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Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus

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Abstract

Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus

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Objectives: To determine the role of autoantibody tests for autoimmune diseases in children with newly diagnosed type 1 diabetes mellitus.
Data sources: MEDLINE, EMBASE and the Cochrane Library. Citation lists of included studies were scanned and relevant professional and patient websites reviewed. Laboratories and manufacturers were contacted to identify ongoing or unpublished research.
Review methods: Following scoping searches on thyroid and coeliac autoantibodies, a systematic review of autoantibody tests for diagnosis of coeliac disease was carried out. Studies were included where cohorts of untreated patients with unknown disease status were included, all patients had undergone the reference test (biopsy) and antibody tests, and sensitivity and specificity were reported or calculable. Selected studies were then evaluated against a quality checklist. Summary statistics of diagnostic accuracy, i.e. sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios, were calculated for all studies. A decision analytic model was developed to evaluate the cost utility of screening for coeliac disease at diagnosis of diabetes.
Results: All antibody tests for diagnosis of coeliac disease showed reasonably good diagnostic test accuracy. Studies reported variable measures of test accuracy, which may be due to aspects of study quality, differences in the tests and their execution in the laboratories, different populations and reference standards. The decision analytic model indicated screening for coeliac disease at diagnosis of diabetes was cost-effective. Sensitivity analyses exploring variations in the cost and disutility of gluten-free diet, the utilities attached to treated and untreated coeliac disease and the decrease in life expectancy associated with treated and untreated coeliac disease did substantially affect the cost-effectiveness of the screening strategies considered.
Conclusions: In terms of test accuracy in testing for coeliac disease, immunoglobulin A (IgA) anti-endomysium is the most accurate test. If an enzyme-linked immunoassay test was required, which may be more suitable for screening purposes as it can be semi-automated, testing for IgA tissue transglutaminase is likely to be most accurate. The decision analytic model shows that the most accurate tests combined with confirmatory biopsy are the most cost-effective, whilst combinations of tests add little or no further value. There is limited information regarding test accuracy in screening populations with diabetes, and there is some uncertainty over whether the test characteristics would remain the same. Further research is required regarding the role of screening in silent coeliac disease and regarding long-term outcomes and complications of untreated coeliac disease.

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Contents

List of abbreviations

AGA	anti-gliadin antibody
ARA	anti-reticulin antibody
ARIF	Aggressive Research Intelligence Facility
BI	burden of illness
BSPED	British Society for Paediatric Endocrinology and Diabetes
CD	coeliac disease
CV	coefficient of variation
df	degrees of freedom
DIG	diffusion-in gel
DOR	diagnostic odds ratio
ELISA	enzyme-linked immunosorbent assay
EMA	anti-endomysial antibody
ESPGAN	European Society for Paediatric Gastroenterology
FN	false negative
FP	false positive
GCD	gluten-containing diet
GFD	gluten-free diet
GSRS	Gastrointestinal Symptoms Rating Scale
HLA	histocompatibility antigens
IBS	irritable bowel syndrome
ICER	incremental cost-effectiveness ratio
IDDM	insulin-dependent diabetes mellitus
ISPAD	International Society for Pediatric and Adolescent Diabetes
IgA	immunoglobulin A
IgG	immunoglobulin G
LE	life expectancy
LR	likelihood ratio
NEQAS	National External Quality Assessment Service
NHS R&D	National Health Service Research and Development
NPV	negative predictive value
NSC	UK National Screening Committee
PGWB	Psychological General Well-being
PPV	positive predictive value
PREV	population
QALY	quality-adjusted life-year
RIA	radioimmunoassay
SF-36	Short Form with 36 Items
SMR	standardised mortality ratio
SROC	summary receiver operating characteristics
SENS	sensitivity

continued

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List of abbreviations *continued*

SPEC	specificity
T3	serum triiodothyronine
T4	serum thyroxine
TAAB	thyroid autoantibodies
TFT	thyroid function test
Tgab	thyroglobulin antibodies
TMA	thyroid microsomal antigen
TN	true negative
TP	true positive
TPO	thyroid peroxidase
TPOab	thyroid peroxidase antibodies
TSH	thyroid-stimulating hormone
TTG	anti-tissue transglutaminase antibody
UK NEQAS	UK National External Quality Assessment Service

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Aim of the review

The aim of this review was to determine the role of autoantibody tests for autoimmune diseases in children with newly diagnosed type 1 diabetes mellitus.

Background

Type 1 diabetes mellitus is one of the most common severe chronic diseases to occur in childhood and adolescence. There is a genetic predisposition towards type 1 diabetes, which also predisposes patients to other autoimmune diseases such as coeliac disease, thyroid disease, Addison's disease (adrenal insufficiency), vitiligo, alopecia and gastric autoimmunity. The association of autoantibodies with disease in the target tissues suggests that there may be a role for autoantibody testing in screening for autoimmune diseases, particularly in at-risk populations such as those with type 1 diabetes.

We used the UK National Screening Committee (NSC) criteria to identify the two most important conditions associated with type 1 diabetes in children, and found that both coeliac disease and thyroid disease met at least some of the criteria. There are detectable antibodies that are markers for both conditions, and both conditions can be present in the patient and do harm before they are detected clinically.

Thyroid disease is the most common autoimmune disease in children with diabetes and can lead to severe morbidity. If overt hypothyroidism is left untreated in type 1 diabetes, metabolic control of the diabetes itself may be complicated, while untreated hypothyroidism in a child may result in the child's genetic growth potential not being realised. The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend testing for thyroid disease at the time of initial diagnosis as a baseline or to uncover asymptomatic thyroid disease, with repeat testing if a child becomes symptomatic or has high titres of antibodies.

Coeliac disease is an inflammatory disease of the upper small intestine that results in malabsorption and other consequent systemic problems. Serum antibody tests have been used as screening tests for coeliac disease both in the general population and in at-risk groups. Coeliac disease is treated by a lifelong gluten-free diet, and in most patients symptoms and gut pathology resolve. The ISPAD guidelines for juvenile diabetes state that the need for and frequency of screening tests is controversial.

Rationale for review

Sufficient evidence has been presented in the report to indicate that thyroid autoantibody tests are unlikely to be cost-effective for screening purposes relative to thyroid function tests. A systematic review of the test characteristics of autoantibody tests for coeliac disease has been carried out, as the use of autoantibody tests for screening purposes meets several of the NSC screening criteria.

Decision-analytic model

In order to inform the review further, we developed a decision-analytic model to estimate the costs and benefits of a single screening episode for coeliac disease at the time of diagnosis of type 1 diabetes in childhood. The model considered a number of screening strategies, including no screening, use of a single antibody test or a combination of antibody tests with or without confirmatory biopsy in those testing positive and a policy of biopsy testing of all children.

Survey of current practice

In order to inform the decision-analytic model in this report and prioritisation of future research concerning other autoantibody screening in children with diabetes, a national survey of current practice was also undertaken.

Methods of the systematic review

Search strategy

MEDLINE, EMBASE and the Cochrane Library were searched using appropriate search filters.

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Citation lists of included studies were scanned and relevant professional and patient websites reviewed. Laboratories and manufacturers were contacted in order to identify ongoing or unpublished research.

Inclusion and exclusion

Cohorts of untreated patients with unknown disease status were included. All patients had to have undergone the reference test (biopsy) and antibody test or tests [immunoglobulin (Ig) A and/or IgG anti-gliadin (AGA), anti-endomysium (EMA), anti-reticulin (ARA) or anti-tissue transglutaminase (TTG)]. Sensitivity and specificity had to be reported or calculable from raw data. Titles and abstracts were reviewed independently by two reviewers, with retrieval of papers where there was disagreement. Retrieved papers were also reviewed independently by two reviewers.

Data extraction

The study design of all papers was reviewed and abstracted by at least two reviewers. All data were extracted by one reviewer on to piloted data abstraction forms. A subset of higher quality studies were double-data extracted, with involvement of a third reviewer to resolve any discrepancies.

Quality assessment

A suitable checklist for the quality evaluation of studies was used. It included assessment of the representative nature of the sample, whether there were explicit exclusion criteria, and took account of the potential sources of bias such as blinding, independence of tests and selection of patients.

Analysis

Summary statistics of diagnostic accuracy, that is sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios, were calculated for all studies. Sensitivities and false-positive rates of individual antibody tests were plotted in summary receiver operating characteristics plots, and the area under the curve calculated to give an indication of the overall diagnostic test performance of the individual antibody tests. Positive and negative likelihood ratios were calculated and pooled for individual antibody tests. Subgroup analyses were carried out according to study quality.

Results

Test accuracy of autoantibody tests

Seventy-six studies were included. Many studies were of poor quality on several indicators, particularly concerning the description of the study design and patient selection. Only 18 studies reported the method of patient selection. All but four studies were in symptomatic, not screening, populations.

All antibody tests showed reasonably good diagnostic test accuracy, with the area under the curve >0.9 for all tests. IgA EMA, IgA ARA and IgA TTG stood out as particularly good tests, followed by IgA AGA and then IgG AGA. IgA EMA tests have the highest pooled positive likelihood ratio and lowest negative likelihood ratio and IgA TTG tests have high positive likelihood ratio compared with AGA tests. Studies reported variable measures of test accuracy, which may be due to aspects of study quality, differences in the tests (including manufacturers and substrates) and their execution in the laboratories, different populations and reference standards.

Decision-analytic model

The use of antibody testing with confirmatory biopsy appeared cost-effective, with cost/QALY estimates ranging from £12,250 to £20,160, and a cost/case detected of £6190 to £9900, with the more accurate tests being the most cost-effective. Antibody testing strategies without confirmatory biopsy were more expensive and led to less overall benefit, due to the costs and disutility associated with the treatment of false positives. The use of more than one antibody test increases the sensitivity of the screening strategy, but also decreases the specificity. We estimated that the use of more than one test led to minimal additional benefit, or even a decrease in benefit, whilst being more expensive, owing to the cost of additional tests and the larger number of false positives requiring more biopsies or unnecessary treatment with gluten-free diet. A screening strategy of biopsying all patients was more expensive than any antibody screening strategy whilst leading to minimal increase in benefit or a loss in benefit compared with the more accurate testing strategies.

Uncertainty over parameter values used in the model was investigated using sensitivity analysis, varying each parameter in the model within a plausible range. Predictably, high test specificity or a low cost and disutility of gluten-free diet improves the relative cost-effectiveness of strategies that do not use confirmatory biopsy for those testing positive. Other than this, there were no variations in a single parameter value, which substantially changed the overall interpretation of results from the base case analysis. However, variations in the cost and disutility of gluten-free

diet, the utilities attached to treated and untreated coeliac disease and the decrease in life expectancy associated with treated and untreated coeliac disease did substantially affect the cost-effectiveness of the screening strategies considered; these parameter values are those for which we found the least evidence in the literature.

Conclusion

In terms of test accuracy in testing for coeliac disease, IgA EMA (using indirect immunofluorescence) is the most accurate test. If an ELISA test was required, which may be more suitable for screening purposes as it can be semi-automated, testing for IgA TTG is likely to be most accurate. The decision-analytic model shows that the most accurate tests combined with confirmatory biopsy are the most cost-effective, whilst combinations of tests add little or no further value. There is limited information regarding test accuracy in populations with diabetes, and there is some uncertainty over whether the test characteristics would remain the same, particularly as there may be a proportion of silent disease. Further research is required regarding the role of screening in silent coeliac disease and regarding long-term outcomes and complications of untreated coeliac disease.

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Chapter 1

Aim of the review

The aim of this review is to determine the role of autoantibody tests for autoimmune diseases in children with newly diagnosed type 1 diabetes mellitus.

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Chapter 2
Background

Diabetes mellitus type 1 in childhood and adolescence

Type 1 diabetes mellitus is one of the most common severe chronic diseases to occur in childhood and adolescence. It is a metabolic disorder characterised by hyperglycaemia and results from defective insulin secretion. The most common form of diabetes in childhood and adolescence is type 1, or insulin-dependent diabetes, which requires insulin replacement. It arises from autoimmune damage to pancreatic islet β-cells.[1]

Reported crude incidence of type 1 diabetes in children and adolescents range from 0.5 to 30.5 per 100,000 population per year, with reported UK rates ranging from 7.8 to 21.6 per 100,000.[2] There is a greater than 10-fold variation in incidence rates across Europe. The incidence of type 1 diabetes in childhood has been rising at an estimated average increase in incidence of 3.4% per year, with a relatively greater increase in incidence in the under fives.[3–5]

Association of type 1 diabetes with other autoimmune diseases

There is a genetic predisposition towards type 1 diabetes, which also predisposes patients to other autoimmune diseases.[6] These diseases can involve endocrine and other tissues. Diseases with an increased incidence in children with diabetes include coeliac disease, thyroid disease, Addison's disease (adrenal insufficiency), vitiligo, alopecia and gastric autoimmunity. Organ-specific autoantibodies associated with other autoimmune diseases are also more frequent in type 1 diabetes patients than in the general population.[7,8]

Principles of screening

Screening is a public health service in which members of a defined population are offered a test to identify those individuals who may have a condition or risk factor and are likely to be helped by treatment.

The association of autoantibodies with disease in the target tissues suggests that there may be a role for autoantibody testing in screening for autoimmune diseases, particularly in at-risk populations such as those with type 1 diabetes.

The authors of this report were commissioned to undertake a rapid review to inform decision-making on this issue.

The UK National Screening Committee (NSC) outlines the principles that should be used to decide whether it is worth screening for a condition.[9] These are shown in *Box 1*.

It is not possible in a rapid review to review adequately the cost-effectiveness of all the tests for all the autoimmune conditions associated with type 1 diabetes and all the parameters relevant to a decision about whether to screen or not. Therefore, in order to prioritise the work, we used the NSC criteria to identify the two most important conditions associated with type 1 diabetes in children and did some early scoping searches and simple decision-analytical modelling which was fed back to the commissioners.

The two most important conditions associated with childhood diabetes identified are coeliac disease and thyroid disease (criterion 1.1). Both conditions also meet criterion 1.2 in that the epidemiology and natural history of these conditions are reasonably well understood (see below for details), there are detectable antibodies that are markers for both conditions and both conditions can be present in the patient and do harm before they are detected clinically. For both conditions there are no other cost-effective primary prevention interventions that should preferentially be put in place (criterion 1.3).

Both conditions also meet the treatment criteria in that there are effective treatments (criterion 1.8), for example, thyroxine for hypothyroidism or gluten-free diet for coeliac disease, and agreed evidence-based policies covering the appropriate treatments (criterion 1.9) (fuller details are given in the text below). There is uncertainty around the effect of treatment in silent coeliac and thyroid disease.

In the light of the above considerations, the NCCHTA editor and the National Screening Panel

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BOX 1 *NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme*[a]

The condition

1.1. The condition should be an important health problem.
1.2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker, and a latent period or early symptomatic stage.
1.3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

The test

1.4. There should be a simple, safe, precise and validated screening test.
1.5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
1.6. The test should be acceptable to the population.
1.7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The treatment

1.8. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
1.9. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
1.10. Clinical management of the condition and patient outcomes should be optimised by all healthcare providers prior to participation in a screening programme.

The screening programme

1.11. There must be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
1.12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
1.13. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
1.14. The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
1.15. There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
1.16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.
1.17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
1.18. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
1.19. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

[a] *Source:* UK National Screening Committee.[9]

requested that the authors focus on these two conditions in the report, with particular emphasis on a systematic review of the test characteristics of the autoantibody tests for coeliac disease.

The two conditions are dealt with sequentially in the report.

In order to inform the decision-analytic modelling in this report and prioritisation of future research concerning other autoantibody screening in children with diabetes, a national survey of current practice was also undertaken and is reported herein.

Survey of current practice in the UK

Methods

We carried out a survey of the current practice and opinion of consultants involved in the care of children with diabetes regarding the use of

TABLE 1 *Autoantibody and thyroid function testing for thyroid disease in children with type 1 diabetes*

	Yes, in all children: *n* (%)	Yes, in symptomatic children only: *n* (%)	No.: *n* (%)	No. of responses
Around the time of diagnosis of type 1 diabetes, do you carry out autoantibody tests for thyroid disease?	68 (47.2)	20 (13.9)	56 (38.9)	144
Do you carry out antibody tests for thyroid disease subsequent to diagnosis?	72 (46.5)	44 (28.4)	39 (27.1)	155
Around the time of diagnosis of type 1 diabetes, do you carry out thyroid function tests?	91 (62.3)	22 (15.1)	33 (22.6)	146
Do you carry out thyroid function tests subsequent to diagnosis?	118 (77.1)	32 (20.9)	3 (2.0)	153

autoantibody tests and surveillance of children with type 1 diabetes for autoimmune diseases. The survey was undertaken through the Clinical Trials Unit of the British Society for Paediatric Endocrinology and Diabetes (BSPED) with the kind agreement of Professor D. Dunger. The Unit holds a list of consultants throughout the UK involved in the care of children with type 1 diabetes. The questionnaire was anonymous but clinicians were requested to identify the centre at which they worked for the purpose of calculating prevalence. The questionnaire and accompanying explanatory letter were piloted with local clinicians. Letters and questionnaires were posted at the beginning of July 2002. A prepaid envelope for the reply was included.

Results

Of 240 consultants, 166 replied, giving an overall response rate of 69.2%; 34% of 111 respondents said that they followed guidelines on testing for other autoimmune diseases. Of these, seven specified the International Society for Pediatric and Adolescent Diabetes (ISPAD) and four the Scottish Intercollegiate Guidelines Network (SIGN) guidelines (see Appendix 1 for extract from the ISPAD guidelines).

Current practice: autoantibody tests for thyroid disease

Nearly half of the consultants used antibody tests for thyroid disease around the time of diagnosis in all children, with 46.5% carrying out tests subsequently (*Table 1*). A further 13.9% tested symptomatic children at diagnosis, with 28.4% testing symptomatic children subsequently. Of those who tested all children subsequent to diagnosis and specified the screening interval, 17.5% tested children annually, 20.0% tested every 1–2 years, and 22.5% every 3 to 5 years. Of those who subsequently tested for thyroid autoantibodies 93.1% said this was part of an annual review.

Whereas 71.8% of respondents used microsomal antigen/thyroid peroxidase, 17.2% used thyroglobulin. If patients were positive for antibodies, but euthyroid, respondents would wait and monitor thyroid function.

Of the respondents, 78 (55.3%) said that there should be routine thyroid autoantibody testing in children with diabetes, whereas 57 (40.4%) said that there should not be routine autoantibody testing.

There was stronger support for thyroid function testing: 82.6% (114 out of 138 respondents) said that there should be routine thyroid function tests in children with diabetes, whereas 14.5% said that there should not be routine thyroid function testing. Thus although a majority of clinicians support routine thyroid autoantibody testing, with greater support for thyroid function testing, there is still a divergence of clinical opinion.

Current practice: autoantibody tests for coeliac disease

Just over half of the consultants used antibody tests for coeliac disease in all children around the time for diagnosis, with 71.8% carrying out tests subsequently. A further 20.4% tested symptomatic children only (*Table 2*). Of those who tested all children subsequent to diagnosis, 50.5% tested children annually, 16.8% tested every 1–2 years, and 12.6% every 3 to 5 years. 88.5% of those who subsequently tested for coeliac autoantibodies said this was part of an annual review.

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TABLE 2 *Autoantibody testing for coeliac disease in children with type 1 diabetes*

	Yes, in all children: *n* (%)	Yes, in symptomatic children only: *n* (%)	No.: *n* (%)	No. of responses
Around the time of diagnosis of type 1 diabetes, do you carry out autoantibody tests for coeliac disease?	80 (51.0)	32 (20.4)	45 (28.7)	157
Do you carry out antibody tests for coeliac disease subsequent to diagnosis?	112 (71.8)	41 (26.3)	3 (1.9)	156

TABLE 3 *Autoantibody tests used (survey)*

	N	%
IgA EMA	131	80.4
IgA gliadin (AGA)	65	39.9
Total IgA (IgA)[a]	55	33.7
IgG gliadin (AGG)	50	30.7
IgA TTG	34	20.9
IgA reticulin (ARA)	8	4.9

[a] Test for IgA deficiency.
AGA, anti-gliadin antibody; IgG, immunoglobulin G; ARA, anti-reticulin antibody.

TABLE 4 *Test combinations used (survey)*

	N	%
EMA	36	23.4
EMA, IgA	21	13.6
AGA, AGG, EMA	20	13.0
AGA, AGG, EMA, IgA	13	8.4
AGA, EMA	9	5.8
TTG	12	7.8
TTG, IgA	5	3.2
Other	38	2.6
Total	154	

Immunoglobulin A (IgA) anti-endomysial antibody (EMA) was the most commonly used test, with 23.4% using only that test, and a further 13.6% using it in combination with measurement of total IgA. IgA anti-tissue transglutaminase antibody (TTG) was used by 20.9% (*Tables 3* and *4*).

If tests were positive 68.1% would undertake a biopsy or refer to a gastroenterologist for biopsy, whereas 13.5% would refer if a second test were positive, with 9.2% having other policies. Clinicians were asked what their policy was if a patient was positive for antibodies, but negative on biopsy. Most would continue to monitor and observe the patient.

Of 141 respondents, 74.5% thought that there should be routine screening for coeliac disease in children with diabetes, whereas 21.3% thought that there should not be routine screening. Thus although a majority of clinicians support routine coeliac autoantibody testing, there is still a divergence of clinical opinion.

Prevalence of treated thyroid disease and biopsy-diagnosed coeliac disease in children with type 1 diabetes

Respondents were asked to provide information on the prevalence of biopsy-diagnosed coeliac disease and of treated hypo- and hyperthyroid disease, and to specify whether the numerators and denominators were exact or estimated.

Out of 14,941 children in total, 297 children with biopsy diagnosed coeliac disease were reported, a prevalence of 2.0 per 100 (95% confidence interval 1.8 to 2.2). The prevalence where both numerator and denominator were reported to be exact was 2.0 per 100 (95% confidence interval 1.7 to 2.4).

Out of 14,941 children in total, 471 children with treated hypothyroid disease were reported, a prevalence of 3.2 per 100 (95% confidence interval 2.9 to 3.4). The prevalence where both numerator and denominator were reported to be exact was 2.7 per 100 (95% confidence interval 2.3 to 3.1).

Out of 14,941 children in total, 11 children with treated hyperthyroid disease were reported, a prevalence of 0.2 per 100 (95% confidence interval 0.2 to 0.3). The prevalence where both numerator and denominator were reported to be exact was 0.2 per 100 (95% confidence interval 0.1 to 0.3)

Chapter 3

Autoantibody testing for thyroid disease

Background

Thyroid disease

Thyroid disease is the most common autoimmune disorder in children with diabetes and can lead to severe morbidity. It can manifest itself as hypothyroidism or, less frequently, as hyperthyroidism. It is well documented that children with type 1 diabetes are at higher risk compared with the general population of developing thyroid disease, and many centres already screen for thyroid disease in children with diabetes.

The care of children and adolescents with type 1 diabetes is described in the ISPAD Consensus guidelines 2000.[10] These recommend testing for thyroid disease at the time of initial diagnosis as a baseline or to uncover asymptomatic thyroid disease, with repeat testing if a child becomes symptomatic or has high titres of antibodies. Extracts from the ISPAD guidelines are given in Appendix 1.

There is no national policy on the frequency, value or method of routine screening for thyroid disease in children with diabetes. It is uncertain whether screening for thyroid disease meets the NSC[9] criteria for population screening, and which test (thyroid function test and/or autoantibody tests) or combination of tests are most appropriate.

In order to answer this question, a broad scoping search was carried out, which sought to provide general information on the association between thyroid disease, thyroid autoantibodies and type 1 diabetes in children and, more specifically, to identify studies investigating the test characteristics of thyroid autoantibody tests relative to thyroid function tests as a reference standard.

