

All strategies were compared with the no screening strategy. The lowest cost per QALY gained was for IgA EMA with confirmatory biopsy for positive results with an incremental cost effectiveness ratio of £12,250 per QALY

gained compared with 'no screening'. The least cost effective strategies were those including IgG AGA tests alone or in combination with other autoantibody tests. Authors reported that the results were sensitive to the disutility of being on a gluten free diet, cost of gluten free diet, differences in utilities between health states and reduction in life expectancy due to 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 tell what is driving the incremental cost effectiveness ratio. Limitations regarding the individual input parameters are discussed throughout the methods section, however the discussion does not address limitations of the overall 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.

### **De novo economic model**

Given the absence of published economic evidence that fully addresses the cost effectiveness of serological testing within the decision making context of this guideline, the GDG requested the development of a de novo model to fill this gap.

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, Inc) and adopted a lifetime horizon. Several test strategies were examined and compared with a no testing strategy. 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 then 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 followed by biopsy for positive results. Strategies with separate IgA deficiency testing were also included. For completeness a no test strategy and a biopsy only strategy were included.

The clinical systematic review identified several studies on the sensitivity and specificity of serological tests for coeliac disease. Evidence synthesis was not performed on these studies for reasons explained in section 6.4. Therefore, data on sensitivity and specificity were taken from a UK based, good quality study, by Hopper et al (2008). This study 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 quality of life impact of having an endoscopy and biopsy, having coeliac disease, having undiagnosed coeliac disease and of being on a gluten free diet. It also takes into account any possible reduced mortality due to undiagnosed coeliac disease. The model included the following costs: the cost of serological tests, the cost of endoscopy and biopsy, the cost of gluten free diet and follow up to the NHS and the cost of delayed diagnosis.

Full details of the model are presented in appendix 6.5.

The model suggests that 'no testing' is the least costly and least effective strategy. This is because no testing costs are required but there is a lower quality of life for people who have coeliac disease who remain undiagnosed. Moving from 'no testing' to any of the testing strategies examined is very cost effective. When comparing the test strategies with each other, not including the 'no test' strategy, the model suggests that there is very little difference between the strategies in terms of cost or effectiveness. This is due to the similarity in diagnostic accuracy between these strategies. The most cost

effective option is to test with IgA tTGA and IgA EMA in combination with an incremental cost effectiveness ratio of approximately £4000 per QALY gained.

As each of the testing strategies have similar sensitivity and specificity, the incremental differences in QALYs between them are very small. However, the biopsy only strategy is much more expensive than the others, costing approximately £380 more than the next most expensive strategy. Therefore, although a biopsy only strategy may be preferential to a 'no test' strategy it is still less cost effective than those that include serological tests before confirmatory biopsy for positive results.

Combinations of EMA and tTGA tests had similar sensitivity and specificity as the individual test strategies. Due to the method of charging for these combinations of tests where laboratories often charge nominal additional fees, this means that combination testing is only slightly more expensive than carrying out a single test and is therefore as cost effective as only carrying out one test.

In sensitivity analysis, results were most affected by the increase in quality of life that may be provided by treating 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. 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. One way sensitivity analysis on the most uncertain parameters in the model showed that the model appears robust to variations in most of the model parameter inputs.

Please note: further sensitivity analyses will be explored as necessary including PSA. A summary of the results of these analyses will be added here following consultation.

#### **2.4.5 Linking evidence to recommendations**

The Guideline Development Group (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 identified that for coeliac disease to be diagnosed dietary exposure to gluten is necessary and therefore noted the need to recommend that the diagnostic process for coeliac disease should not be considered in infants who have not started gluten intake.
- 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 all, but also highlighted the additional support which may be needed where individuals have a co-existing condition, such as type 1 diabetes.
- The GDG debated the lack of any quality evidence about the amount of gluten which should be present in the gluten containing diet to maximise the diagnostic potential of the serological tests and notably the intestinal biopsy. While the GDG agreed that this amount was not known they did develop a recommendation which acknowledged the lack of evidence and utilised the GDG experience and expertise to give a guide to the amount of gluten to be eaten.
- The GDG also considered situations where people with suspected, but as yet unconfirmed by biopsy, who had already begun to exclude gluten from their diet, may be reluctant to re-commence or unable to be on a gluten containing diet. The GDG considered that the support and expertise of a gastrointestinal specialist would 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 and as such agreed to not recommend their use.
- The GDG considered from the clinical evidence and the economic model that the serological test of choice is that of combination testing for IgA tTGA and IgA EMA, as it is clinically accurate and the most cost effective

compared with no testing. They did however note that both of these tests individually are appropriate for use in the diagnostic process for coeliac disease, as they are also clinically accurate and cost effective compared with no testing.

- The GDG recognised that the deamidated gliadin tests may be useful but noted, as the evidence for them is limited, that they cannot be currently recommended.
- The GDG discussed the evidence for point of care/self tests and noted that these tests may be useful in future in the diagnostic process for coeliac disease but that currently the evidence is not available to recommend their use. The GDG also discussed the need for a recommendation which advises those who may have used the self tests to discuss the results with healthcare professionals and where coeliac disease is suspected patients should have laboratory-based serological tests.
- The GDG discussed the evidence relating to the use of IgA tTGA in those with liver disease and agreed while the evidence was limited that the available evidence in combination with their expertise allowed for the development of a recommendation that IgA EMA may be the test of choice for those with liver disease.
- The GDG discussed the use of HLA DQ2 and DQ8 testing and noted that as DQ2 or DQ8 is present in around a quarter of the UK population that testing positive for it is of limited value in the diagnosis of coeliac disease. However they did note 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 lab and developed a recommendation to reflect this.
- The GDG noted the lack of evidence regarding the possibility of repeated serological testing for coeliac disease. The GDG further discussed repeat testing and developed a recommendation that repeat testing is not warranted unless there are continuing signs and symptoms of coeliac disease.