Presentation and prognosis

Hypothyroidism

Hypothyroidism during childhood and adolescence can be congenital or acquired, and involves subnormal activity of the thyroid gland and decreased secretion of the major thyroid hormones thyroxine and triiodothyronine. Hashimoto's thyroiditis, a common cause of hypothyroidism, involves inflammation of the thyroid gland resulting from thyroid cell damage mediated either by antithyroid antibody-dependent cell-mediated cytotoxicity and/or by direct cytotoxicity by sensitised effector T-lymphocytes.[11] If overt hypothyroidism is left untreated in type 1 diabetes, the decrease in basal metabolic rate may complicate lipid disturbances and metabolic control of the diabetes itself, with a risk of adverse outcomes in pregnant women.[12,13] In addition, untreated hypothyroidism in a child that has not reached puberty may result in the child's genetic growth potential not being realised. Presentation can include goitre in 10–20%, or there may be weight gain and facial fullness, decreased growth rate and tiredness and lethargy.[10]

Hyperthyroidism

Thyrotoxicosis, or hyperthyroidism, arises when there are excessive amounts of unbound circulating thyroid hormone resulting in accelerated metabolism of body tissues. Underlying causes include overactivity of the gland, tumour or, more commonly, Graves' disease, an autoimmune disorder.[14] Presentation can include agitation, tachycardia, weight loss, heat intolerance, tremor and possibly unstable metabolic control.[10]

Sub-clinical thyroid disease

Thyroid disease can have a long sub-clinical course. Sub-clinical (biochemical) thyroid disease is characterised by elevated thyroid-stimulating hormone (TSH) levels with normal serum thyroxine (T4) levels (hypothyroidism) or, less frequently, lowered TSH levels with normal T4 levels (hyperthyroidism). The majority of patients with sub-clinical (biochemical) thyroid disease are asymptomatic, or have non-specific symptoms, although mild symptoms may be retrospectively found to be present upon questioning of the patient.[15] Symptoms may also not be attributed to thyroid disease but interpreted as being secondary to diabetes.[16]

A proportion of patients with sub-clinical disease may go on to develop overt hypo- or hyperthyroidism, which may or may not be associated with clinical symptoms.[15] It is estimated that (adult) patients with sub-clinical

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hypothyroidism progress to overt disease at a rate of 5% per year.[17] No data was found that relates to progression rates from sub-clinical to clinical thyroid disease in children with diabetes.

Diagnosis

Thyroid function test

A thyroid function test (TFT) is used for diagnosing sub-clinical or clinical thyroid disease. Serum thyrotrophin (TSH) levels are determined in combination with serum thyroxine (T4) and serum triiodothyronine (T3) levels, as the interpretation of TSH results depends on T4 and T3 levels. Hypothyroidism is confirmed by low total (free) thyroxine levels and raised TSH levels, hyperthyroidism by raised total (free) thyroxine, raised triiodothyronine, with TSH suppressed below the normal range.[10] Sub-clinical hypothyroidism is generally associated with a value of TSH of >3.5–5 mU/litre, whilst 6–9 mU/litre is considered mildly elevated and >10 mU/litre elevated. A TSH value of <0.1 mU/litre is associated with sub-clinical hyperthyroidism.[12,18]

A normal TSH concentration has a high negative predictive value in ruling out thyroid disease in a healthy individual in the absence of confounding factors. Serum TSH has a sensitivity of 89–95%, and specificity of 90–96% for overt thyroid dysfunction in unselected populations.[18] The American Thyroid Association Guidelines[19] state that serum TSH measurement is the single most reliable test to diagnose common forms of hypo- and hyperthyroidism: an elevated serum TSH level is present in both overt and mild hypothyroidism, whilst virtually all types of hyperthyroidism are accompanied by suppressed serum TSH concentrations. Thyroid dysfunction may affect diabetes control, which in turn may affect the results of a TFT.[20]

Antibody testing

It has been suggested that using immunological tests to identify auto-antibodies against thyroglobulin or thyroid peroxidase may be useful for identifying existing thyroid disease or for predicting the likelihood of developing thyroid disease.

Thyroid peroxidase (TPO) autoantibodies [equivalent to thyroid microsomal antigen (TMA)] and thyroglobulin autoantibodies can be detected using a range of standard immunological techniques such as haemagglutination, radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA) or immunofluorescence.[21–23] More modern techniques such as ELISA are relatively cheap and easy to use, can be automated and result in less variation in results compared with older methods such as haemagglutination. Thyroglobulin antibodies (Tgab) are rarely detected in the absence of thyroid peroxidase antibodies and are of little diagnostic value (Plant T, Immunology Laboratories, Queen Elizabeth University Hospital, Birmingham NHS Trust: personal communication, 2001; Coleborn P, Pathology Laboratories, Heartlands Hospital, Birmingham NHS Trust: personal communication, 2001).

There is no national or international standard level that determines antibody positivity. Most test kits have their own inherent cut-off point, and results from ELISAs are usually expressed in arbitrary units. Direct comparisons between quantitative results are therefore not possible. There are no guidelines that describe what constitutes low or high antibody titres, or regarding the predictive value of different antibody titres. There are also no guidelines or estimates concerning typical antibody titre ranges in individuals with no thyroid dysfunction, sub-clinical or overt thyroid disease. Some studies refer to 'significant' or 'high' antibody levels; however, these levels are not directly comparable. There is, however, reasonable consistency in terms of positivity and negativity of results in laboratories in the UK. Accredited laboratories must have external quality assurance systems in place. Most UK laboratories carrying out immunological tests are members of the UK NEQAS scheme and results show generally good agreement on positivity/negativity between laboratories using different methodologies and test kits (Plant T, Immunology Laboratories, Queen Elizabeth University Hospital, Birmingham NHS Trust: personal communication, 2001). The study by d'Herbomez and colleagues[24] evaluated the use of eight commercial kits manufactured in six different countries for the detection of thyroperoxidase antibodies. The overall consistency between tests in terms of positive and negative results was good or very good (between 88.3 and 98.8% agreement).

A blood test is necessary for both TFTs and antibody tests. A single sample can be used for both TFT and antibody test. However, as TFT and antibody testing is often carried out at different, specialised laboratories, it may be necessary to provide more than one serum sample. The use of capillary blood may be more acceptable to children and, depending on the laboratory facilities and laboratory and clinical experience, can be used for TFTs and for antibody tests.

Treatment

Effective treatment is available for clinical thyroid disease: hypothyroidism is treated with L-thyroxine, with monitoring of TSH levels, and hyperthyroidism is treated with drugs that interfere with the production of thyroid hormone (anti-thyroid drugs such as carbimazole, methimazole and propylthiouracil or with radioactive iodine).[10,13]

There is no consensus regarding the role of thyroxine therapy in patients with sub-clinical hypothyroidism. Dayan and Daniels[25] reviewed two placebo-controlled trials of thyroxine therapy in adult patients with sub-clinical hypothyroidism. Symptom scores improved with treatment: however, the patients and treatment in the trials were not necessarily representative: in one trial, the majority of patients had treated hyperthyroidism rather than chronic autoimmune thyroiditis, and in the other trial a fixed dose of thyroxine was given rather than a dose to normalise the serum thyrotrophin concentration. Dayan and Daniels[25] recommend treatment if a patient has symptoms potentially attributable to hypothyroidism, the TSH level is above 10 mU/litre or the patient is at risk of progression to overt hypothyroidism (because of, amongst other factors, a strongly positive test for antibodies). Perros and colleagues[15] describe the practice at the Royal infirmary in Edinburgh, where thyroxine treatment is initiated when patients have a serum TSH concentration >10 mU/litre and are antibody positive. Beckett and Toft,[26] referring to the consensus statement for the management of hypo- and hyperthyroidism,[27] state that patients whose TSH levels are consistently >5 mU/litre should be treated with thyroxine, particularly if they have TPO antibodies, a history of treatment of thyrotoxicosis or a goitre. Whilst the above examples relate to adults with diabetes, Lorini and colleagues[13] state that treatment in children should be initiated if TSH >10mU/litre.

Overall, there appears to be no consensus regarding treatment if TSH levels are between 6 and 9 mU/litre, and treatment may vary according to the clinician's recommendation and the presence of what are deemed to be additional risk factors such as antibody positivity. There is no effective intervention to prevent the development of clinical thyroid disease in patients with thyroid autoantibodies. There is general agreement regarding the treatment of individuals with overt (clinical) disease, but not for individuals with sub-clinical disease (with or without antibody positivity).

Table 5 lists possible outcomes of tests and some recommendations made. There is no national policy regarding further interventions (type of tests or frequency) and clinical practice across the UK varies (see the section 'Survey of current practice in the UK', p. 4).

There is no known effective primary prevention intervention for autoimmune thyroid disease. Autoimmune thyroid disease is primarily linked to

TABLE 5 *Possible test outcomes for thyroid function tests and antibody tests*

Possible test outcome		Intervention
TFT	**Antibody test**	
Normal	Negative	Continued symptom monitoring. The ISPAD guidelines recommend regular clinical examination of the thyroid gland for detection of goitre.[10] Many centres carry out annual TFTs.
Normal	Positive	There is no national consensus. Some studies recommend more frequent TFTs on the basis of a higher risk.[16] The ISPAD guidelines recommend repeat TFTs if a child has high titres of antibodies[10]
Sub-clinical level	Negative	There is no national consensus. Treatment with thyroxine is usually recommended if TSH levels are >10 mU/litre.[13,28] If levels are between 6 and 9 mU/litre the decision to treat will depend on the clinician and the presence of what are considered to be other risk factors such as antibody positivity. In the study by Perros *et al.*,[15] patients were treated with thyroxine if the TSH level exceeded 10 mU/litre and they were antibody positive. There are no recommendations regarding sub-clinical disease in the ISPAD guidelines
Sub-clinical level	Positive	
Abnormal level	Negative	There is general agreement that treatment would be initiated at this clinical level of thyroid function regardless of antibodies
Abnormal level	Positive	

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TABLE 6 *Prevalence of overt (clinical) thyroid disease in population with diabetes and the general population*

Population with diabetes	Control groups/general population
ISPAD consensus guidelines 2000[10] Prevalence of overt hypothyroidism in young people with diabetes 1–5% in the UK Perros *et al.*, 1995[15] Population: adult patients with diabetes at the Diabetic Outpatient Clinic of the Royal Infirmary, Edinburgh Incidence of overt thyroid disease per year: 1.45% Lorini *et al.*, 1996[13] Review of prevalence of overt hypothyroidism in children with diabetes 1–3%, thyrotoxicosis 0.5–7% (various sample populations) McKenna *et al.*, 1990[23] Population: IDDM patients with at least one admission to the paediatric service of the Diabetes Treatment Unit at New England Deaconess Hospital Overt thyroid disease: 3.5%	Hunter *et al.*, 2000[30] 0.14% prevalence for hypothyroidism in all individuals <22 years old in the Scottish region of Tayside Perros *et al.*, 1995[15] Incidence of overt thyroid disease in the general population per year 0.3% (from the Whickham survey)[31]
IDDM, insulin-dependent diabetes mellitus.	

a genetic predisposition rather than to external factors, although these may play a role in triggering or exacerbating the condition. There is circumstantial evidence to suggest that excessive dietary iodine may exacerbate thyroid autoimmunity.[29] The likely reason for the association between thyroid disease and type 1 diabetes is a common genetic predisposition towards co-existing autoimmune destruction of pancreatic islet cells and thyrocytes.[15,16]

Prevalence of thyroid disease in children

Table 6 shows the prevalence of overt (clinical) thyroid disease in populations with diabetes compared with the general population or control populations. Only one study was identified[30] which estimated the prevalence of thyroid disease in a young (<22 years) population without diabetes. It can be seen that the prevalence of thyroid disease in people with diabetes (both adults and children) is higher than in populations without diabetes.

Thyrotoxicosis also occurs more frequently in children with type 1 diabetes with prevalence varying between 0.5 and 7%.[13] It is diagnosed less frequently than hypothyroidism and may be transient or precede hypothyroidism (or vice versa),[10] with an estimated 1% of children with type 1 diabetes suffering from Graves' disease.[8]

Thyroid disease can be considered an important health problem, in view of both the adverse health consequences, particularly for those with diabetes and the relatively high frequency in which it is found in children with diabetes.

Prevalence of thyroid autoantibodies in the population with type 1 diabetes

Thyroid autoantibodies are more prevalent in those with type 1 diabetes compared with the general population. Studies have measured varying prevalence of between 3 and 50% depending on the methodology of the study and patient characteristics (age, sex, ethnicity and genetic background).[13,21] Positive autoantibodies have been reported to increase with chronological age of the patient, with higher levels in female adolescents and young adults,[21] whilst patients with type 1 diabetes and Hashimoto's thyroiditis are likely to have a positive family history of disease.[12]

The levels of thyroid autoantibodies in populations with diabetes in the studies identified for this report vary between 3 and 54.3% for those studies measuring TPO/TMA antibodies (mean 20%) and 0–23% for those studies looking at any thyroid antibodies (mean 15.6%) (see Appendix 2).

Table 7 shows the percentage of autoantibodies in populations with diabetes relative to control populations in four studies. There are large variations in the reported values, depending on populations and methodology employed, with overall higher percentages in the diabetic groups.

TABLE 7 *Thyroid antibody positivity in populations with diabetes and control groups*

Study	Population with diabetes	Control groups
Hansen *et al.*, 1999[32] Denmark	16% Population: all patients <18 years old with IDDM in the Danish county of Funen	1.9% Population: relatives of hospital staff in the county of Funen
Lindberg *et al.*, 1997[22] Sweden	44% Population: 52 children with newly diagnosed IDDM admitted to Malmo General Hospital	16% Population: school children without diabetes and without known thyroid disease
Radetti *et al.*, 1995[33] Italy	3.9% Population: unselected children with IDDM at various university hospital paediatric departments (Italy, Croatia, Austria, Slovenia)	1.2% Population: Arizona, Utah and Nevada school children monitored because of possible radiation exposure
McCanlies *et al.*, 1998[12] USA	7–38% Review of prevalence of autoantibodies (various populations)	<1–7% Review of prevalence of autoantibodies (general population)

Thyroid disease and thyroid autoantibodies in type 1 diabetes

The majority of individuals with clinical or sub-clinical hypo- or hyperthyroidism are antibody positive, for either thyroid peroxidase antibodies (TPOab) or Tgab, or both, with TPOabs being present more frequently. Equally, autoantibody-positive individuals are more likely to have clinical or sub-clinical thyroid disease. Lorini *et al.*,[13] quote prevalence figures of 1–3% for overt hypothyroidism in all type 1 diabetes patients and 26–42.1% in type 1 patients with diabetes and with thyroid autoantibodies. In contrast, thyroid autoantibodies can also be present in euthyroid individuals, or be absent in hypo- or hyperthyroid individuals, although this occurs less frequently.[15,32,34]

The ISPAD guidelines state that the majority of young people with a goitre and positive thyroid antibodies have Hashimoto's thyroiditis, but most are euthyroid. They further estimate that thyroid autoantibodies, particularly microsomal antibodies, occur in 20–30% of young people with diabetes, with overt hypothyroidism occurring in 1–5% and compensated hypothyroidism (asymptomatic, with normal thyroxine levels and modestly raised TSH) in 1–10%.[10]

Appendix 2 shows the prevalence of antibodies in children with diabetes together with the frequency of sub-clinical and clinical hypo- and hyperthyroidism.

It can be seen that where thyroid disease is measured in both antibody-positive and -negative groups, overall it occurs more frequently in the antibody-positive groups.[32,35,36]

The predictive value of thyroid autoantibodies as an indicator of thyroid disease is, however, low. *Table 8* shows the test characteristics of antibody tests including the positive predictive value (PPV, based on study prevalence), which is the likelihood that individuals with a positive test result actually have the disease. The PPV values are low relative to the thyroid function test and range from 0 to 0.25.

It should be noted that the studies from which these data were taken are very heterogeneous in terms of sample sizes, population, follow-up times (if any) and measurement techniques. Nonetheless, the PPVs are all very low, indicating that antibody testing is of little value for identifying individuals with thyroid disease.

Lorini and colleagues[13] state that antibody positivity can be used to identify symptomless patients with Hashimoto's (autoimmune) thyroiditis, but that the predictive value of overt dysfunction is low. MacCuish[8] states that the presence of circulating autoantibodies cannot be used to predict imminent onset of clinical thyroid disease, although it can show susceptibility.

It is argued that testing for autoantibody positivity should be carried out to characterise the risk of developing thyroid dysfunction and the need for future thyroid testing (using a TFT), whilst a TFT (measurement of TSH levels) should be carried out to identify actual thyroid dysfunction.[23]

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TABLE 8 *Thyroid antibody test characteristics*[a]

Study	Sensitivity	Specificity	PPV	NPV
Court and Parkin, 1982[35]	0.75	0.89	0.18	0.99
Gilani *et al.*, 1984[37]	1	0.87	0.22	1
Menon *et al.*, 2001[38]	1	0.47	0.05	1
Sanchez-Lugo, 1991[39]	1	0.86	0.1	1
Wong 1994[40]	0	0.97	0	1
Darendeliler *et al.*, 1994[36]	0.75	0.85	0.25	0.98
McKenna *et al.*, 1990[23]	0.5	0.84	0.13	0.97
Hansen *et al.*, 1999[32]				
Sub-clinical and overt hypothyroidism	0.6	0.14	0.18	0.98
Overt hypothyroidism	0.67	0.15	0.12	0.99

[a] All parameters calculated from raw data in studies, except McKenna *et al.*[23] where data were presented in this form.

However, there is a lack of data on progression rates to overt disease for asymptomatic antibody-positive individuals or those with biochemical thyroid dysfunction, and it is therefore difficult to estimate the predictive value of either autoantibody positivity or abnormal TSH levels over the long term. The study by Lorini and colleagues[13] shows that 20% of antibody-positive individuals developed overt thyroid disease over a 0–10-year follow-up period. In the study by Radetti and colleagues[33] 36% of antibody-positive individuals had sub-clinical (32.7%) or overt (3.6%) thyroid disease; a further 14.5% developed sub-clinical thyroid disease over 1 year of follow-up. Finally, the study by Riley and colleagues[16] shows that 38.5% of antibody-positive individuals either had or developed hypothyroidism – 3.4% before the onset of diabetes, 8.5% within the first year and 26.5% between 1 and 29 years after onset of diabetes (hypothyroidism is classified here as elevated TSH or low T4 level). Details of the studies are given in Appendix 2.

Equally, there appears to be no association between the extent of antibody positivity (i.e. higher levels) and an increasing likelihood of overt disease. In the study by Radetti and colleagues,[33] which evaluated 1419 children, it was not possible to determine a predictive pattern of disease owing to the variability of antibody levels before diagnosis and at onset of disease. The study by Hansen and colleagues[32] also shows no association between level of antibody positivity and overt or sub-clinical disease. Antibody levels tend to fluctuate in untreated and treated patients.[13,33]

The Whickham survey cohort,[31] which assessed the risk of thyroid disorders in the general population, showed that the annual risk of developing hypothyroidism was 4% in women who had raised TSH levels and were antibody positive, 3% for women who had raised serum levels only and 2% for women who were antibody positive only. Therefore, the measurement of both parameters would be best for estimating the risk. It is not known whether the differences in annual risks would be similar for patients with diabetes. No data were found regarding similar risk factors in children with diabetes.

It can be concluded that autoantibodies are a marker of the likelihood of developing thyroid disease, but are of low predictive value. Similarly, sub-clinical disease identified through using a TFT test (with or without antibodies present) appears not to be a reliable marker of whether an individual will develop overt thyroid disease. At the same time, the TFT is a useful tool for uncovering already existing, symptomatic or asymptomatic thyroid disease in children with diabetes.

Although there is a 'latent period' where there are raised autoantibodies or the patient has abnormal TFTs but is euthyroid, the natural history of such conditions is such that progression to clinical disease does not always occur.

Current practice in childhood diabetes in the UK

The ISPAD guidelines recommend regular clinical examination of the thyroid gland in young people with diabetes for the detection of goitre. Thyroid function and thyroid antibody tests should be performed as a baseline or to uncover asymptomatic thyroid disease. Repeat TFTs should then be carried out if a child with diabetes

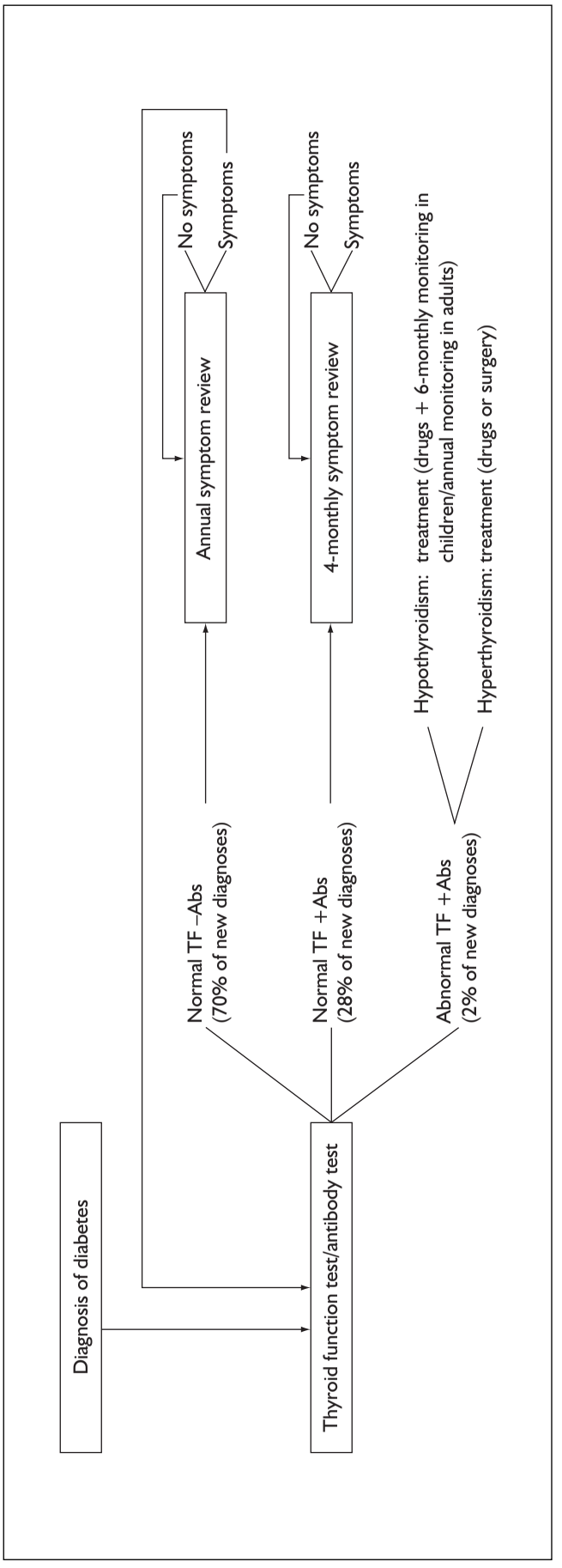

FIGURE 1 *Thyroid disease in type 1 diabetes in childhood: possible patient pathways*

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develops a goitre or has slow growth velocity, symptoms suggestive of thyroid disease or high titres of thyroid antibodies.[10]

Our survey confirmed that many centres repeat the TFTs as part of an annual review, and screening shortly after diagnosis with both TFT and antibodies to characterise the risk of future thyroid dysfunction and the need for future testing has been advocated. Possible patient pathways based on the practice of one centre (with estimates of test results at diagnosis) are described in *Figure 1*.

Autoantibody tests for screening for thyroid disease in childhood

If we match the evidence about autoantibody tests for thyroid disease above against the NSC criteria[9] for establishing a screening programme (see *Box 1* in Chapter 2), we see that several key criteria are not met.

1.4 There should be a simple, safe, precise and validated screening test.
The predictive value of antibodies in diagnosing thyroid disease is low relative to thyroid function tests (see the section 'Thyroid disease and thyroid autoantibodies in type 1 diabetes', p. 11). Similarly, the value of antibodies in predicting potential progression to thyroid disease is uncertain. Given that definitive diagnosis requires a TFT that is no more uncomfortable or unacceptable than an autoantibody test, there is little value in these tests as a screening test

- Conclusion: Criterion not met.

1.7 There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
There is currently no consensus on further test strategies in antibody-positive individuals (see *Table 5*). A decision to treat would not be made on the basis of the antibody test alone, but would depend on the results of an additional thyroid function test.

- Conclusion: Criterion not met.

1.14 The opportunity cost of the screening programme should be economically balanced in relation to expenditure on medical care as a whole.
As the definitive test is cheap and equally acceptable, the extra expenditure on autoantibody screening adds negligible incremental benefit for the extra cost.

- Conclusion: Criterion not met.

Secondary research required

The poor predictive value of autoantibody tests relative to TFTs appears to rule out their use as a screening test. A systematic review confined to the child population with diabetes could provide further confirmatory evidence on the test characteristics of thyroid autoantibody tests relative to TFTs as the reference standard for identification of thyroid disease requiring treatment. Sufficient evidence has been presented here, however, to indicate that thyroid autoantibody tests are unlikely to be cost-effective for screening purposes. While thyroid autoantibody tests could be considered as a tool for risk assessment used to determine the frequency of thyroid function testing, rather than as a screening test, the poor predictive value of autoantibody tests will also limit their usefulness in risk stratification. This could usefully be quantified in a decision-analytic model.

Chapter 4

Systematic review of autoantibody tests for coeliac disease

Background

Coeliac disease

Coeliac disease is an inflammatory disease of the upper small intestine that results in malabsorption and other consequent systemic problems. In individuals with coeliac disease, eating gluten-containing foods induces characteristic inflammatory changes in the mucosa of the small bowel, which impairs the absorption of nutrients from food. Proteins in the gluten of wheat (gliadin), barley (secalin) and rye (hordein) trigger coeliac disease, and although a recent report has identified a specific gliadin peptide that triggers an immune response,[41] the precise mechanism is unknown.[42]

Presentation and prognosis

In infancy, coeliac disease can present in a miserable baby with diarrhoea with pale, bulky and offensive-smelling stools, abdominal distension, lack of appetite, failure to thrive and muscle wasting, typically after the introduction of gluten-containing solids to the diet. Over 2 years of age, this presentation is rare and more typical symptoms include diarrhoea or constipation, anaemia, failure to thrive, loss of appetite and short stature. Further symptoms are mouth ulcers, weight loss, abdominal pain and bloating, fatigue, infertility and osteoporosis. While patients may be acutely ill, many have chronic and non-specific symptoms and neurological presentations have also been described. Before the introduction of treatment with a gluten-free diet, published mortality rates were between 10 and 30%,[43] but prognosis is now hugely improved: a relative survival ratio of 0.98 has recently been reported.[44] In the longer term, coeliac disease carries an increased risk of malignancy, particularly small bowel lymphoma.[45] The increase in risk appears to be related to malabsorption and non-compliance with a gluten-free diet.[44]

Although at one time coeliac disease was thought to be primarily a childhood condition, this is no longer thought to be the case. Feighery reports that the peak age for incidence of coeliac disease is in the fifth decade.[45] Coeliac Society statistics indicate that most UK patients are diagnosed between the ages of 30 and 45 years (http://www.coeliac.co.uk/). Moreover, coeliac disease in childhood, particularly the classical presentation with diarrhoea in infancy, has become more uncommon. The reasons for this remain controversial. The male-to-female ratio is usually reported as around 1:2.[43]

There is a genetic susceptibility to coeliac disease that also predisposes individuals to type 1 diabetes.[45,46] Histocompatibility antigens (HLA) types -DR3 and -DQ2 are associated both with coeliac disease and diabetes.[43,47] The genetics of both coeliac disease and diabetes are complex and the factors triggering gluten sensitivity are unknown.

Dermatitis herpetiformis involves an itchy blistering skin rash and IgA deposits in normal skin, with similar intestinal changes to those found in coeliac disease. It also responds to a gluten-free diet.

Diagnosis

Diagnostic criteria for children were revised by the European Society for Paediatric Gastroenterology (ESPGAN) in 1990 and represent the reference standard for the diagnosis of coeliac disease.[48] Diagnosis in children requires small bowel mucosal atrophy on biopsy and improvement on a gluten-free diet. In coeliac disease, biopsy specimens show villous atrophy (flattening of the villi, the projections from the mucosal wall) with crypt hyperplasia, while earlier in the disease process there is lymphocyte proliferation into the epithelium and lamina propria (layers of the bowel wall beneath the mucosa). Biopsy is now usually carried out in the course of an endoscopy but sometimes a special capsule is used.

Blood tests for serum antibodies are used in order to decide whether a biopsy procedure is indicated. The tests available are for IgA and IgG gliadin (AGA) (ELISA), IgA reticulin (ARA) (indirect immunofluorescence with rat tissue substrate) and IgA endomysial antibodies (EMA) (monkey oesophagus or human umbilical cord as substrate).

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Some people have reported that IgA AGA tests are sensitive (75–95%) but have relatively poor specificity (90–95%) compared with EMA tests.[43,47] Coeliac disease is associated with IgA deficiency; therefore, patients with both coeliac disease and IgA deficiency will not be detected by serological tests based on IgA,[45] so total IgA tests are often combined with EMA tests. The enzyme tissue transglutaminase is a sensitive and specific target of autoantibodies and an ELISA test for IgA tissue transglutaminase antibodies (TTG) has recently been introduced[45] with reported sensitivity ranging from 85 to 100% and specificity from 90 to 100%.[49] If these figures are correct, these may prove to be cheaper and less labour intensive than EMA tests. One study in children has found no difference in the test characteristics of TTG and EMA tests,[49] while another study in a type 1 diabetes population suggested that TTG was more sensitive than EMA testing.[50] Tests become negative following the introduction of a gluten-free diet. Serum antibody tests have been used as screening tests for coeliac disease both in the general population and in at-risk groups.

Treatment

Coeliac disease is treated by a lifelong gluten-free diet, and in most patients symptoms and gut pathology resolve. In the UK, selected gluten-free foods are prescribable within the NHS.

Prevalence

Traditionally coeliac disease was thought to have a prevalence of around 1 in 1000 population.[42,45] There were, however, wide variations in reported prevalence with higher prevalences in some European countries but a low prevalence of 1 in 6000 in the USA. With the introduction of new autoantibody tests, population screening studies have found prevalences as high as 1 in 200, and a study of blood donors in the USA found a prevalence of 1 in 250.[42,51]

As people with coeliac disease are identified through screening, so our understanding of the clinical spectrum of the disease has changed and it is now thought that coeliac disease may have been under-diagnosed. A coeliac disease 'iceberg' has been described comprising not only clinical coeliac disease, but also silent undiagnosed coeliac disease and what has been described as latent coeliac disease, with serological changes which in some cases have been documented to precede histological changes.[42,47]

A screening study of a birth cohort of 2.5-year-old Swedish children using IgA AGA and EMA tests with biopsy of positive children found a prevalence of 1.2%, in a cohort where 0.7% had already been identified as having coeliac disease.[52] It has been estimated that case finding by carrying out serological screening of patients presenting with symptoms described in the literature as associated with coeliac disease could find in excess of 30 new cases in a general practice of 6000 patients.[53] However, the costs and benefits of screening for coeliac disease have not been evaluated.[42]

Coeliac disease in type 1 diabetes

An increased prevalence of coeliac disease has been consistently reported in type 1 diabetes in both adults and children[47] and autoimmune thyroid diseases. Screening studies in children have generally reported prevalences of 1–6%, with a prevalence of 16% in Algeria (coeliac disease is common in children from the Sahara). In adults the reported prevalence ranged from 2 to 8%.[46] The high prevalence probably reflects the genetic predisposition of those with type 1 diabetes for coeliac disease, as in a further study a prevalence of 5.7% in type 1 patients with diabetes was found, compared with 1.9% among their first-degree relatives, with a lower prevalence in healthy controls.[54]

The high prevalences reported are based on detection using autoantibody screening tests, and scrutiny of the studies showed only 15% of coeliac patients had been diagnosed prior to screening. Thus many patients have not presented symptomatically, although they were probably at risk of long-term complications including malignancy and osteoporosis and, in children, growth failure.[46] Such patients have been reported to experience increased well-being, retrospectively recognising symptoms after starting a gluten-free diet, although a placebo effect may be involved. Reports of the effect of a gluten-free diet in improving glycaemic control in patients with diabetes diagnosed with coeliac disease have been inconsistent, reporting either no effect or improvement.[46,47] The benefits and costs of the diagnosis and treatment of coeliac disease in asymptomatic patients have not been adequately quantified,[46] although one study estimated a cost per case detected of £950 for the screening of newly diagnosed type 1 patients with diabetes.[47]

Current practice in childhood diabetes in the UK

The ISPAD guidelines for juvenile diabetes state that the need for and frequency of screening tests is controversial, but recommends that the possibility of coeliac disease should be considered

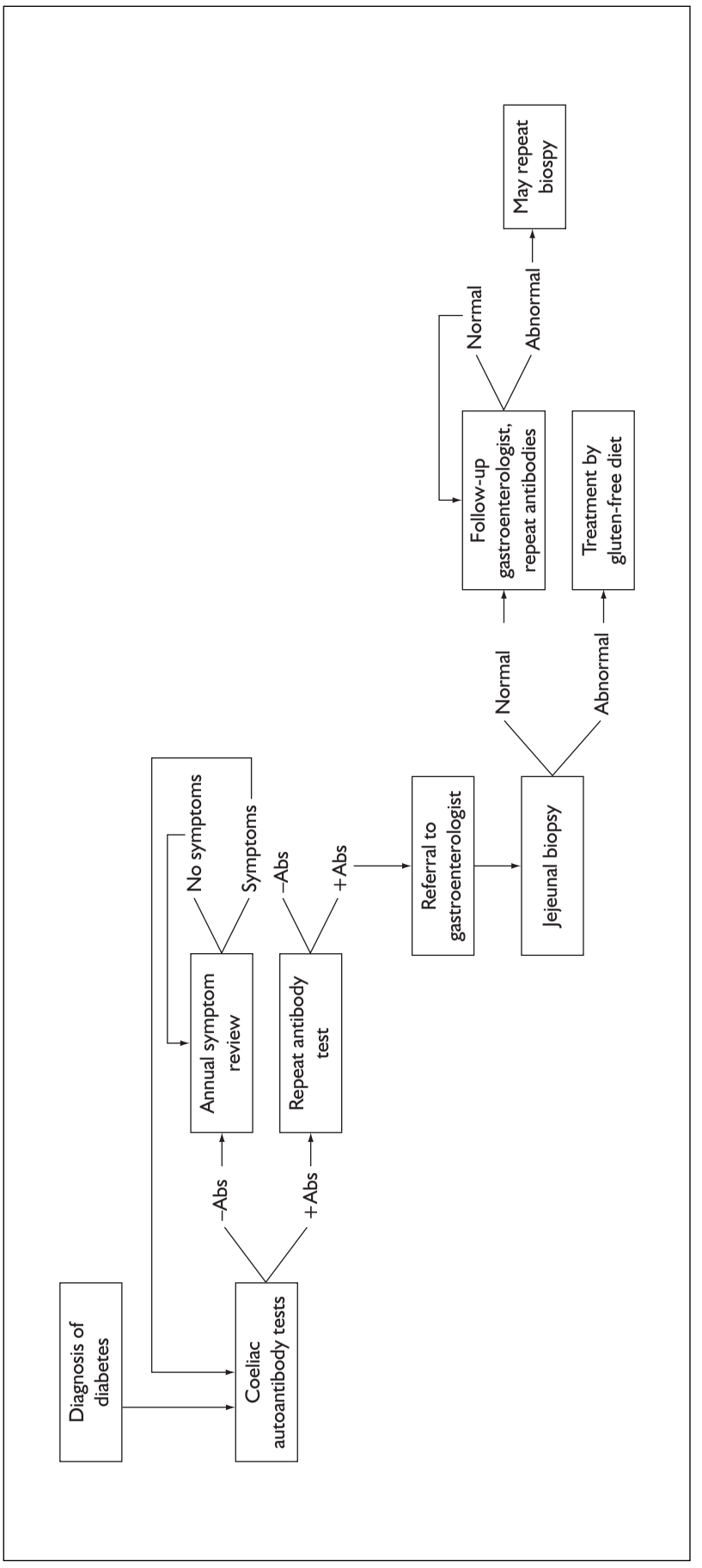

FIGURE 2 *Coeliac disease and childhood diabetes: possible patient pathways*

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in patients with gastrointestinal symptoms, poor growth or anaemia and that immunological screening should be considered around the time of diagnosis. Possible patient pathways (assuming that children are screened at diagnosis and subsequently tested only if they become symptomatic) are shown in *Figure 2*.

Our survey has shown that current practice varies between centres. It is apparent that autoantibody tests for coeliac disease are used in two main ways in the child population with diabetes:

- in a symptomatic child, as diagnostic tests to inform the decision on whether to proceed to jejunal biopsy
- in asymptomatic children, as a screening test, with the aim of identifying and treating coeliac disease at an early stage, thus preventing the appearance of symptomatic disease and the longer term harm that might result.

Autoantibody tests for coeliac disease in the childhood population with diabetes

When the NSC criteria[9] for screening (see *Box 1* in Chapter 2) were considered, using autoantibodies for screening for coeliac disease was not ruled out, as there are no clearly breached criteria as there are in thyroid disease (the definitive diagnosis in coeliac disease is endoscopy and biopsy – which is more invasive, more expensive and less acceptable than a blood test), although there are areas of uncertainty.

Rationale for review

Following the background scoping stage, the review team identified a number of areas where systematic reviews were required. These included the prognosis and outcomes of coeliac disease, with particular reference to silent disease and antibody screening tests and screening strategies for coeliac disease. It was not possible to address all questions in the report.

The report commissioned by the National Health Service Research and Development (NHS R&D) programme is a systematic review of test accuracy of antibody screening tests for coeliac disease, which is presented here. In addition, a decision analytic model of antibody testing for coeliac disease in childhood diabetes is presented. Cost data to use with the decision-analytic framework have been assembled, and the analysis is informed by a survey of current practice of paediatric endocrinologists regarding other autoimmune diseases and autoantibody testing in children and adolescents with diabetes.

Methods for reviewing effectiveness

Review question

What are the test characteristics of individual antibody screening tests and of combinations of tests for the detection of coeliac disease when compared with the reference standard of small bowel biopsy?

Search strategy

A search strategy was developed with the aim of detecting any study investigating individual or combinations of autoantibody tests for coeliac disease relative to the reference standard of small bowel biopsy. There were no restrictions in the search strategy regarding study design or language.

MEDLINE (1966–March 2002), EMBASE (1980–March 2002) and the Cochrane Library (2001, version 4) were searched using MeSH subject headings (coeliac disease/) and keywords, which encompass coeliac disease (for example, 'coeliac disease', 'gluten enteropathy' and 'coeliac sprue'), autoantibody testing (for example, 'gliadin', 'antigliadin') and a search filter for diagnostic tests (including such terms as 'sensitivity' and 'specificity'). The full search strategy is listed in Appendix 3.

Citation lists of included studies were scanned for additional studies, and relevant professional and patient websites (for example, that of the Coeliac Society) were reviewed.

In order to identify ongoing or unpublished studies, a letter requesting information about relevant studies was sent to all UK and international immunology laboratories participating in the UK National External Quality Assessment Service (NEQAS) via their mailing list. Manufacturers of test kits known to be used in the UK were also contacted (contact list provided by NEQAS Immunology).

Systematic reviews were sought using search strategies based on that developed by the Aggressive Research Intelligence Facility (ARIF; available on request) and by the Centre for Reviews and Dissemination. Reviews were sought

in Clinical Evidence, MEDLINE, health technology assessment databases, in-house databases and the Cochrane Library. No previous systematic reviews on test accuracy of antibody tests for coeliac disease were identified.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

- Study design: cohorts (positive cases and disease free from same population) or controlled trials of screening.
- Population: symptomatic patient populations, or populations at a higher risk of developing coeliac disease (for example patients with type 1 diabetes or first-degree relatives of individuals with coeliac disease).
- Screening test: individual or combinations of autoantibody tests (IgA and/or IgG anti-gliadin, anti-reticulin, anti-endomysial or anti-tissue transglutaminase antibodies).
- Reference standard: mucosal histology following small bowel biopsy.
- Outcome: sensitivity and specificity must be reported or calculable from raw data.

The exclusion criteria were as follows:

- Studies that do not independently evaluate the tests against the reference standard.
- Studies where the patient population has been treated for coeliac disease with a gluten-free diet at the time of testing.
- Studies with 'disease controls' and 'healthy controls' that did not come from the same patient population as the coeliac disease cases.

Titles and abstracts were reviewed independently by two reviewers, with retrieval of papers where there was disagreement. All retrieved papers were also reviewed independently by two reviewers, with differences of opinion resolved by discussion.

Data extraction strategy

The study design of all papers was reviewed and abstracted by at least two reviewers.

Data were extracted by one reviewer on to piloted data abstraction forms. Owing to the high volume of included studies (n = 76), double-data extraction was not performed at this stage. A subset of higher quality studies (n = 18) were subsequently double-data extracted with involvement of a third reviewer to resolve any discrepancies.

Foreign language publications were screened using English abstracts if available. French, German, Italian (with the aid of a dictionary) and Spanish papers were read by members of the review team. A translation of relevant sections was obtained for a Hungarian paper, which was subsequently excluded. A translation of a Portuguese paper could not be obtained at the time of completion of the report.

Data were extracted in terms of population characteristics and setting, study quality, characteristics of reference test and antibody test(s) and results (sensitivity and specificity and/or raw data, i.e. true and false positives and true and false negatives). Where a relevant sub-sample within the study was described (where patients had both the reference and antibody test), data were extracted for this sub-sample only.

Quality assessment strategy

The most suitable study design for determining test accuracy is one where a single cohort of consecutively or randomly recruited patients with unknown disease status is subjected independently and blindly to both the reference test and the test under evaluation.[55,56] Selection of patients on the basis of known disease or test status or according to other pre-selection criteria can lead to bias in the estimation of test accuracy.[56]

Studies were excluded if the decision to biopsy was influenced by the results of the antibody test, as there may be reluctance to biopsy those individuals with a negative test result resulting in verification bias.[57]

Studies were also excluded if any patients had been treated, as treatment following one test could influence the result of a subsequent test, with patients being classified as false positive or negative depending on whether the reference test or antibody test had been performed first.[57]

Recruiting patients according to disease status, as in a case-control study, may bias the results as detection rates can vary according to the severity of the disease. Co-morbidity may also influence detection rates, which is why choosing healthy controls will bias the specificity.[55] Case–control studies were therefore also excluded.

Both tests should be performed blindly (i.e. without knowledge of the tests result of either test), as the interpretation of a test result could otherwise be influenced – particularly if the result is borderline – resulting in an overestimation of test accuracy. This is particularly relevant if indirect immunofluorescence is used, as the interpretation relies on the operator's assessment,

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whereas an ELISA result is likely to be more objective as a number or unit is derived, which is compared with the threshold.

Selection of patients should occur randomly or consecutively in order to avoid selection bias. Selection bias can take the form of spectrum bias when the study population is not representative of the spectrum of disease that would occur in the screening population in practice. A degree of selection bias is likely in the studies reviewed here, as the more symptomatic patients are more likely to be referred for a biopsy.

The selection of a single cohort, at least as regards selection of subjects from a single patient population (as far as could be determined from the paper), with biopsy verification of both positive and negative antibody test results was an inclusion criterion.

A suitable checklist for the quality evaluation of studies was used (*Table 9*).[56] It included assessment of the representative nature of the sample, whether there were explicit exclusion criteria, and took account of the potential sources of bias described above.[55]

Methods of analysis and synthesis

Study characteristics including patient details, factors relating to quality and test characteristics and outcomes were tabulated and described narratively. Summary statistics of diagnostic accuracy, that is, sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs) were calculated (or checked if stated) for all studies. As the majority of studies did not report confidence intervals, these were calculated where possible from raw data using the method of Wilson.[58]

Sensitivities and specificities

Sensitivities and specificities were plotted, with confidence intervals, in order to permit graphical assessment.

SROC curves

Sensitivities and false-positive rates of individual antibody tests were plotted as summary receiver operating characteristics (SROC) curves in order to allow a graphical assessment of test performance, with tests showing a high sensitivity and specificity clustering in the top left-hand corner of the SROC space. The SROC curves were derived using the unweighted regression method of Littenberg and

TABLE 9 *Study quality assessment criteria and interpretation*

Standard	Interpretation
Was the selection method described?	Was the patient sample random or consecutive, or otherwise clearly described (for example, all patients attending a clinic in a given time period)?
Was the antibody test measured independently (blind) of the reference test?	Did the antibody test precede the biopsy, or were there other descriptions of adequate blinding of observers?
Was the reference test measured independently (blind) of the antibody test?	Did the biopsy precede the antibody test, or were there other descriptions of adequate blinding of observers?
Was the choice of patients assessed by the reference test independent of the antibody test results?	Studies/patient groups where biopsy was offered on the basis of positive tests results were excluded
Was the antibody test measured independently of all other clinical information?	Was there any selection bias, for example, had referrals been made on the basis of antibody testing in the community setting?
	Was it possible to tell whether there was any selection bias regarding the included patients?
Was the reference standard and antibody measured before any interventions were started?	Were the patients on a gluten-containing diet when sera were taken and biopsies carried out?
	Was it possible to tell what the patients' diet had been at that stage?
	Patient groups on gluten-free diets at the time of testing and biopsy were excluded

Moses.[59] The 95% confidence intervals for the SROC curved were calculated from the 95% confidence intervals of the slope (b) and the intercept (a) of the logistic regression line. If the sensitivity or specificity were either zero or one, 0.5 was added to all values in the 2×2 table (numbers of true positives, false positives, true negatives and false negatives). The area under the SROC curve was calculated to give an indication of the overall diagnostic test performance of the individual antibody tests, with values close to one indicating a good test performance. The Q value was calculated, which signifies the point at which sensitivity and specificity are equal, that is, the point at which the test has an equal chance of correctly identifying an individual with or without the disease.

The 95% confidence interval for the slope (b) of the logistic regression line for all collections of studies spanned zero, indicating that b did not differ significantly from zero. The curves presented in the section 'Assessment of effectiveness' (p. 30) employed the best estimate for b in each case, resulting in asymmetric curves. The 95% confidence intervals on the SROC curves were also derived using the best estimate for b. The values of b are sufficiently small that they have a negligible impact on the value for the area under the curve or its 95% confidence interval or shape.

The values used in the decision-analytic model were the Q values (overall best test performance with equal sensitivity and specificity) for individual antibody tests. In addition, the sensitivity was fixed at 0.99, and the corresponding specificity (with confidence intervals) calculated from the SROC curve. Equally, the specificity was fixed at 0.99, and the corresponding sensitivity (with confidence intervals) was calculated from the SROC curve.

When there were four or fewer studies that investigated a particular antibody test, the results are shown in a SROC plot without a curve being drawn.

The following selection criteria applied to the inclusion of study results in the SROC plots: where a range of thresholds for positivity were used in one study, the results reflecting the manufacturer's threshold were used;[60] where a range of in-house thresholds were used, the results using the middle threshold was used;[61] where different methods were used in one study, those results obtained using ELISA were used, as this is in keeping with the majority of studies;[62] where sensitivity and specificity could not be calculated from raw data, results were excluded,[63–65] where studies used a range of gliadin preparations, the results using commercial gliadin were used;[66] where sensitivity could not be calculated, as there were no cases to be detected, the results were excluded;[67] the study by Meini and colleagues[68] was excluded, as the population consisted of IgA-deficient children only.[69]

Normal quantile plots

Normal quantile plots were calculated using MetaWin version 2[70] in order to explore the distribution of data, whether there were any population effects and whether there was any evidence of publication bias.[71] It should be noted that on the graphs the effect size corresponds to lnDOR.

Pooled likelihood ratios

The likelihood ratios describe how many times a person with disease is more likely to receive a particular test result than a person without the disease. Positive likelihood ratios >10 or negative likelihood ratios <0.1 are thought to provide strong diagnostic evidence (depending on pre-test probability). As the regression analysis did not identify any threshold effects, data were pooled using the DerSimonian Laird method with a random effects model using RevMan 4.1 software. Graphs were drawn using SigmaPlot 8 (SSPS Inc.).

Subgroup analyses

Subgroup analyses were carried out according to study quality. Those studies with well described selection methods were analysed separately, where there were sufficient data.

Quantity and quality of the research available

Quantity of evidence available

The database searches yielded 614 references. Twelve additional potentially relevant references were identified through contacting the NEQAS laboratories and through citation searching; 456 studies were excluded, as they were clearly not relevant. The remaining 170 full text papers were reviewed independently by the two reviewers.