## **2.5      *Research recommendations***

- Dietary assessment of gluten content of diet before serological testing. What is the gluten dietary content which is necessary for the optimal accuracy of serological tests and intestinal biopsy?
- While it is evident that a gluten containing diet is necessary to ensure that serological test results are as accurate as possible and also to ensure that intestinal biopsy results are as clear as possible the amount of gluten needed in the diet is unknown.
- How many people with undiagnosed coeliac disease are mis-diagnosed as having other conditions, and what are the cost implications of this?
- People with coeliac disease often have significant health problems that resolve with correct diagnosis and appropriate treatment. Where coeliac disease is undiagnosed, or mis-diagnosed as another condition, health problems continue, resulting in the use of in-appropriate interventions and use of resources, such as visits to GPs or out-patient clinics. This may also limit further investigation (and thus the correct diagnosis to be made) and the health problems continue or increase, with a corresponding effect on the person's quality of life.
- What is the optimal sequence (considering clinical and cost effectiveness) of serological testing for coeliac disease, and when should testing be repeated?
- Although there is considerable evidence on the accuracy of single tests for coeliac disease, there is a lack of research on the optimal sequencing of these tests, including the role of self-testing or point-of-care testing. Research should also be conducted to establish the clinical and cost effectiveness of repeat testing and whether it should be undertaken, and if so, at what intervals.

- Is there any effect of a gluten free diet on glycaemic control in those with type 1 diabetes? (longitudinal follow up of T1D with newly detected CD)
- There is some evidence that glycaemic control may be improved in those with type 1 diabetes who have coeliac disease and follow a gluten free diet though this evidence is not conclusive. There are also many opinions as to whether those with type 1 diabetes, especially newly diagnosed children, should be tested for coeliac disease as they already have to adjust to the diabetes. It would therefore be useful to know if a gluten free diet does impact on glycaemic control in those with type 1 diabetes.
- What are the information needs of people with coeliac disease during diagnostic process
- There is a lack of evidence on the information needs of those undergoing the diagnostic process for coeliac disease

### **3 References, glossary and abbreviations**

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## **3.2 Glossary and abbreviations**

### **3.2.1 Glossary**

#### **2 x 2 table**

A table which summarises diagnostic information (true and false positives and negatives) which 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 individuals 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**

Negative test diagnostic result in a subject who does possess the attribute for which the test is conducted.

**False positive**

Positive test diagnostic result in a subject who 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 between studies in the estimates of effects.

**Negative predictive value**

The proportion of patients with negative test results who are correctly diagnosed.

**Odds ratio**

A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' 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. 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 in the group. A relative risk (RR) of 1 indicates no difference between comparison groups.

**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**

Negative test diagnostic result in a subject who does not possess the attribute for which the test is conducted.

**True positive**

Positive test diagnostic result in a subject who does possess the attribute for which the test is conducted.

### 3.2.2 Abbreviations

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

## 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/guidance/index.jsp?action=download&o=41788](http://www.nice.org.uk/guidance/index.jsp?action=download&o=41788)

The aim of this guideline is to provide evidence-based recommendations to guide healthcare professionals on 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 the National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') in 'The guidelines manual 2009 (available at: [www.nice.org.uk](http://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, was prepared by the Short Clinical Guidelines Technical Team in consultation with relevant literature and following a workshop 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**

This 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 shown in appendix ??.

#### **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 2008 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 specific key clinical questions developed from the guideline scope. The guideline recommendations were evidence based where 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 quality 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) by NICE (available from [www.nice.org.uk](http://www.nice.org.uk)). 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 test 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. Numerical summaries and analyses are followed by short evidence statements summarising what the evidence shows (full details can be found 'The guidelines manual' (2009) by NICE (available from [www.nice.org.uk](http://www.nice.org.uk)).

#### **4.2.8 Evidence to recommendations**

Following discussion of the clinical and cost effectiveness evidence, including consideration of the quality of the available evidence, and the using the experience of Guideline Development Group members, recommendations were drafted. The evidence to recommendations section of the guideline aims to reflect this decision-making process and provide transparency about the development of the recommendations. The Guideline Development Group was able to agreed 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 will be available on the website for consultation from 15th January 2009 to 12th February 2009, and registered stakeholders will be informed by NICE that the documents were available. Non-registered stakeholders can 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 will be collated

and presented anonymously for consideration by the Guideline Development Group, responses and any changes to the guideline will be agreed by the Short Clinical Guidelines Technical Team and the Guideline Development Group prior to completion of 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.

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**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.

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**5.1.2 Guideline Review Panel**

***[To be inserted into final guideline]***

**5.1.3 List of stakeholders**

***[To be inserted into final guideline]***

**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: ***[to be inserted in final guideline]***.

**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](http://www.nice.org.uk)).

**Please note the appendices are available as separate files.**