Ninety-four of these papers were excluded for the following reasons (some studies fall into more than one category – the initial reason for exclusion is stated here):

- Reference test (biopsy) performed on the basis of an antibody test result (n = 18).

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- Reviewers were unable to determine which (subsample of) patients had the reference test (for example, out of a sample containing untreated, treated or challenged coeliac disease patients and various controls), or how the selection for the reference test occurred (n = 19).
- Case-control study (control group not biopsied or selected for certain characteristics) (n = 24).
- Non-primary study (review, comment, letter, etc.) (n = 12).
- Other reasons (including case-series, sensitivity/specificity not calculable, pre-selection of groups according to certain test or disease characteristics, selection unclear, tissue culture instead of serum samples) (n = 21).

The remaining 76 studies were mostly poorly described in terms of study design (see the section 'IgG AGA (anti-gliadin) antibodies', p. 40) but were initially included on the basis that they either appeared to refer to patient cohorts (in some cases the cohort was a sub-sample of a larger patient group) or did not contain sufficient information to be ruled out as a cohort, and the sensitivities and specificities were stated or calculable.

Eighteen of these 76 studies were clearly described as cohorts with explicit selection methods. These studies have been described, and the data analysed separately in a sensitivity analysis.

No controlled trials investigating diagnostic test/treatment strategies were identified.

The inclusion and exclusion process is shown in the flow diagram below (*Figure 3*).

Main study characteristics

Patient characteristics

The total patient population consisted of 8053 patients (mean 106 per study, range 10–441 patients). Patients were children, adults or a mixture of both, across all ages (total age range 2 months to 88 years). There were 44 studies investigating children (up to 18 years), 22 studies investigating both adults and children and four adult studies. Six studies give no details of patient age. Details of age are in some studies stated for cases or controls only. There was a mixture of male and female patients, with overall slightly more female patients (53.6% female, 46.4% male based on 23/76 studies which give details on sex).

Patients are either symptomatic or at a higher risk of developing coeliac disease. Symptoms/characteristics reported in the studies are gastrointestinal (11 studies), short stature (four

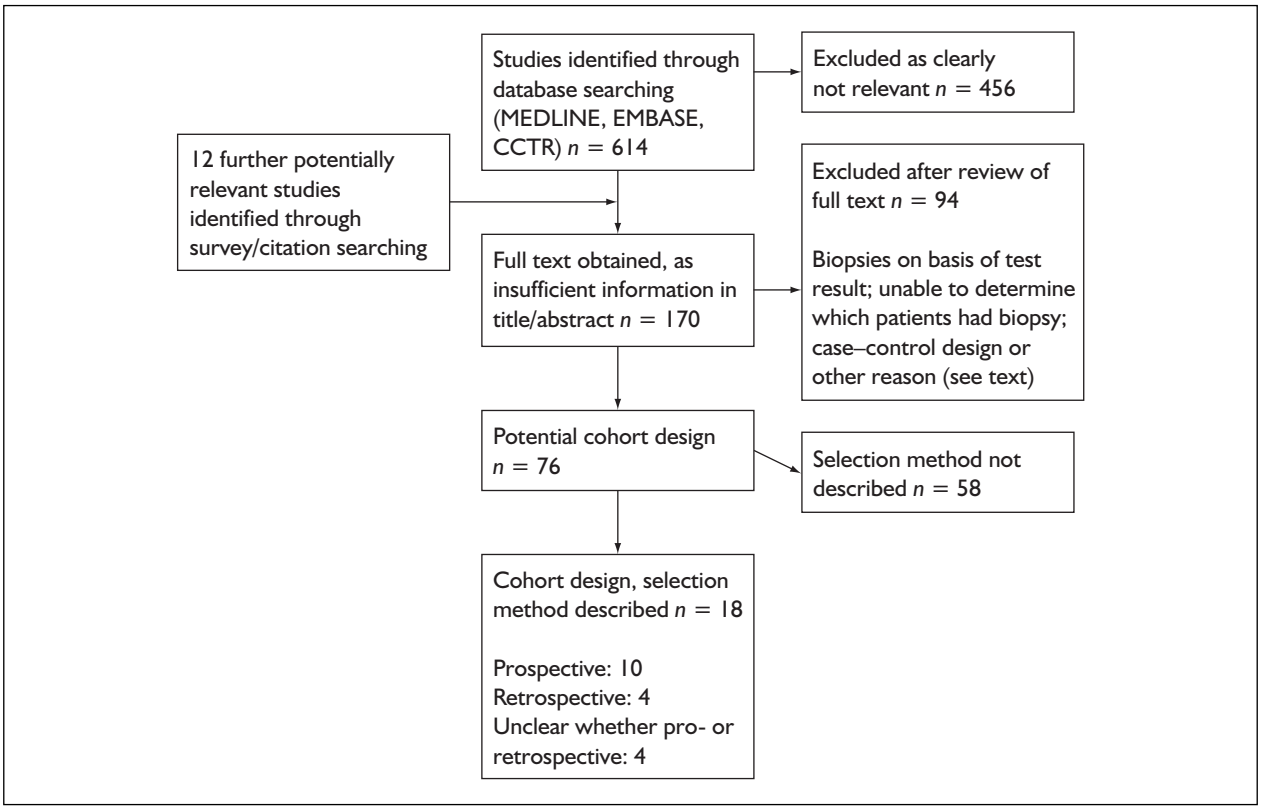

FIGURE 3 *Inclusion and exclusion of studies*

studies), symptoms suggestive of coeliac disease (14 studies), family history of coeliac disease (two studies), patients with diabetes (two studies), IgA-deficient children with recurrent respiratory problems (one study), adults with primary biliary cirrhosis (one study), non-specific symptoms (one study) and a mixture of gastrointestinal symptoms, short stature, failure to thrive, anaemia, tiredness, family history, etc. (31 studies). Nine studies give no details of symptoms.

Setting

All studies are set in a secondary care environment (university hospital, children's hospital, gastroenterology clinics, etc.). Three studies give no details of the setting.

Reference tests

Twenty-six studies stated that the ESPGAN or revised ESPGAN criteria were used at least in part for establishing a diagnosis of coeliac disease.

Forty-three studies used a variety of different classifications, for example, subtotal or total villous atrophy, partial fulfilment of the ESPGAN criteria (for example, histology results only) or histological classification according to Marsh or Alexander, while seven studies gave no details. There are likely to be variations between studies in terms of threshold regarding normal, slightly abnormal, subtotal or total villous atrophy.

The methods of taking the biopsies varied, with 13 studies using endoscopes, 17 using capsules and 33 using both (capsules usually for children and endoscopic methods usually for adults). Two studies stated that standard paediatric suction biopsy techniques were used; 11 studies gave no details. It is unlikely that the method of taking the sample would have an influence on the interpretation of the histology.

Table 10 lists the main study characteristics for the 18 cohort studies where the selection method was described. Details of all studies can be found in Appendix 5 (main study characteristics) and Appendix 6 (details on reference standard).

Antibody tests

The majority of studies measured IgA and IgG AGA and IgA EMA, with a smaller number measuring IgA ARA, IgA TTG or others. TTG testing is a recent development with studies from 1998 onwards reporting the measurement of this antibody. ELISA is used for AGA and TTG measurements, with some variations in the type of ELISA (different in-house methods, test kits, diffusion-in-gel (DIG) ELISA, micro-ELISA, etc.), whilst indirect immunofluorescence is used for EMA determination (with monkey oesophagus or human umbilical cord as substrate). Tests use a variety of cut-off points for positivity, with threshold reported in different units (e.g. ELISA units, arbitrary units, optical density).

Table 11 lists the antibodies measured and main methods used.

Three studies look at test combinations of IgA antijejunum, IgG antijejunum, IgA antichicken desmin and IgA antihuman desmin; however, these are not likely to be relevant to clinical practice and will not be further described.

The test combinations listed in *Table 12* were reported.

Five studies investigate the effect on sensitivity and specificity of varying the threshold for positivity and two studies investigate the effect of using different antigen (gliadin) preparations.

Table 13 lists the antibodies and test methods for the 18 cohort studies where the selection method was described. Full details for all studies are listed in Appendix 8.

Quality of evidence available

There was little disagreement between reviewers in terms of excluding papers when there was evidence of the study not meeting the inclusion criteria. There were, however, problems in classifying papers where information on selection methods or study design was scant or missing. Particular difficulties arose in classifying studies that were described as 'case–control' studies by the authors or included the terms 'cases' and 'controls' in the abstract. It was initially thought that many studies with a case–control design could be excluded on the basis of the abstract, as in many of such studies the 'controls' (for example, healthy blood donor sera controls) will not have had a reference standard biopsy diagnosis. Whilst some of these were correctly described as such and could be excluded, in practice the term 'control' was often used to describe any group of patients that did not have coeliac disease, whether the patients were drawn from the same, a similar or different clinical populations, or were ascertained retrospectively or prospectively. In fact, some studies reporting 'cases' and 'controls' were a poorly described cohort, with patients being separated into cases and controls once the disease status had been determined during the course of

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TABLE 10 *Main study characteristics (well-described cohorts)*

Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where all patients had both tests)
Ascher *et al.*, 1990, Sweden[72]	Hospital, department of paediatrics	Prospective cohort, consecutive patients	Children with symptoms suggestive of CD	6 months–16.5 years (median 17 months)	130
Auricchio *et al.*, 1988, Italy/Finland/Spain (multicentre)[73]	(University) hospitals	Prospective cohort of 1st degree relatives giving informed consent	First degree relatives (adults and children) of patients with CD	Adults and children	152
Bardella *et al.*, 1991, Italy[74]	Not stated	Prospective cohort, consecutive patients	Adults and children with gastrointestinal symptoms, anaemia, tiredness or weight loss	15–69 years (median 28); 19 M, 41 F	60
Basso *et al.*, 2001, Italy[63]	University hospital, department of paediatrics	Consecutive biopsies; retrospective evaluation of sera	Children with suspected CD	1–16 years; 25 M, 47 F	72
Bode *et al.*, 1993, Denmark[75]	Hospital, paediatric department	Prospective cohort, consecutive patients	Children with gastrointestinal symptoms, failure to thrive, short stature or other symptoms	0.33–15.5 years (median 2.75 years); 117 M, 74 F	191
Bode and Gudmand-Hoyer, 1994, Denmark[76]	University Hospital, department of medical gastroenterology	Cohort (not clear if pro- or retrospective), consecutive patients	Adults with suspicion of CD	17–81 years (median age 51); 36 M, 64 F	100
Bottaro *et al.*, 1995, Italy[77]	University paediatric hospital	Retrospective cohort; all patients with biopsy 1991–1993	Children with gastrointestinal problems, short stature or anaemia	Ages range from <1 to >10 years	245
Carroccio *et al.*, 2002, Italy[78]	University hospitals	Cohort (unable to determine if pro- or retrospective); consecutive patients	Children and adults with gastrointestinal symptoms, anaemia or poor growth/weight loss	7 months–84 years; 84 M; 107 F	191
Corazza *et al.*, 1997, Italy[79] *(research letter)*	University hospital	Cohort (unable to determine if pro- or retrospective); consecutive patients	No details	No details	78

continued

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TABLE 10 *Main study characteristics (well-described cohorts) (cont'd)*

Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where all patients had both tests)
Feighery *et al.*, 1998, Ireland[80]	Gastroenterology clinic	Retrospective cohort; consecutive patients	Adults and children with gastrointestinal symptoms, anaemia, weight loss, short stature, failure to thrive or recurrent oral ulceration	Within range of 1–84 years	441
Kelly *et al.*, 1987, Ireland[81]	Children's hospital	Prospective cohort, consecutive patients	Children with symptoms suggestive of CD	9 months–15 years (median 6 years)	77
Mäki *et al.*, 1991, Finland[82]	Not stated	Prospective cohort of first-degree relatives giving consent	First-degree healthy relatives (adults and children) from coeliac families	No symptoms	122
Mantzaris *et al.*, 1995, Greece[83]	Hospital department of gastroenterology	Cohort, consecutive patients; unable to determine if pro- or retrospective	Not clearly stated	No details	129
McMillan *et al.*, 1991, UK[84]	Hospital gastroenterology clinic	Retrospective cohort, consecutive patients	Children and adults with gastrointestinal symptoms, tiredness, weight loss or short stature	26–80 years (mean 40 years); 36 M, 60 F	96
Meini *et al.*, 1996, Italy[68]	University hospital, department of paediatrics	Prospective cohort, consecutive IgA-deficient patients	IgA-deficient children referred to immunology department owing to recurrent respiratory tract infections or low IgA levels	2–15 years; 32 M, 33 F	65
Not *et al.*, 1997, Italy[85]	Paediatric clinic	Prospective cohort, consecutive patients	Children with symptoms indicative of CD, including failure to thrive and recurrent gastrointestinal problems	Within range 1–20 years	45
Russo *et al.*, 1999, Canada[86]	University hospital, paediatric gastroenterology clinic	Prospective cohort, consecutive patients	Children with suspicion of CD	7 months–18.1 years (mean 5.2 years); 63 M, 32 F	95
Vogelsang *et al.*, 1995, Austria[87]	Departments of internal medicine and paediatrics, University Hospital	Prospective cohort, consecutive patients	Children and adults with gastrointestinal symptoms, weight loss or joint/bone pain	15–79 years (median 33 years); 41 M, 61 F	102

CD, coeliac disease; M, male; F, female.

TABLE 11 *Summary of antibody tests used in studies*

Antibody	No. of studies	Methodology
IgA AGA	50	48 studies use a type of ELISA alone or in addition to other tests [37 use ELISA (also described as enzyme immunoassay, 3); 4 DIG-ELISA; 2 micro-ELISA; 1 immunofluorescence and ELISA; 1 ELISA and DIG-ELISA; 1 ELISA, DIG-ELISA and CAP; 1 indirect immunofluorescence and ELISA; 1 strip AGA test/dot immunobinding assay and ELISA; 1 fluorescent immunosorbent test, 1 no details]
IgG AGA	45	37 studies use a type of ELISA alone or in addition to other tests (28 ELISA; 2 DIG-ELISA and ELISA; 4 DIG-ELISA; 2 micro-ELISA; 2 fluorescent immunosorbent test; 4 immunofluorescence; 1 immunoassay; 1 strip AGA test/dot immunobinding assay and ELISA; 1 no details)
IgA EMA	45	All studies use indirect immunofluorescence; 26 use monkey oesophagus as a substrate, 7 use human umbilical cord and 7 use both; 4 studies have no information on substrate
IgG EMA	5	All studies use indirect immunofluorescence; 3 use monkey oesophagus as a substrate, 2 use human umbilical cord
IgA ARA	15	14 studies use indirect immunofluorescence (10 use rat liver/stomach/kidney as a substrate, 1 uses monkey oesophagus, no details on substrate for the other 3); 1 study uses ELISA
IgG ARA	6	5 studies use indirect immunofluorescence (2 use rat liver/stomach/kidney as a substrate); 1 study uses ELISA
IgA TTG	13	All studies use ELISA
IgG TTG	2	All studies use ELISA

TABLE 12 *Test combinations reported*

Test combination	No. of studies
IgA AGA or IgG AGA	9
IgA AGA and IgG AGA	5
IgA AGA and IgA EMA	3
IgA AGA or IgG EMA	1
IgA EMA and IgA ARA and IgA AGA	1
IgA AGA or IgG EMA	1
IgA TTG or IgG TTG	1
IgA AGA or IgG AGA or IgG ARA	1
IgA EMA or IgA ARA or IgA AGA	1

the study. Many studies were unclear in terms of sequence of events (were tests performed concurrently or did one test precede another?), and the selection of patients was not usually described. It was difficult to ascertain whether any selection criteria had operated prior to the inclusion of the patients into the study.

Furthermore, many studies did not calculate results appropriately, with sensitivities and specificities being calculated by combining results from various subgroups including biopsied untreated cases, biopsied treated or gluten challenged cases, biopsied and non-biopsied controls. This was the case for some studies investigating test accuracy and compliance or effects of gluten challenge simultaneously. Only studies where it was possible to calculate sensitivities and specificities on the basis of untreated biopsied patients were included.

The effect of the poor description of studies on the review process was that many full text papers had to be reviewed before a decision on inclusion or exclusion could be reached, as the abstract had referred to cases and controls or had insufficient information. Furthermore, it became evident that many full-text studies also did not contain sufficient information, which is why sensitivity analyses were subsequently carried out for a subset of studies (18/76).

These 18 studies were cohorts with a clear description of the selection method of patients (usually consecutive). Ten were prospective cohorts, four were retrospective and for four it was not possible to determine whether they were pro- or retrospective.

The description of study design of the remaining 58/76 of the initially included studies was poor. Whilst it was possible in some cases to determine

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TABLE 13 *Antibody tests (well-described cohorts)*

Author, year	Antibody tested	Method	Details of method (test kit; substrate; manufacturer)	Thresholds for positivity	Information on reproducibility
Ascher *et al.*, 1990[72]	IgA AGA	Solid-phase immunoassay (ELISA)	Pharmacia Diagnostics (Uppsala, Sweden)	>35 AU (threshold calculated to optimise PPV)	5 samples run in 8 replicates on 10 different occasions by 7 persons and variation calculated (total coefficient of variation = 8.3–11.5%)
Auricchio *et al.*, 1988[73]	IgA AGA	ELISA	In-house methods, some Pharmacia kits	Values above the 90th percentile of a healthy age-matched population	'Good correlation' between in-house and commercial tests, not verified
	IgG AGA	ELISA			
	IgA ARA	ELISA			
	IgG ARA	ELISA			
Bardella *et al.*, 1991[74]	IgA AGA	Solid-phase enzyme immunoassay (ELISA)	Pharmacia Gluten IgA EIA kit	>25 AU	None
Basso *et al.*, 2001[63]	IgA AGA	ELISA	Pharmacia & Upjohn (Sweden)	3.66 U/ml	All tests performed in duplicate
	IgG AGA	ELISA		40 U/ml	
	IgA EMA	Immunofluorescence	Eurospital		
	IgA Tissue transglutaminase	ELISA	Eurospital (Trieste, Italy); Medipan Diagnostics (Selchow, Germany); Inova Diagnostics (San Diego, CA, USA); Arnika (Milan, Italy)	5AU 40 U/ml 20 units 0 U/ml	
Bode *et al.*, 1993[75]	IgA AGA	DIG-ELISA	Described elsewhere	IgA >10.5 mm	Each serum sample analysed twice (difference never exceeded 1 mm)
	IgG AGA	DIG-ELISA		IgG >14 mm	
	IgA AGA or IgG AGA	DIG-ELISA			
	IgA AGA	DIG-ELISA		IgA ≥ 10 mm	
	IgG AGA	DIG-ELISA		IgG ≥ 13 mm	
	IgA AGA or IgG AGA	DIG-ELISA			

continued

TABLE 13 *Antibody tests (well-described cohorts) (cont'd)*

Author, year	Antibody tested	Method	Details of method (test kit; substrate; manufacturer)	Thresholds for positivity	Information on reproducibility
Bode and Gudmand-Hoyer, 1994[76]	IgA AGA	DIG-ELISA	Described elsewhere	IgA >10.5 mm (borderline 9.5 ≤ IgA ≤ 10.5 mm)	Each serum sample analysed twice (difference never exceeded 1 mm)
	IgG AGA	DIG-ELISA		IgG >14 mm (borderline 13 ≤ IgG ≤ 14 mm)	
Bottaro *et al.*, 1995[77]	IgA AGA	ELISA	IPR-Immuno Pharmacology Research (Catania, Italy)	IgA >10%	None
	IgG AGA	ELISA		IgG >25%	
Carroccio *et al.*, 2002[78]	IgA AGA	ELISA	Alpha-Gliatest, Eurospital Pharma (Trieste, Italy)	10% of reference serum = upper normal limit	None
	IgG AGA	ELISA	Alpha-Gliatest, Eurospital Pharma (Trieste, Italy)	20% of reference serum = upper normal limit	None
	IgA EMA	Indirect immunofluorescence	Monkey oesophagus; Anti-Endomisio, Eurospital Pharma (Trieste, Italy)	1 = titre positive at dilutions between 1/5 and 1/20 2 = 1/40–1/80 3 = 1/100 4 = 1/200 5 = >1/200	None
Corazza *et al.*, 1997[79]	IgA and IgG AGA combined	Micro-ELISA	Gliastick kit, Eurospital (Trieste, Italy)	Colour change on both dipstick pads (dubious result if colour change in one)	Readings repeated by 2nd observer (100% agreement)
	IgA EMA	Indirect immunofluorescence	Monkey oesophagus		
Feighery *et al.*, 1998[80]	IgA EMA	Indirect immunofluorescence	Monkey oesophagus	Staining in reticulin-type pattern	None
	IgG AGA	Immunoassay	DELFIA system	3 AU	
Kelly *et al.*, 1987[81]	IgG AGA	ELISA	In-house method	ELISA index above that of control group range	None
Mäki *et al.*, 1991[82]	IgA AGA	ELISA	Not described	0.20 ELISA units/ml	None
	IgG AGA	ELISA		0.20 ELISA units/ml	
	IgA ARA	Indirect immunofluorescence	Not described	Titre ≥ 5	

continued

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TABLE 13 *Antibody tests (well-described cohorts) (cont'd)*

Author, year	Antibody tested	Method	Details of method (test kit; substrate; manufacturer)	Thresholds for positivity	Information on reproducibility
Mantzaris *et al.*, 1995[83]	IgA EMA	Indirect immunofluorescence	Monkey oesophagus		None
McMillan *et al.*, 1991[84]	IgA AGA	Indirect immunofluorescence	Rat liver, kidney and mouse stomach sections, pretreated with aqueous solution of gliadin; Biodiagnostics UK	Titre ≥ 20	None
	IgG AGA	Indirect immunofluorescence	As above	Titre ≥ 20	
	IgA AGA	ELISA	Labmaster (Turku, Finland)	Titre ≥ 20	
	IgG AGA	ELISA	As above	Titre ≥ 20	
	IgA EMA	Indirect immunofluorescence	Monkey oesophagus; Biodiagnostics UK	Titre ≥ 20	
	IgG EMA	Indirect immunofluorescence	As above	Titre ≥ 20	
	IgA antijejunum	Indirect immunofluorescence	Sections of black-hooded rat jejunum	Titre ≥ 20	
	IgG antijejunum	Indirect immunofluorescence	As above	Titre ≥ 20	
Meini *et al.*, 1996[68]	IgA AGA	ELISA	Eurospital	≥ 25 AU/dL	None
	IgG AGA	ELISA	Eurospital	≥ 25 AU/dL	
Not *et al.*, 1997[85]	IgA EMA	Indirect immunofluorescence	EMA, Eurospital (Trieste, Italy); monkey oesophagus and human umbilical cord	Honeycomb-like fluorescence	Slides evaluated by 2 independent operators
Russo *et al.*, 1999[86]	IgA AGA	ELISA	Described elsewhere	0.25 ELISA units	Immunofluorescence sections read on two separate occasions by blinded observer (no discrepancies)
	IgG AGA	ELISA		0.30 ELISA units	
	IgA EMA	Indirect immunofluorescence	Monkey oesophagus; in-house method	Characteristic pattern	
	IgA EMA	Indirect immunofluorescence	Human umbilical cord; in-house method		
Vogelsang *et al.*, 1995[87]	IgA AGA	ELISA	No details	IgA ≥ 0.21 AU/ml	None
	IgG AGA	ELISA	No details	IgG ≥ 0.23 AU/ml	
	IgA EMA	Indirect immunofluorescence	Monkey oesophagus; Bios (Barcelona, Spain)	Comparison with positive and negative control sera	

whether recruitment of patients was prospective (n = 21) or retrospective (n = 7), for 30 studies it was not clear whether the study was conducted prospectively or retrospectively.

Regarding the other quality criteria assessed, there was little difference between the two groups of studies (chi squared test not significant for any quality criteria). It can therefore not be assumed that the overall study quality of the well-described cohorts is better than that of the other studies. *Table 14* shows the differences in quality between the two groups.

It should be noted that studies were initially retrieved on the basis that they might have a cohort design, although sufficient information may have been absent, whilst studies that had a clear description of a non-cohort study design were excluded. Thus, poorer quality studies may have been included on the basis that there was insufficient information to exclude them. It is difficult to assess how far a poor quality assessment is a reflection of poor reporting by the authors rather than poor methodological quality.

Table 15 shows the quality assessment for the 18 higher quality studies. Full details of the quality assessment for all the studies can be found in Appendix 7.

Assessment of effectiveness

ARA (anti-reticulin) antibodies

Fifteen studies reported the use of IgA ARA. *Figure 4* shows sensitivities and specificities of the included studies with 95% confidence intervals where availability of raw data allowed their calculation (n = 13). For one study,[88] calculation of the sensitivity only was possible. Full data are given in Appendix 8. There was a large amount of variation between sensitivities, with values ranging from very low (11%) to intermediate (50%) to very high (100%). There was little variation between specificities, with 9/12 studies reporting 100% specificity, and three of the remaining studies reporting above 95% specificity.

A SROC curve was calculated for IgA ARA based on 12 studies (*Figure 5*), where availability of raw data allowed calculation of sensitivities and specificities. Three studies were excluded.[64,82,88] There was no evidence that the log odds ratio was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant. The area under the curve is 0.982 (95% CI 0.958 to 0.992), indicating good test performance. Despite this high value for the area under the curve, it should be noted that if a test with a high sensitivity were required, this test would not be very informative.

Five studies reported the use of IgG ARA. A SROC plot was drawn for IgG ARA based on four studies (*Figure 6*). One further study was excluded, as there were insufficient raw data to calculate sensitivities and specificities.[88] Again, there was high variation between sensitivities, with specificity consistently high.

A normal quantile plot was also calculated for IgA ARA (*Figure 7*). It can be seen that not all data points are within the 95% confidence interval bands, suggesting that the data may not be normally distributed, which may be a reflection of the variation in sensitivities. The shape of the curve also suggests that the studies may come from different populations. There is no obvious gap in the curve, which gives no indication of publication bias.

TABLE 14 *Comparison of study quality (well-described cohorts and other studies)*

Quality criteria	Consecutive cohorts (n = 18)	Other (n = 58)
Antibody test measured independently (blindly) of reference standard	33.3% (n = 6)	25.9% (n = 15)
Reference standard measured independently (blindly) of antibody test	44.4% (n = 8)	44.8% (n = 26)
Choice of patient assessed by reference standard independent of test (clear statement)	72.2% (n = 13)	70.7% (n = 41)
Test measured independently of all other clinical information	0% (n = 0)	6.9% (n = 4)
Tests performed in untreated patients (clear statement)	88.9% (n = 16)	89.7% (n = 52)

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TABLE 15 *Quality assessment (well-described cohorts)*

Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Ascher *et al.*, 1990[72]	✓	CT	✓	✓	CT	✓	
Auricchio *et al.*, 1988[73]	✓	CT	CT	CT	CT	✓	Reference test performed in 152/170
Bardella *et al.*, 1991[74]	✓	CT	CT	✓	CT	CT	
Basso *et al.*, 2001[63]	✓	✓	CT	CT	CT	✓	Not every test performed in all patients
Bode *et al.*, 1993[75]	✓	✓	✓	✓	CT	✓	Biopsies resulted from positive tests in 4 patients
Bode and Gudmand-Hoyer, 1994[76]	✓	CT	CT	✓	CT	✓	
Bottaro *et al.*, 1995[77]	✓	CT	CT	✓	CT	✓	
Carroccio *et al.*, 2002[78]	✓	CT	CT	✓	CT	CT	
Corazza *et al.*, 1997[79] *(research letter)*	✓	✓	✓	✓	CT	✓	
Feighery *et al.*, 1998[80]	✓	CT	CT	CT	CT	✓	Patients included for whom concurrent biopsies and serology were available

continued

TABLE 15 *Quality assessment (well-described cohorts) (Cont'd)*

Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Kelly *et al.*, 1987[81]	✓	CT	✓	✓	CT	✓	
Mäki *et al.*, 1991[82]	✓	CT	CT	CT	CT (for children)	✓	Antibody test in all, 122/148 biopsied
Mantzaris *et al.*, 1995[83]	✓	CT	✓	CT	CT	✓	
McMillan *et al.*, 1991[84]	✓	✓	✓	✓	CT	✓	
Meini *et al.*, 1996[68]	✓	✓	✓	✓	CT	✓	Reference test performed in all, antibody test in 60/65
Not *et al.*, 1997[85]	✓	✓	CT	✓	CT	✓	
Russo *et al.*, 1999[86]	✓	CT	✓	✓	CT	✓	
Vogelsang *et al.*, 1995[87]	✓	CT	CT	✓	CT	✓	

CT, cannot tell.

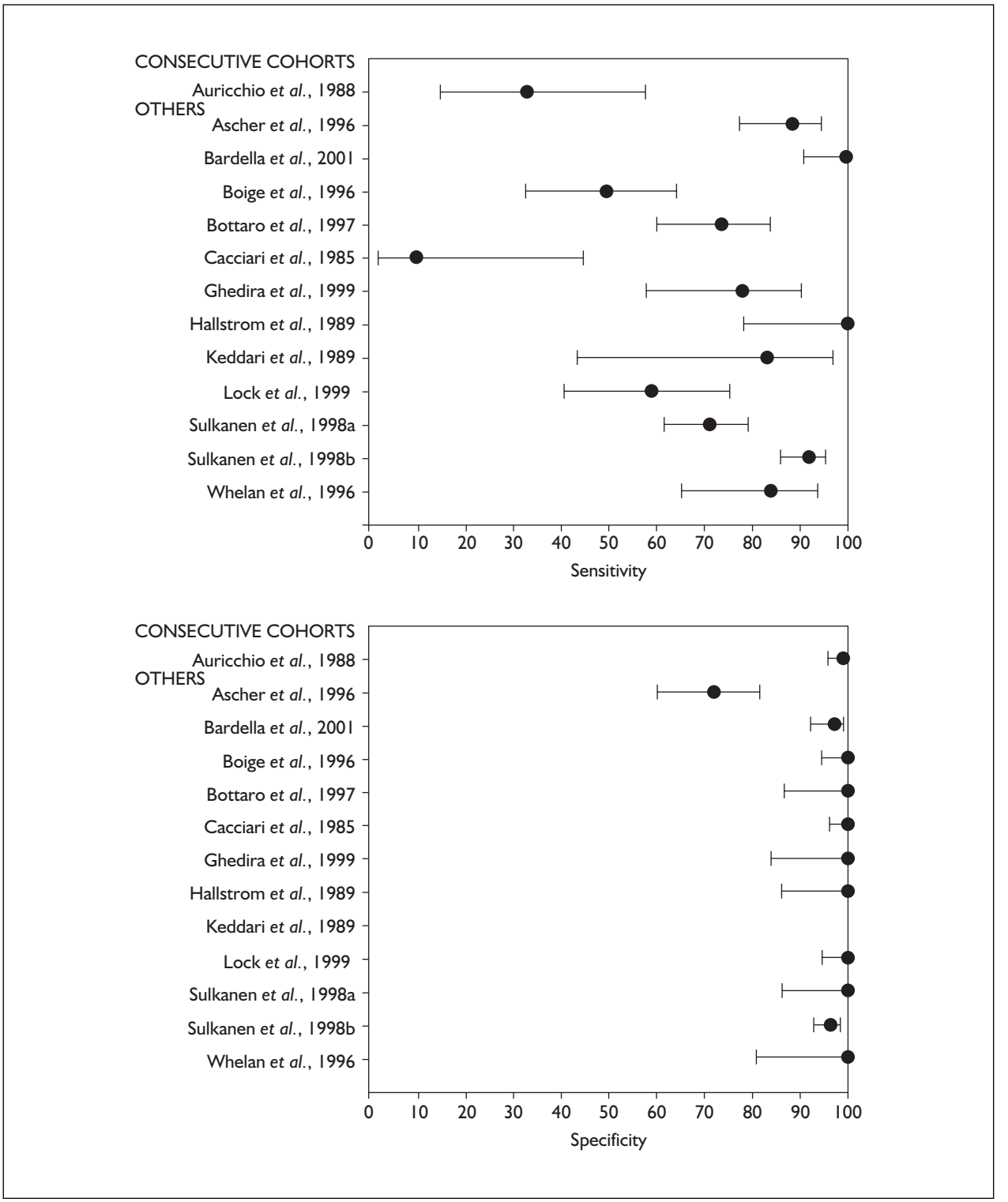

FIGURE 4 *IgA ARA sensitivity and specificity (with 95% confidence intervals)*

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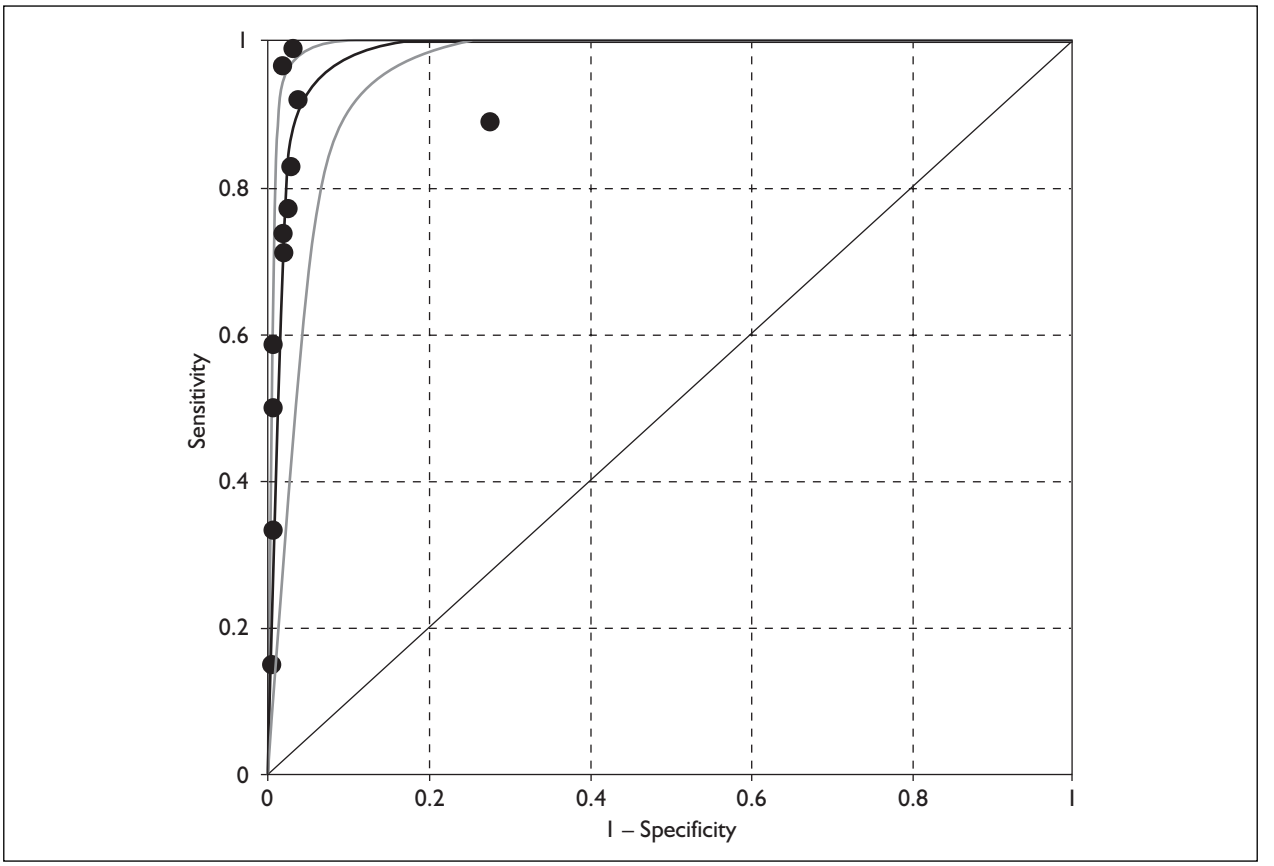

FIGURE 5 *IgA ARA SROC curve*

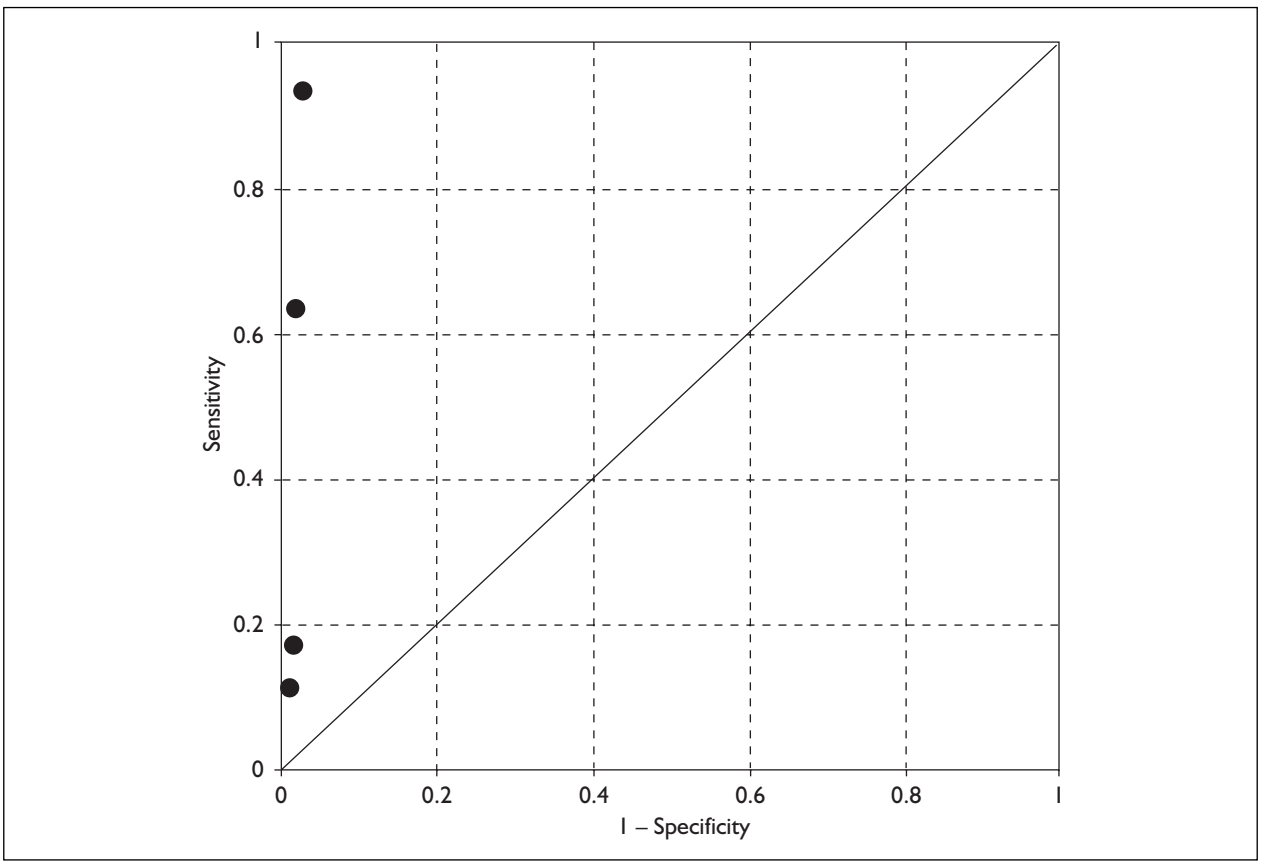

FIGURE 6 *IgG ARA SROC plot*

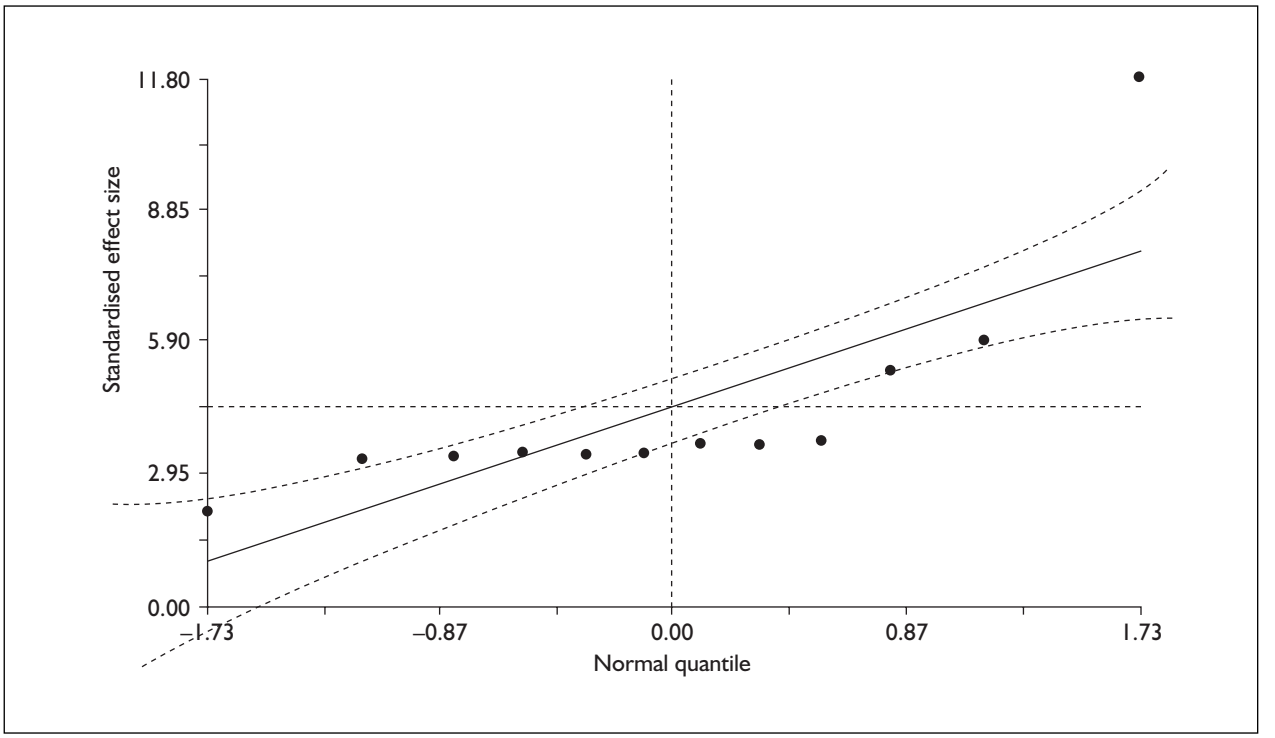

FIGURE 7 *IgA ARA normal quantile plot*

The studies were then combined in meta-analyses. The DerSimonian Laird random effects method was used to estimate summary likelihood ratios (*Figure 8*). The pooled positive likelihood ratio for all IgA ARA studies was >10, indicating a very useful test given a positive test result, whilst the pooled negative likelihood ratio was between 0.1 and 0.5 indicating a moderately useful test given a negative test result.

IgA AGA (anti-gliadin) antibodies

Figures 9 and *10* show sensitivities and specificities of the included studies with 95% confidence intervals where availability of raw data allowed their calculation. Where authors used several test methodologies, all sensitivities and specificities are shown. Well-described cohorts are shown at the top of the graph. There was variation in both sensitivity and specificity, particularly in sensitivity for the well described cohorts, and there were some outliers. Sensitivities overall were slightly lower than specificities, with the majority of sensitivities lying roughly between 50 and 95%, and the majority of specificities between 60 to 100%. Full data are given in Appendix 8.

A SROC curve was calculated based on 42 studies (*Figure 11*). Two further studies[67,68] were excluded as the sensitivity could not be calculated (0/0 cases detected by the test). There was no evidence that the log odds ratio was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant. The area under the curve is 0.938 (95% CI 0.910 to 0.957), indicating overall good test performance, although the observed heterogeneity should be taken into account.

A SROC curve was also calculated for those studies where the selection method was well described (11 studies; *Figure 12*). There was no evidence that the log odds ratio was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant. The area under the curve is 0.957 (95% CI 0.829 to 0.991), again indicating good test performance, although it should be noted that sensitivities varied greatly between studies.

A normal quantile plot was calculated for all IgA AGA studies (*Figure 13*). It can be seen that all data points are within the 95% confidence interval bands, suggesting that the data are normally distributed. The shape of the curve suggests that the studies may come from different populations, which is the case for the included studies. There is no obvious gap in the curve; however, the spacing between data points varies, indicating the possibility of missing studies or other bias.

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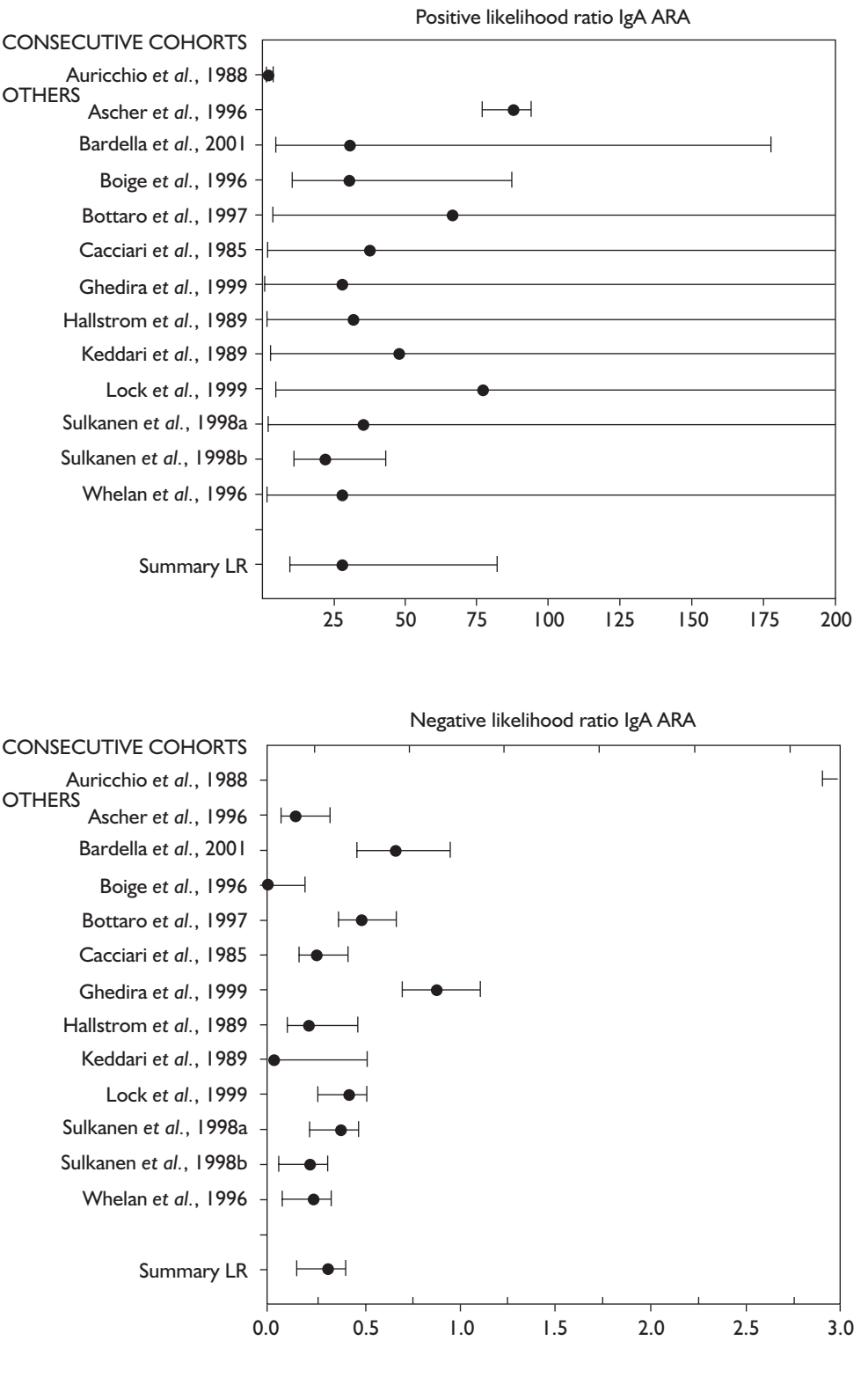

FIGURE 8 *IgA ARA likelihood ratios*

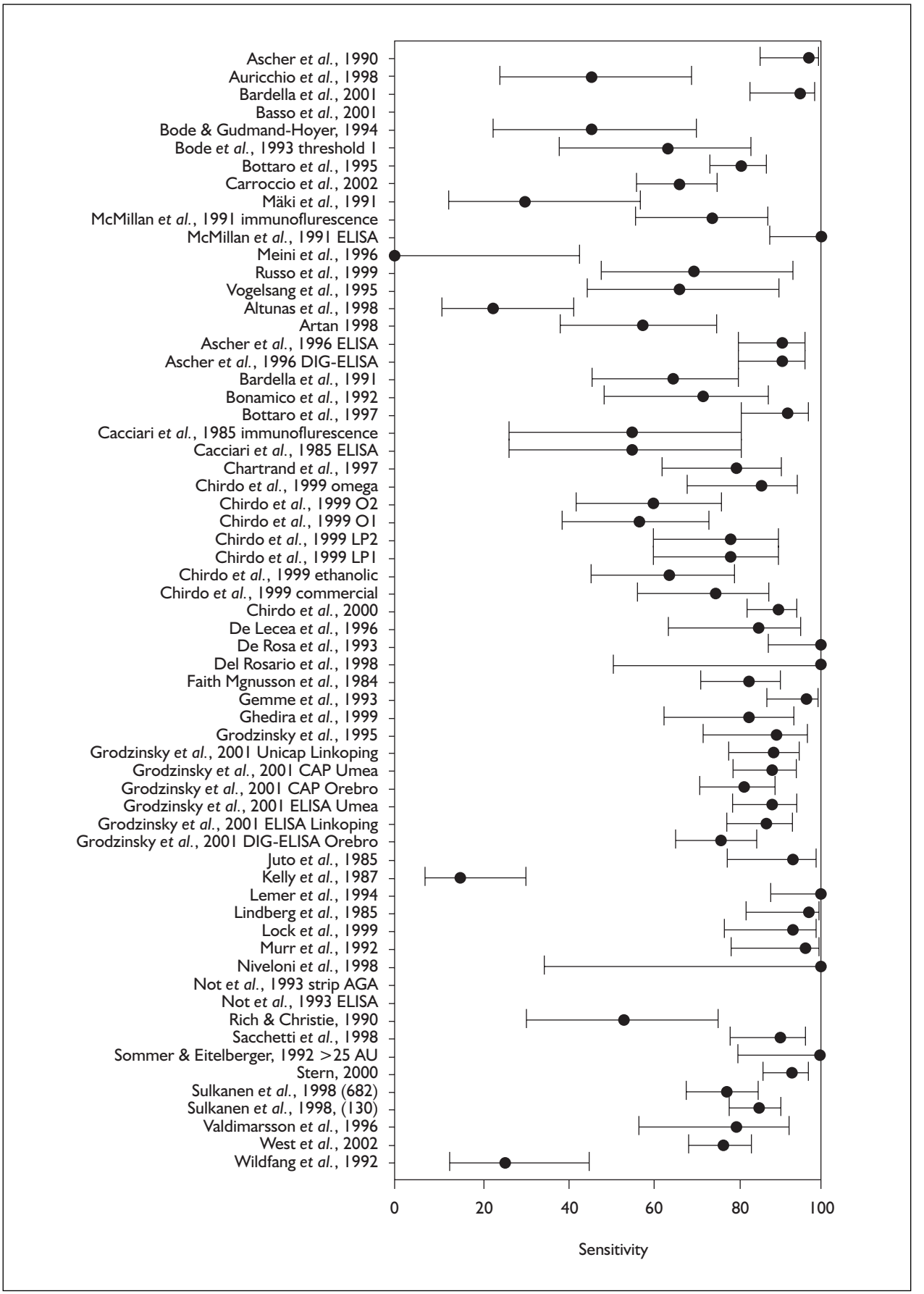

FIGURE 9 *IgA AGA sensitivity*

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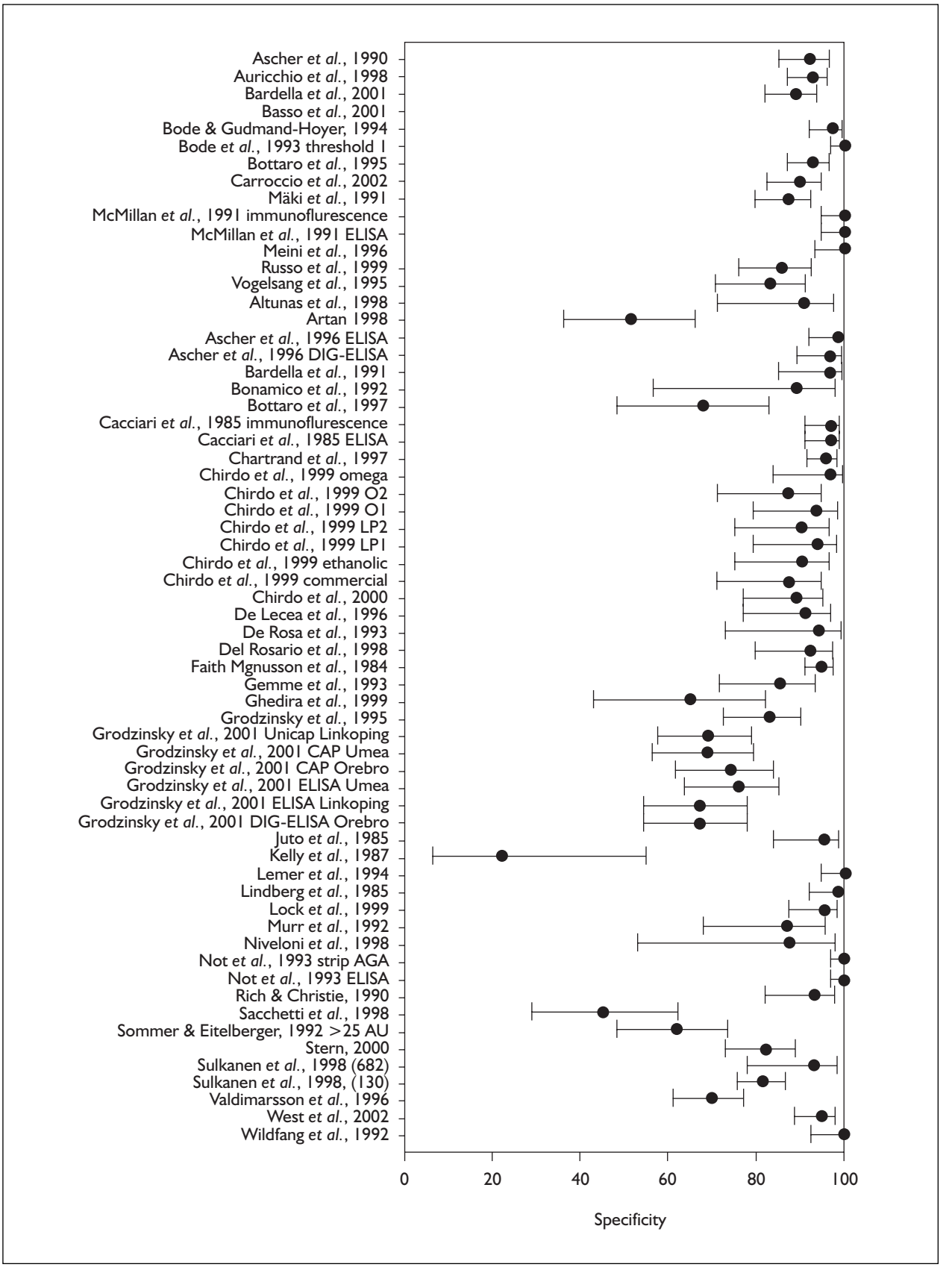

FIGURE 10 *IgA AGA specificity*

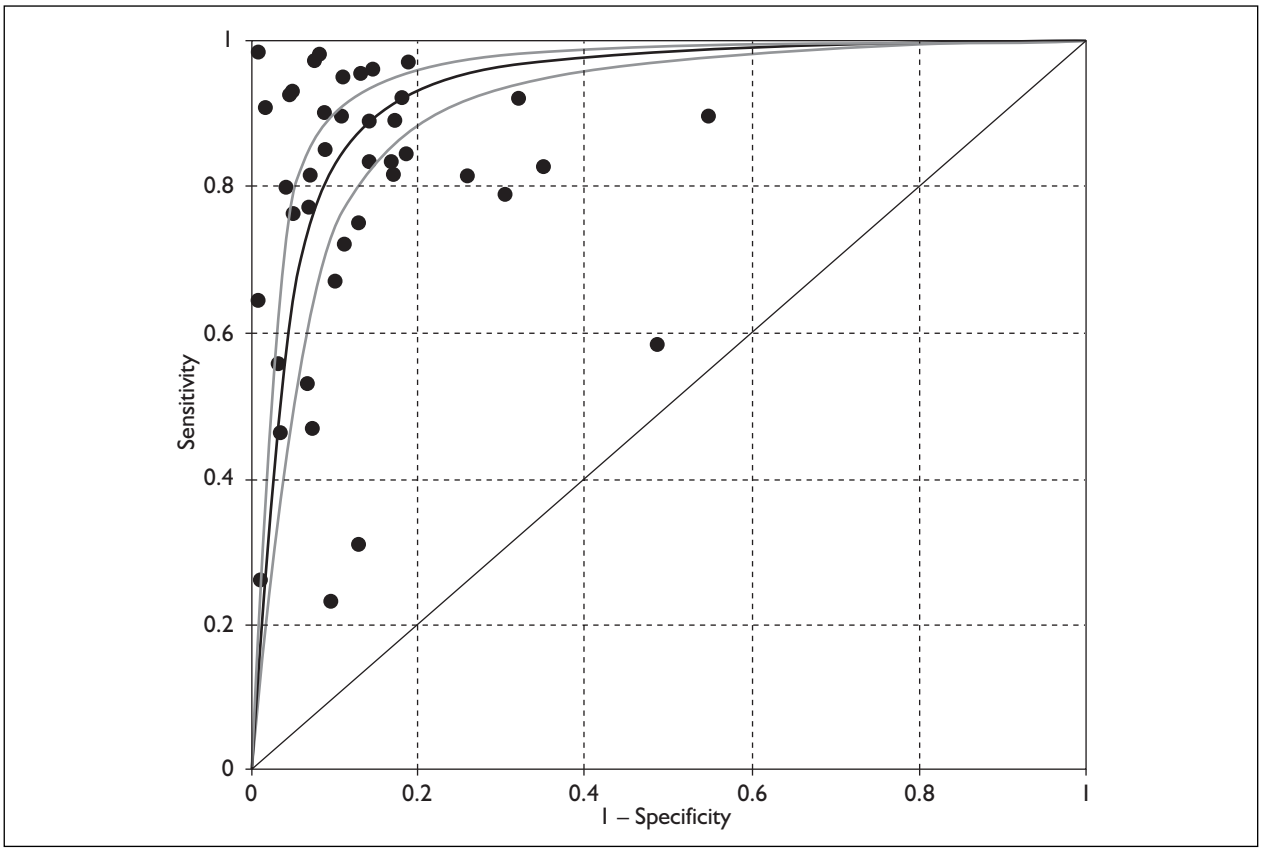

FIGURE 11 *IgA AGA SROC curve (all studies)*

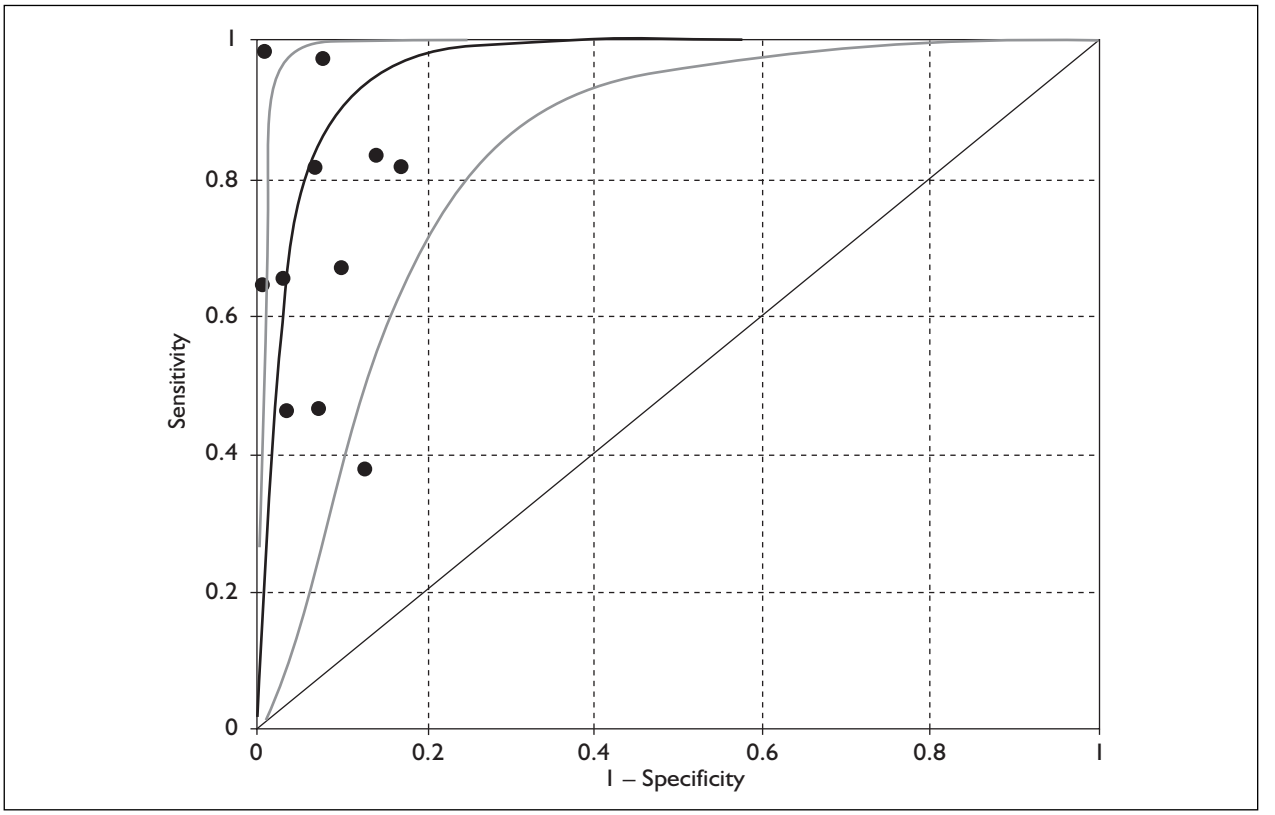

FIGURE 12 *IgA AGA SROC curve (well-described cohorts)*

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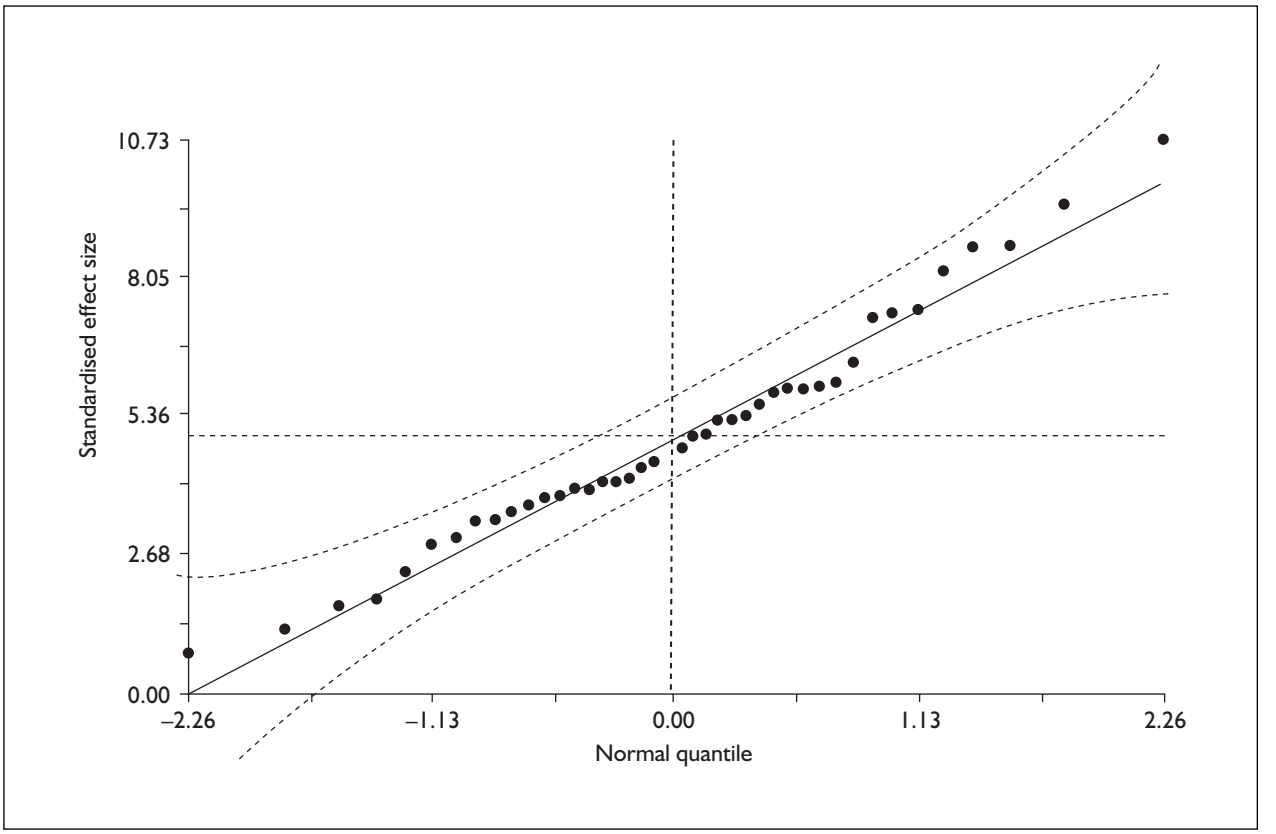

FIGURE 13 *IgA AGA normal quantile plot (all studies)*

The studies were then combined in meta-analyses. The DerSimonian Laird random effects method was used to estimate summary likelihood ratios (see *Figures 14* and *15*). The pooled positive likelihood ratios for all IgA AGA studies and for the subgroup of well-described studies were >5, indicating a moderately useful test given a positive likelihood ratio, whilst the pooled negative likelihood ratios were between 0.1 and 0.5, also indicating a moderately useful test given a negative test result.

IgG AGA (anti-gliadin) antibodies

Figures 16 and *17* show sensitivities and specificities of the included studies with 95% confidence intervals where availability of raw data allowed their calculation. There was similar variation compared with IgA AGA in both sensitivity and specificity and some outliers are present. There was slightly more variation in sensitivities for the well-described studies compared with the remaining studies. Specificity overall was slightly lower for IgG AGA than to IgA AGA. Full data are given in Appendix 8.

A SROC curve was calculated based on 35 studies (*Figure 18*). One further study[67] excluded as the sensitivity could not be calculated (0/0 cases detected by the test). There was no evidence that log (odds ratio) was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant. The area under the curve is 0.908 (95% CI 0.877 to 0.938), indicating moderately good test performance, although the observed heterogeneity should be taken into account.

A SROC curve was also calculated for those studies where the selection method was well described (11 studies; *Figure 19*). There was no evidence that the log odds ratio was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant and a symmetrical SROC curve was plotted. The area under the curve is 0.845 (95% CI 0.733 to 0.916), again indicating moderately good test performance.

A normal quantile plot was calculated for all IgG AGA studies (*Figure 20*). It can be seen that all data points are within the 95% confidence interval bands, suggesting that the data are normally distributed. The shape of the curve suggests that the studies may come from different populations, which is the case for the included studies. There is

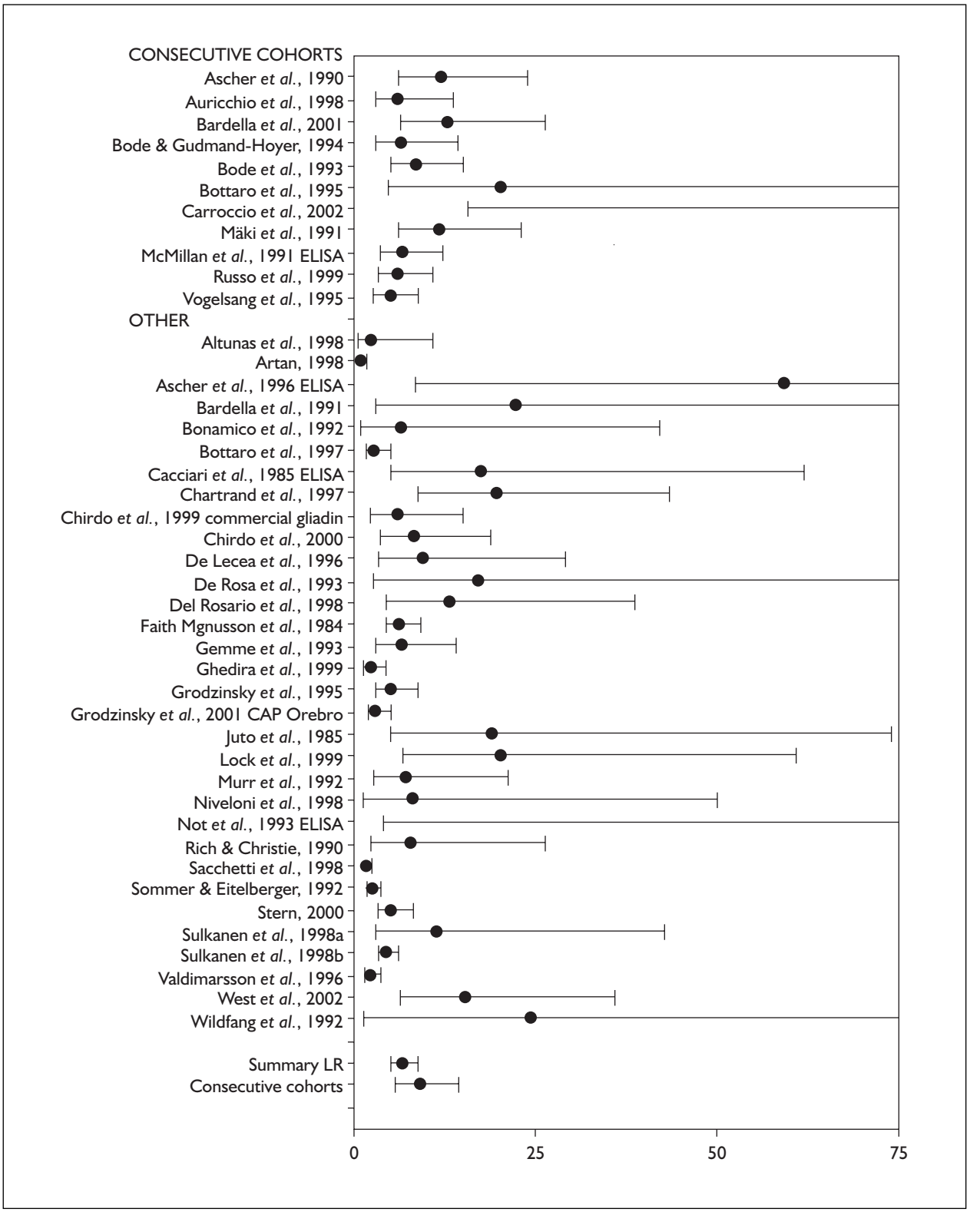

FIGURE 14 *IgA AGA positive likelihood ratios*

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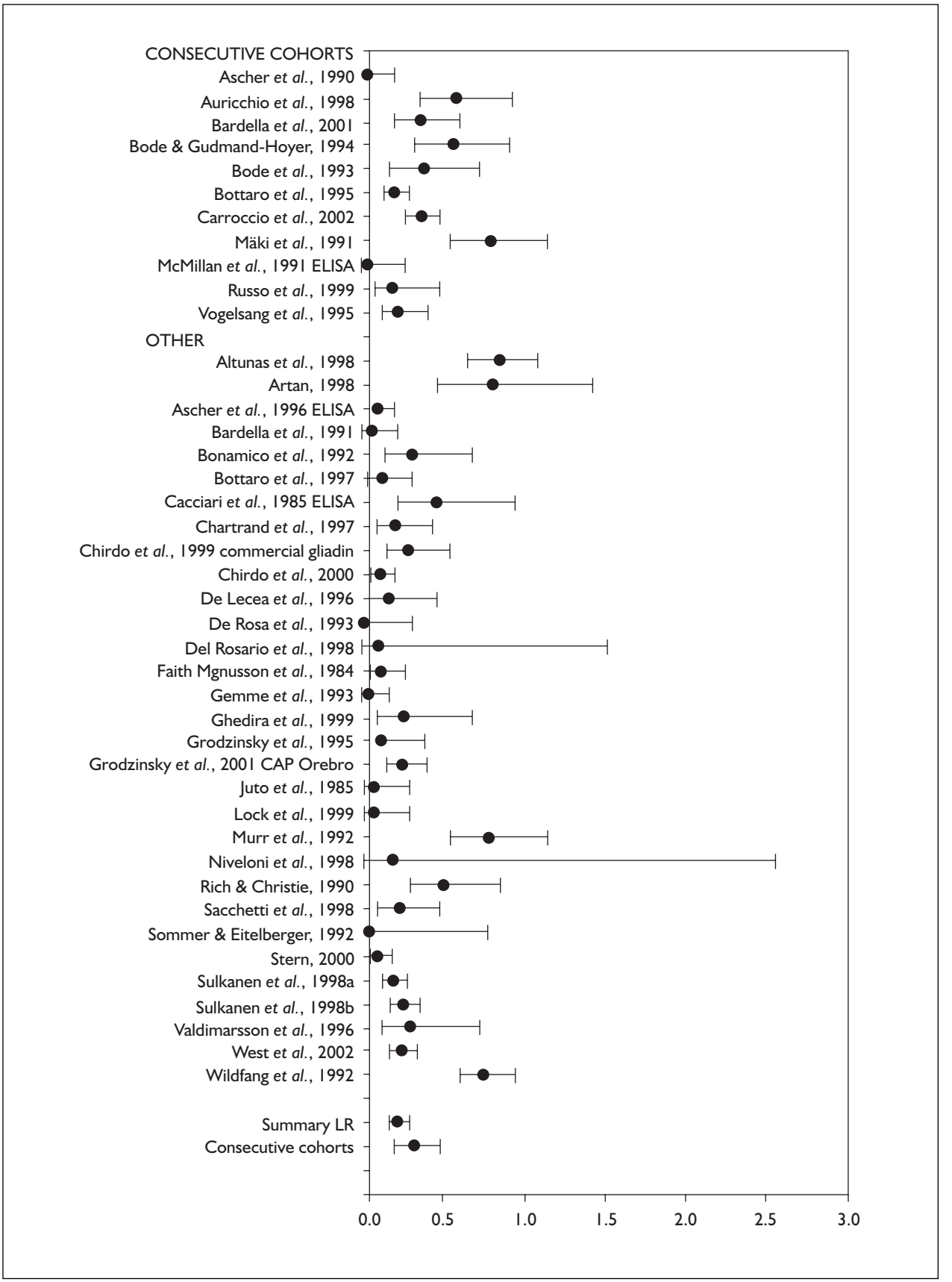

FIGURE 15 *IgA AGA negative likelihood ratios*

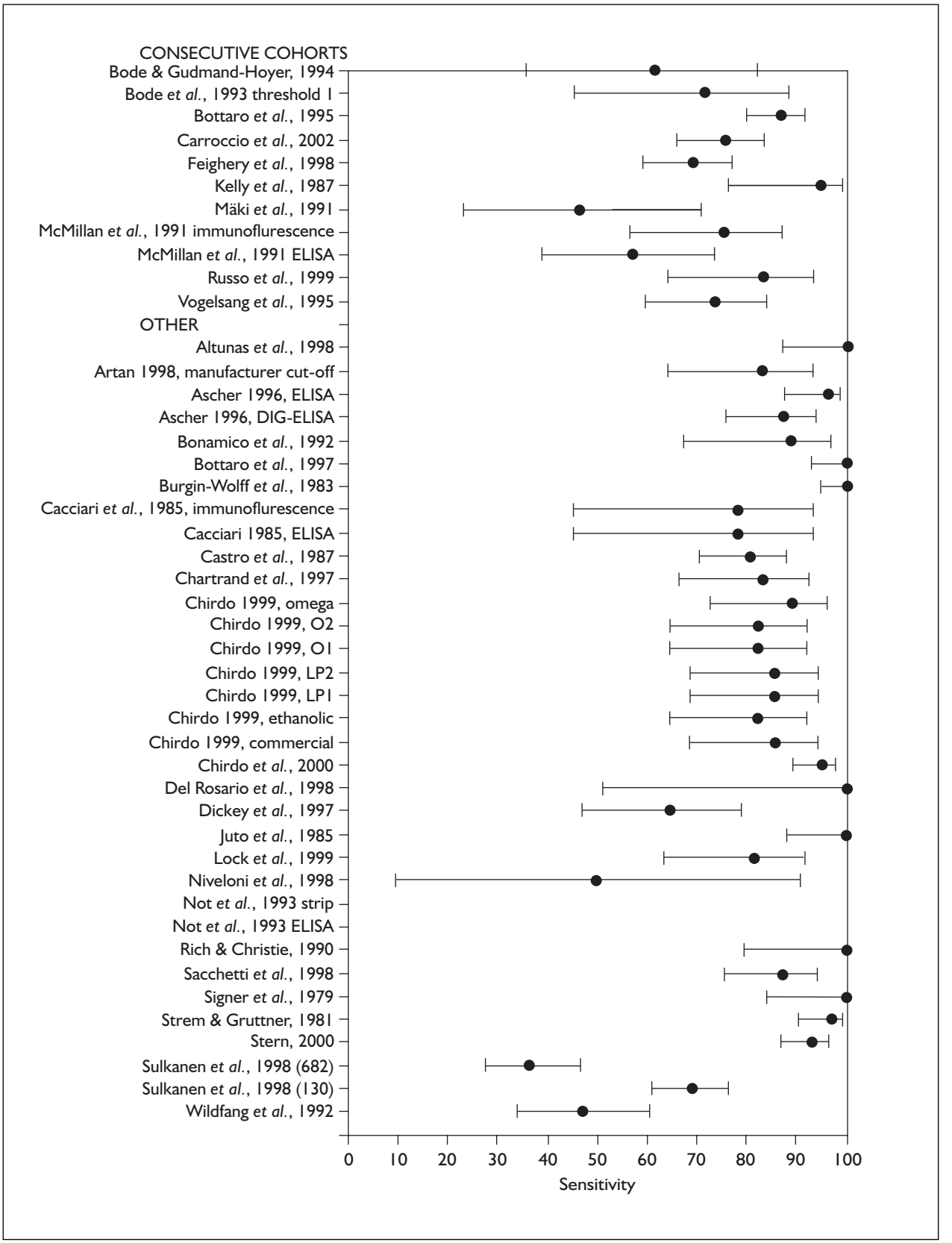

FIGURE 16 *IgG AGA sensitivity (with 95% confidence intervals)*

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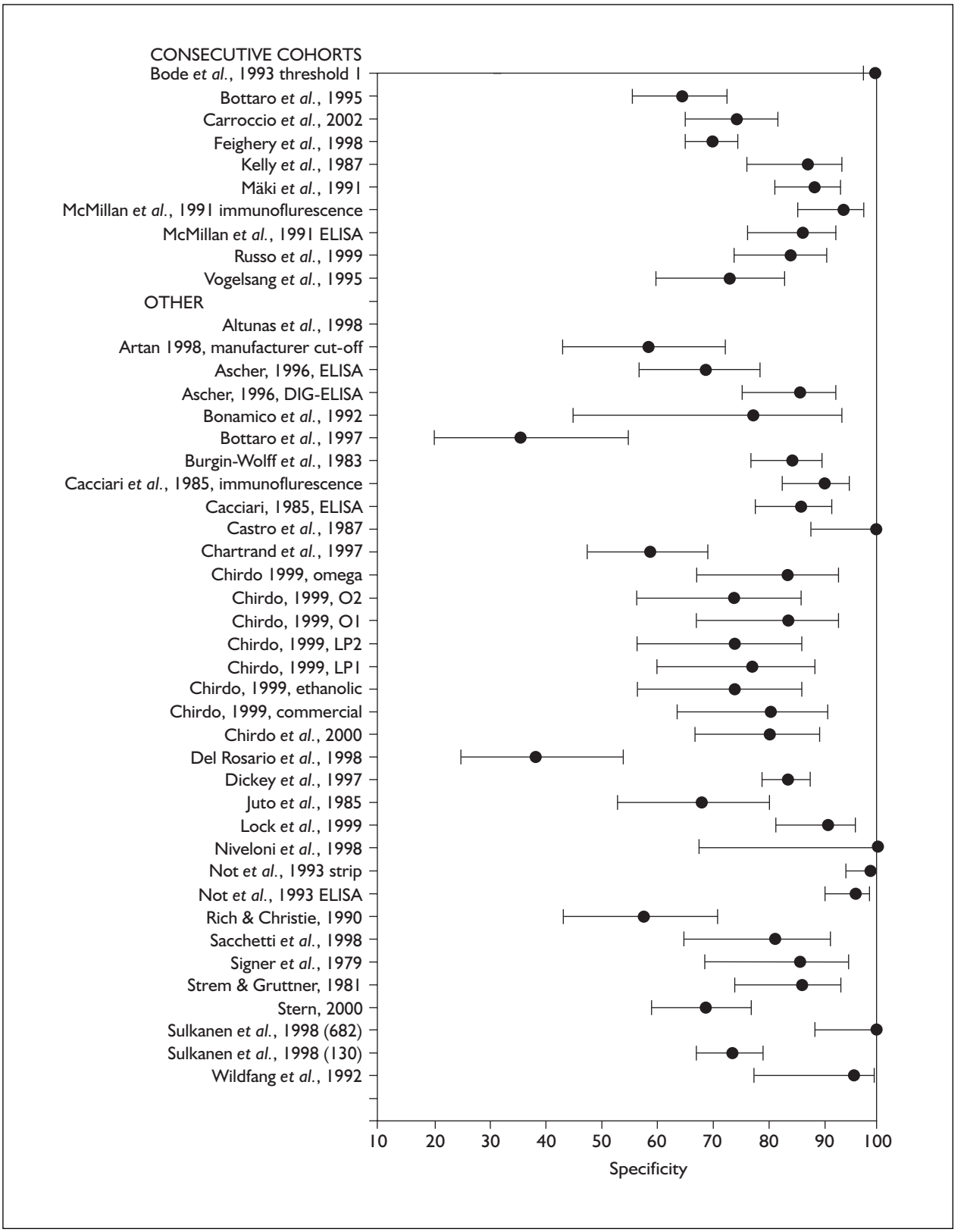

FIGURE 17 *IgG AGA specificity (with 95% confidence intervals)*

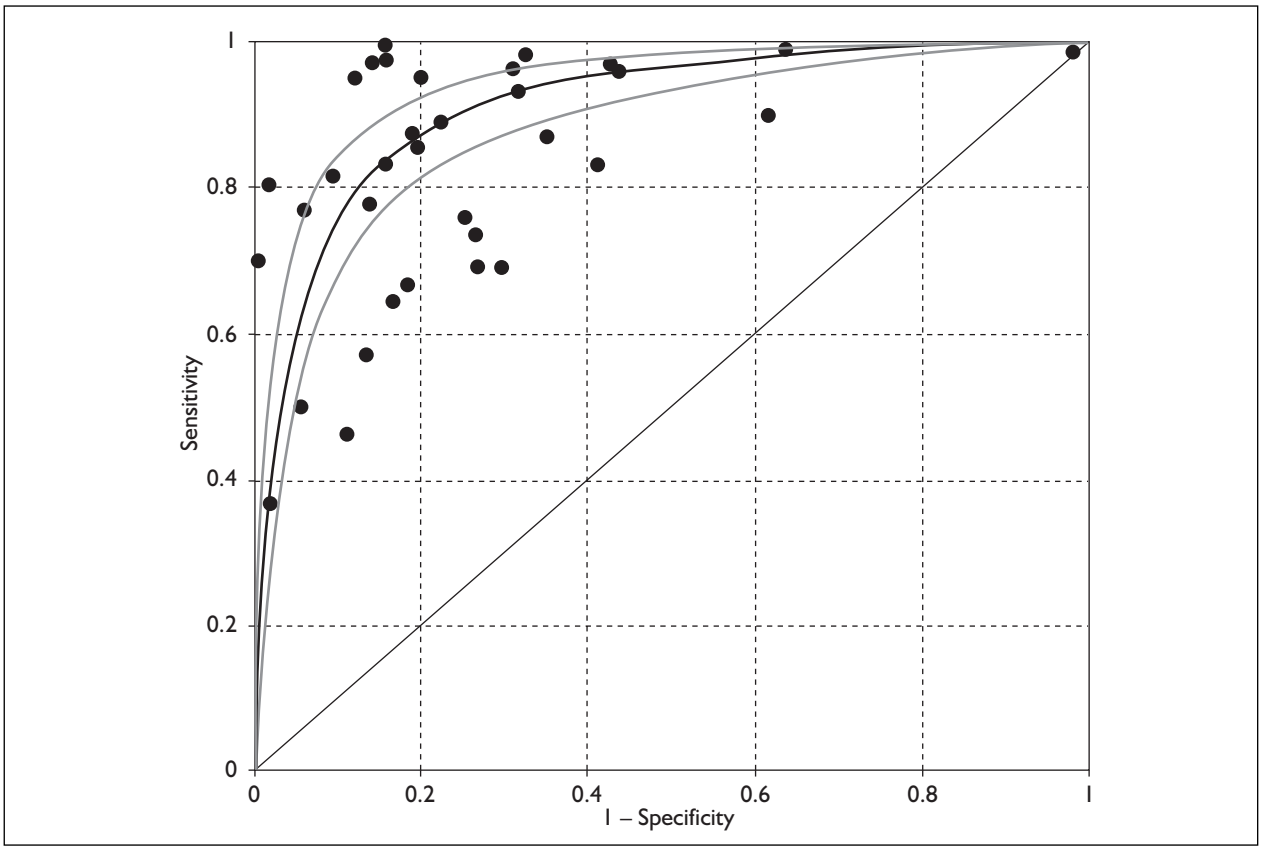

FIGURE 18 *IgG AGA SROC curve (all studies)*

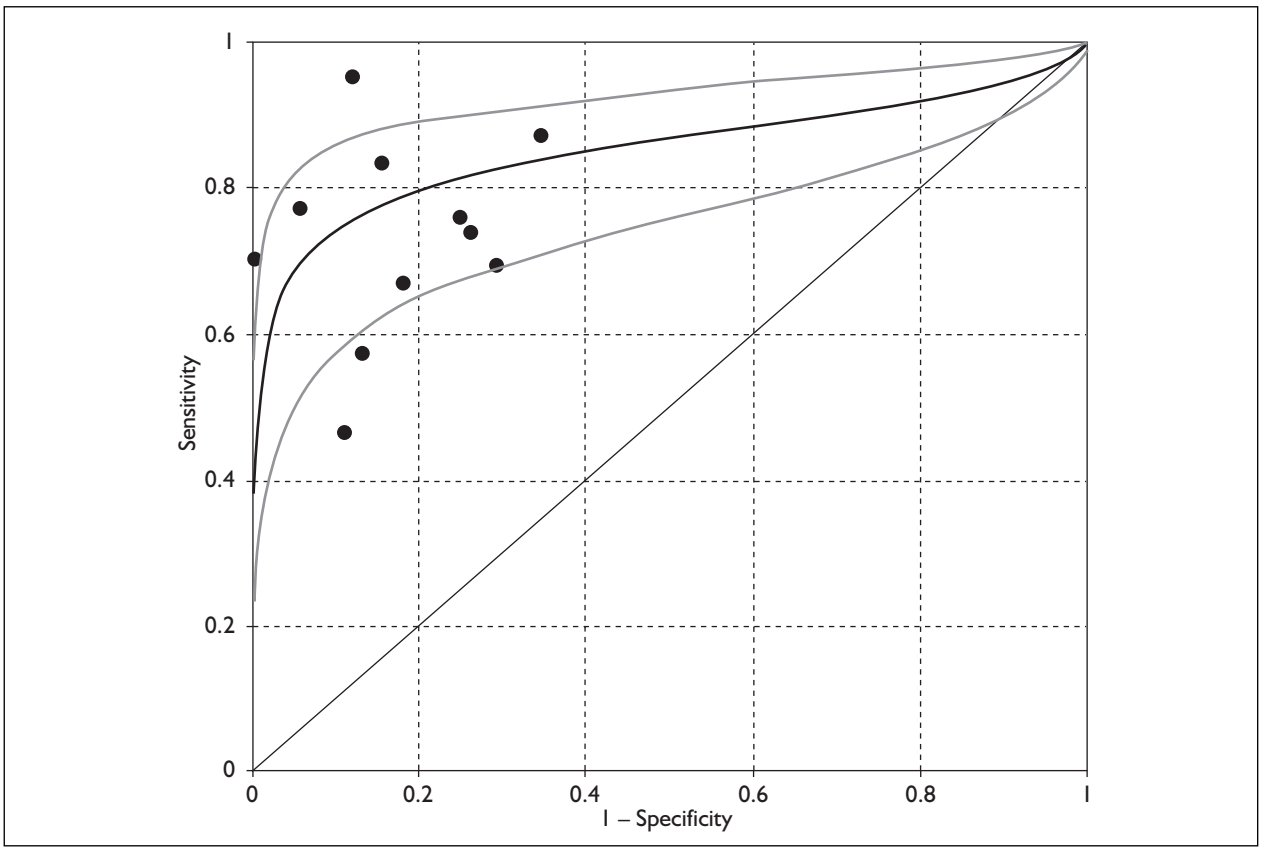

FIGURE 19 *IgG AGA SROC curve (well-described cohorts)*

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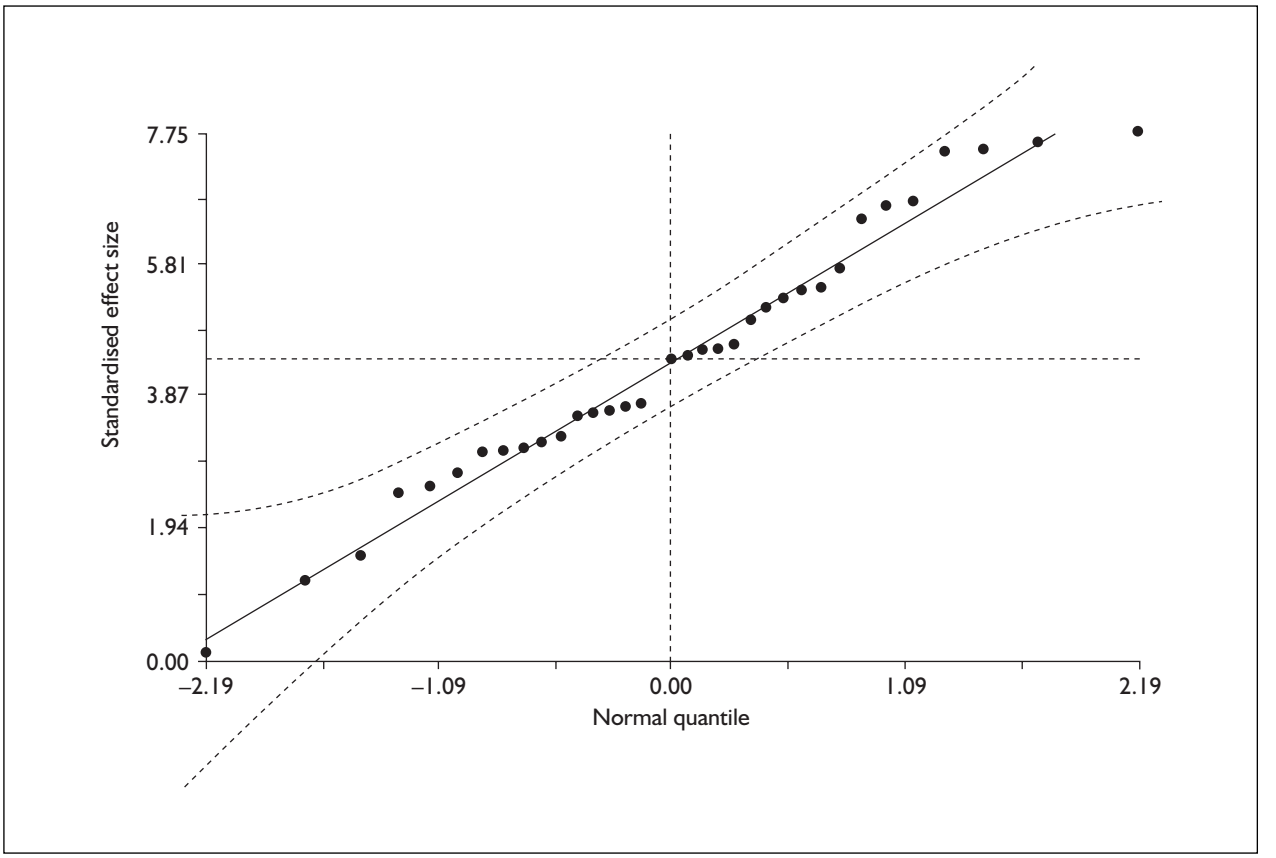

FIGURE 20 *IgG AGA normal quantile plot*

no obvious gap in the curve; however, the spacing between data points varies, indicating the possibility of missing studies.

The studies were then combined in meta-analyses. The DerSimonian Laird random effects method was used to estimate summary likelihood ratios (*Figure 21*). The pooled positive likelihood ratios for all IgG AGA studies and for the subgroup of well-described studies was <5, indicating that the test is not very informative given a positive test result, whilst the pooled negative likelihood ratios for both groups were between 0.1 and 0.5, indicating a moderately useful test given a negative test result.

EMA (anti-endomysial) antibodies

Figures 22 and *23* shows sensitivities and specificities of the included studies with 95% confidence intervals where availability of raw data allowed their calculation. There was variation between sensitivities, and some outliers, although overall there was less heterogeneity compared with the other antibody tests. The sensitivities were highest overall for IgA EMA compared with the other antibody tests, with the majority of sensitivities lying roughly between 70 and 100%. Twelve studies showed a sensitivity of 100% and a further 15 studies a sensitivity of >90%. There was little difference between specificities, with a specificity of 100% for 28/42 studies and >95% for a further 11 studies, which are comparable to the high specificities of IgA ARA. Full data are given in Appendix 8, *Table 35*.

A SROC curve was calculated based on 42 studies (*Figure 24*). Where studies had results for both monkey oesophagus and human umbilical cord as substrate, the results using human umbilical cord were chosen, as this reflects more current practice. There was no evidence that the log odds ratio was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant. The area under the curve is 0.992 (95% CI 0.988 to 0.995), indicating very good test performance, although the range of reported sensitivities needs to be taken into account.

A SROC curve was also calculated for those studies where the selection method was well described (eight studies; *Figure 25*). There was no evidence that the log odds ratio was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant. The area

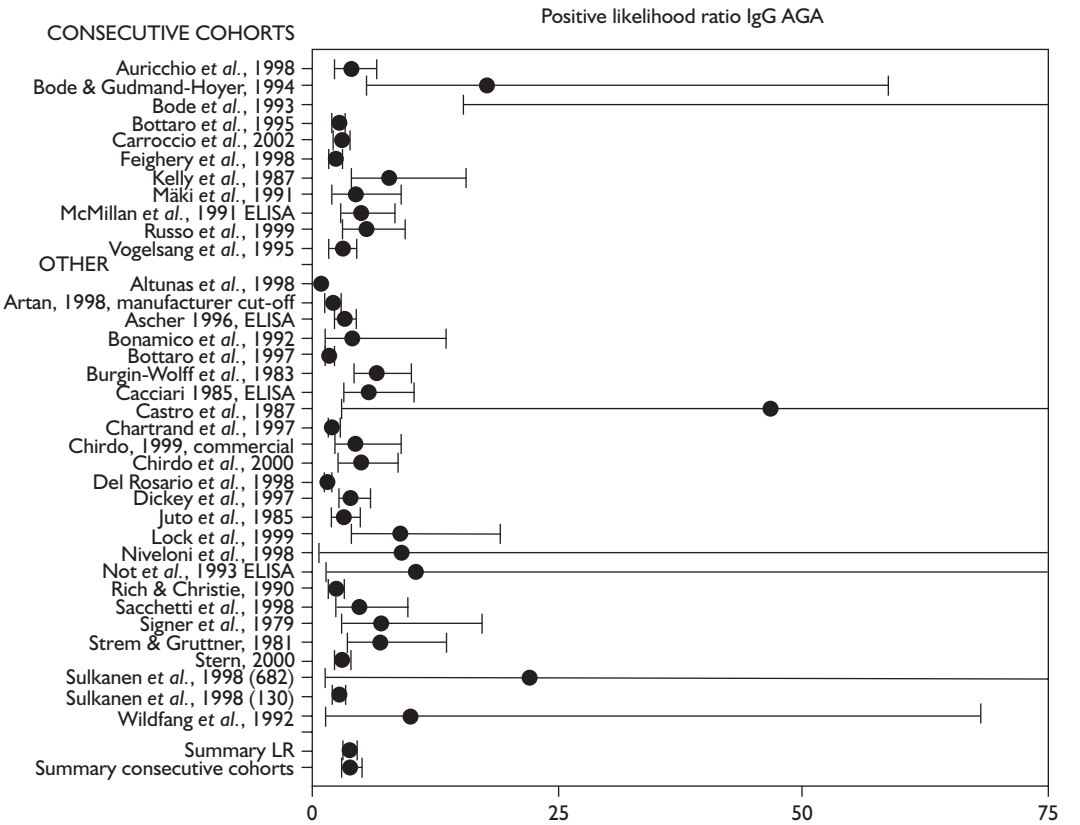

FIGURE 21 *IgG AGA likelihood ratios*

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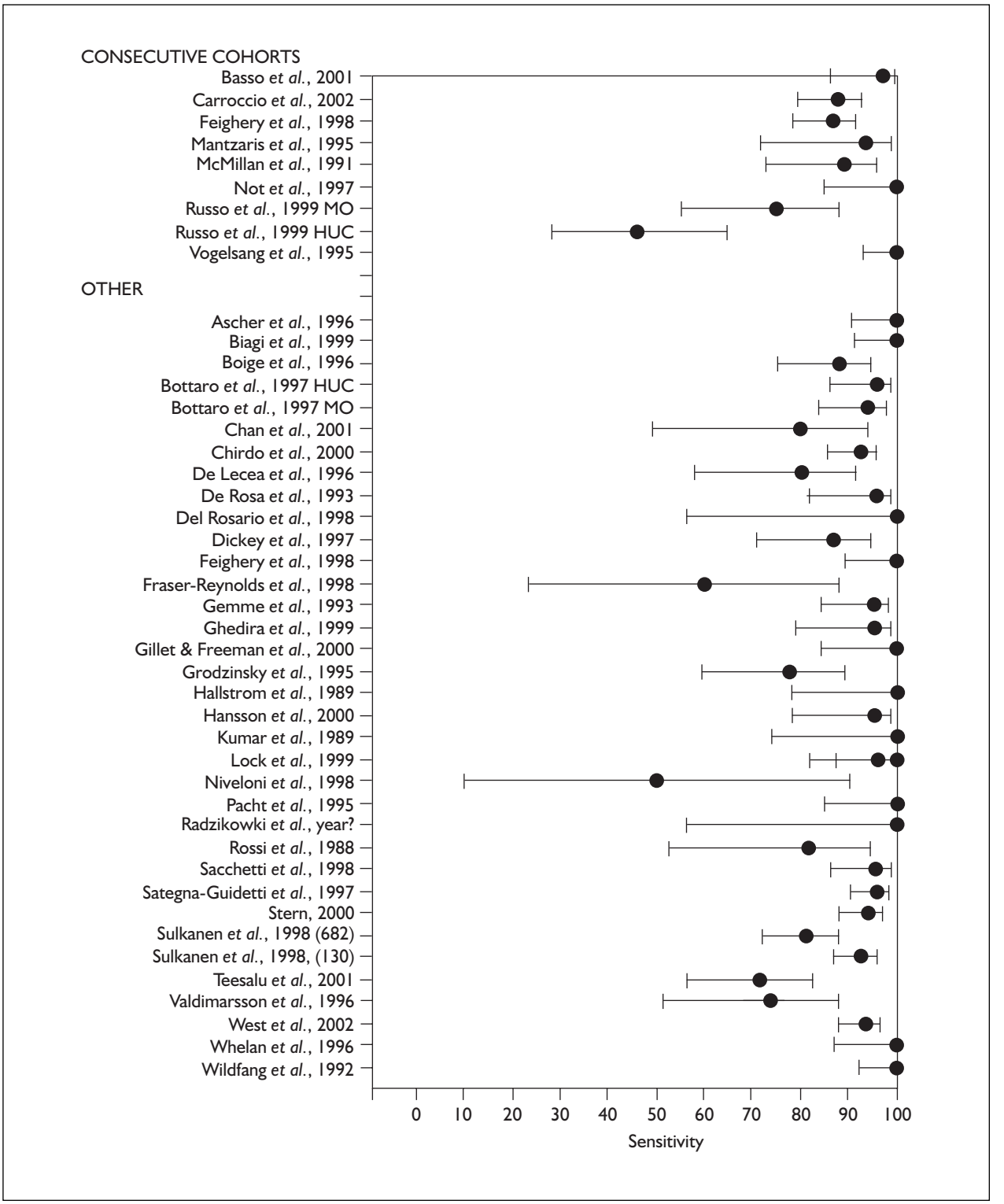

FIGURE 22 *IgA EMA sensitivity (with 95% confidence intervals)*

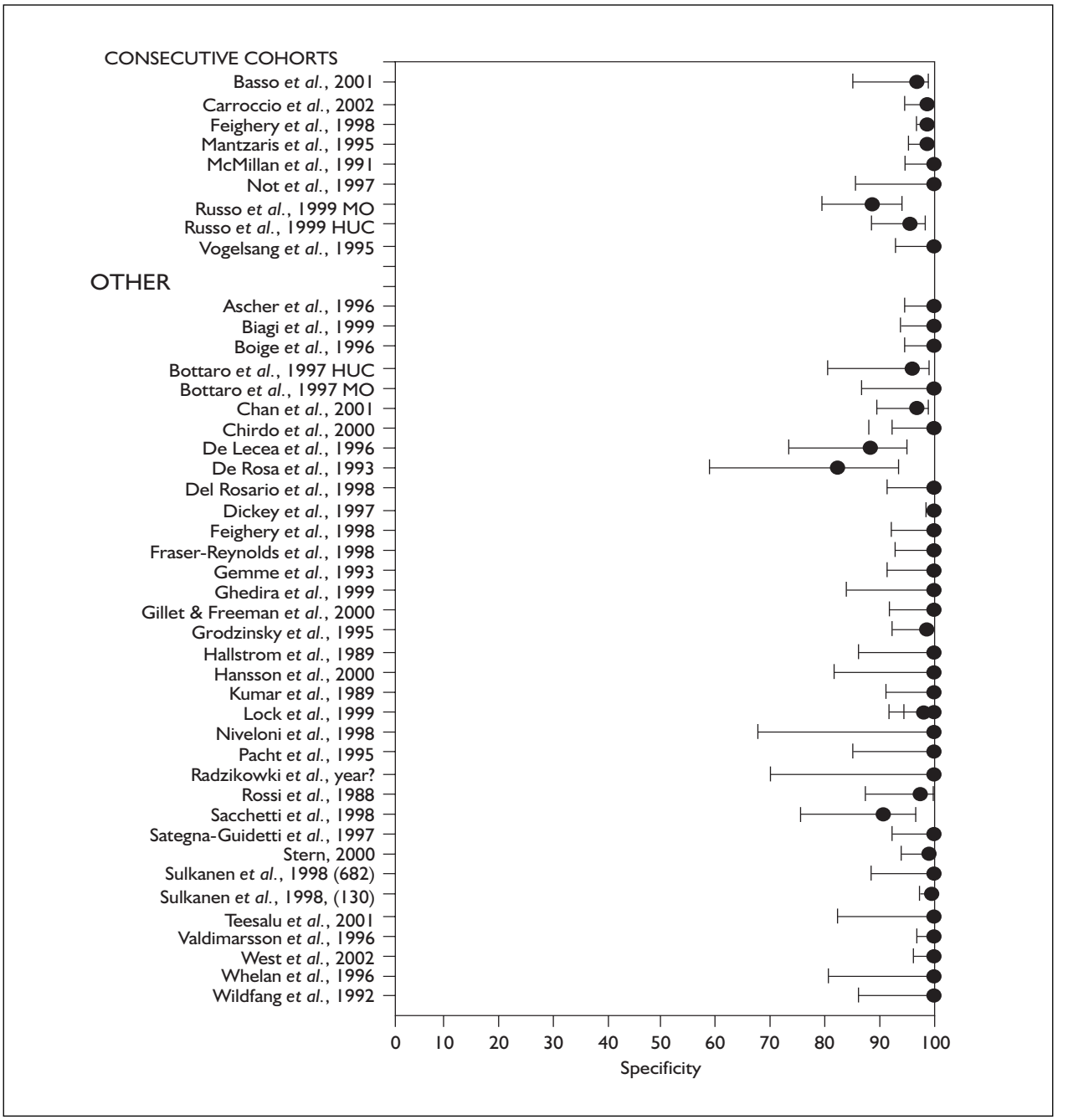

FIGURE 23 *IgA EMA specificity (with 95% confidence intervals)*

under the curve is 0.987 (95% CI 0.948 to 0.996), again indicating very good test performance.

SROC curves were calculated separately for studies using monkey oesophagus or human umbilical cord as substrate. The areas under the curve are very similar: 0.993 (95% CI 0.988 to 0.995) for studies using monkey oesophagus (n = 31; *Figure 26*) and 0.986 (95% CI 0.976 to 0.991) for studies using human umbilical cord (n = 14; *Figure 27*).

A SROC plot was drawn for IgG EMA based on three studies (*Figure 28*). Specificities were comparably high, but sensitivities were very low.

A normal quantile plot was calculated for all IgA EMA studies (*Figure 29*). It can be seen that, with the exception of one outlier, all data points are within the 95% confidence interval bands, suggesting that the data are normally distributed. The shape of the curve suggests that the studies may come from

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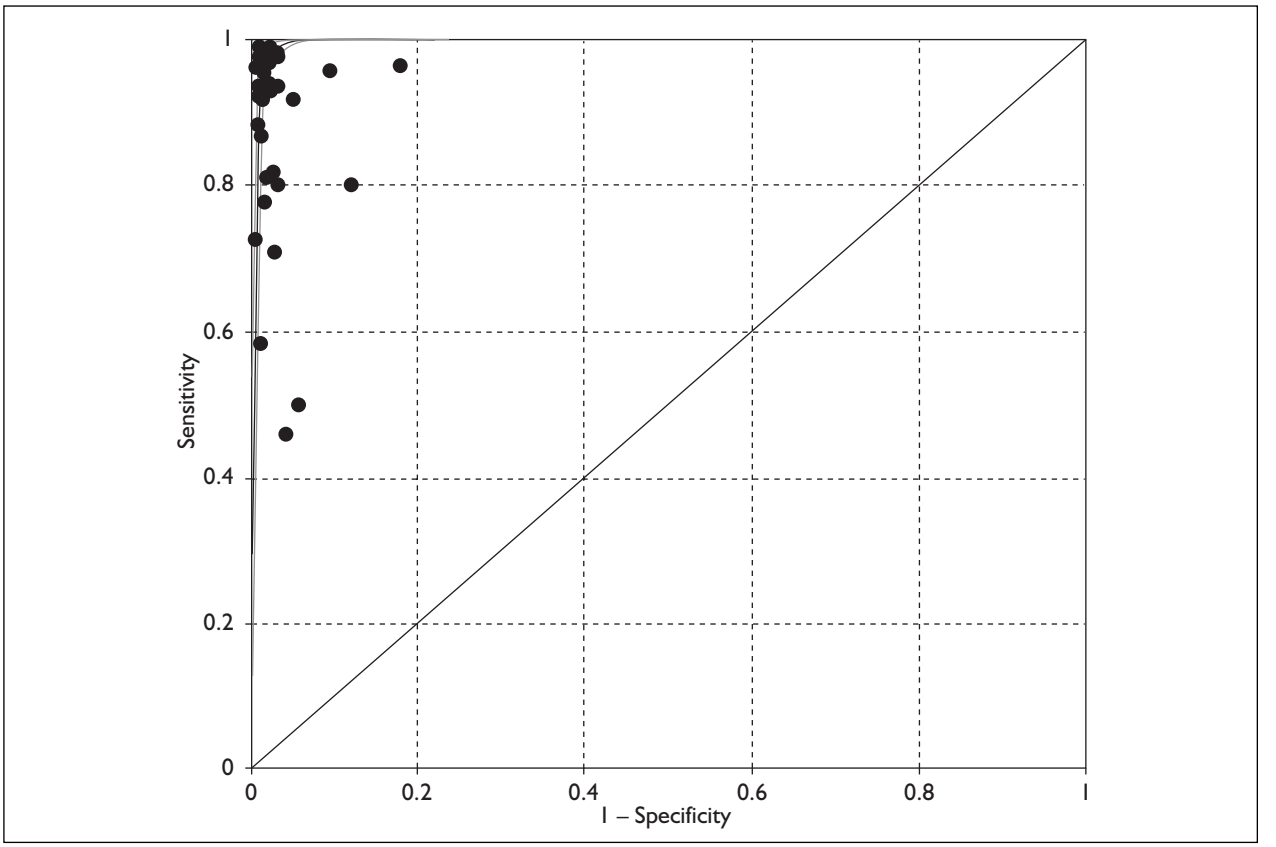

FIGURE 24 *IgA EMA SROC curve (all studies)*

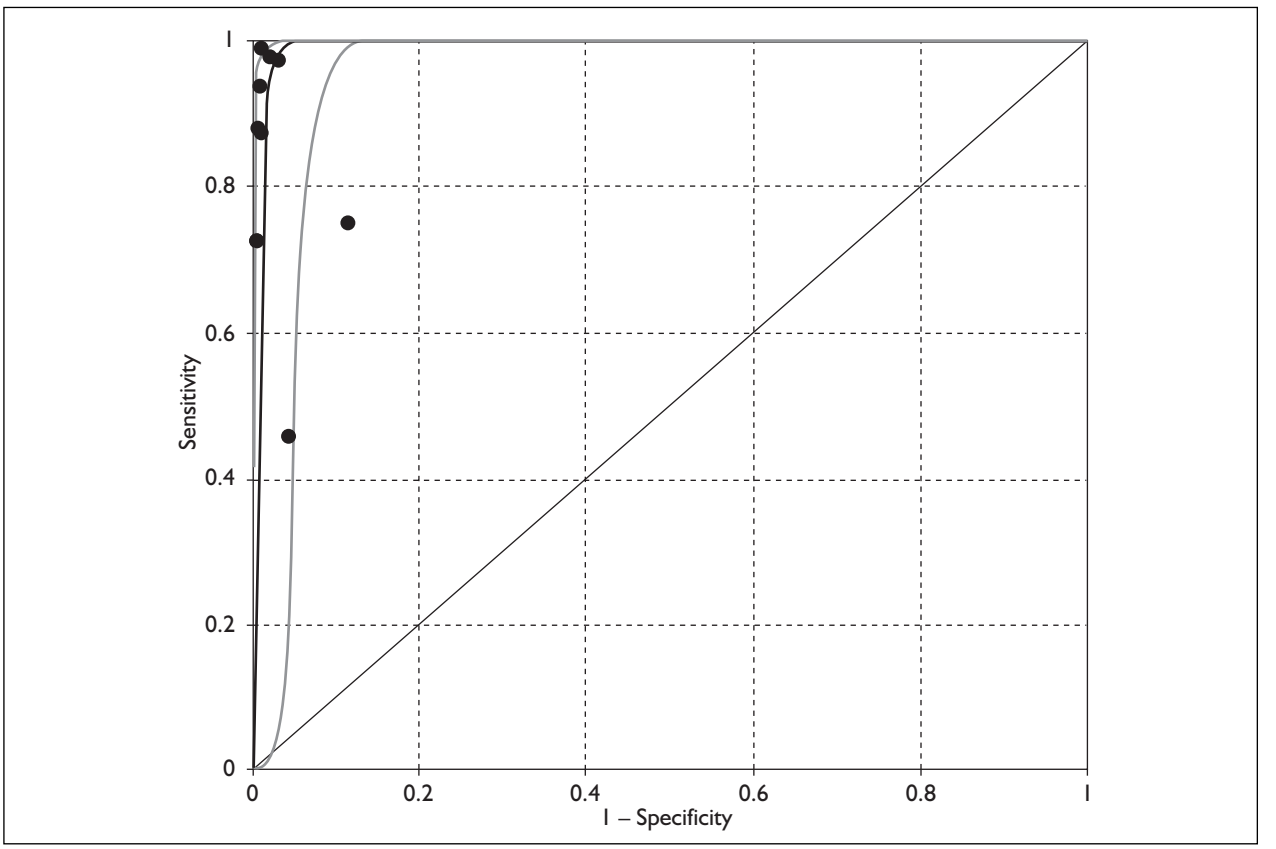

FIGURE 25 *IgA EMA SROC curve (well-described cohorts)*

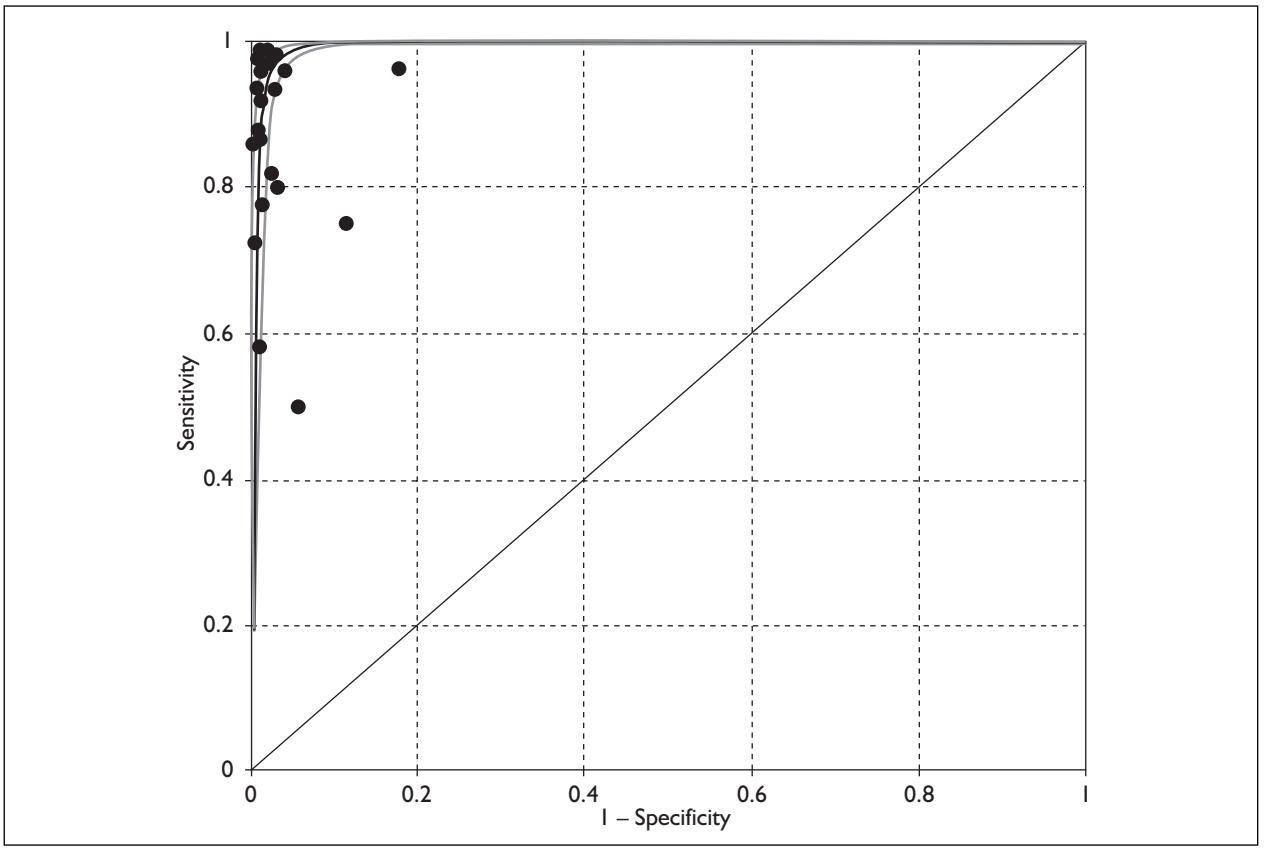

FIGURE 26 *IgA EMA (substrate: monkey oesophagus) SROC curve*

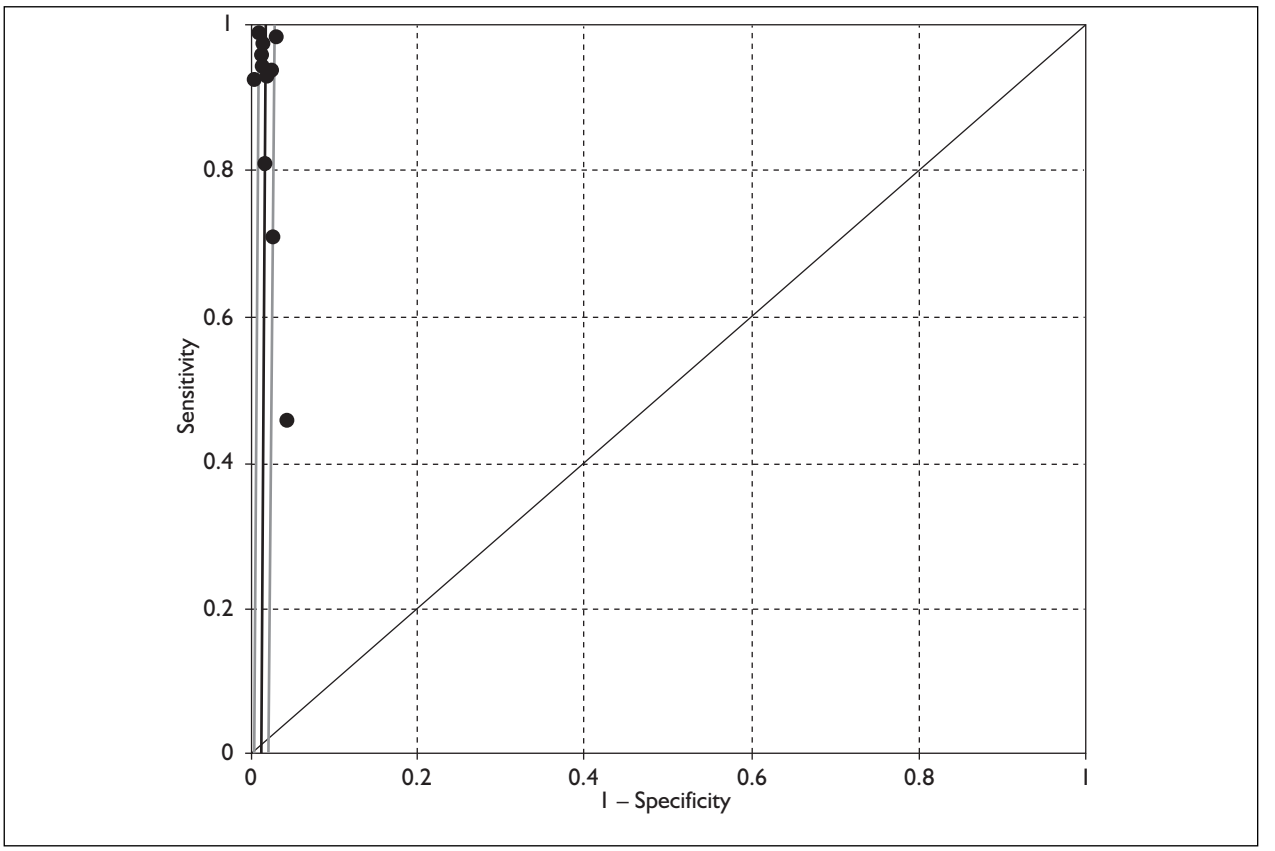

FIGURE 27 *IgA EMA (substrate: human umbilical cord) SROC curve*

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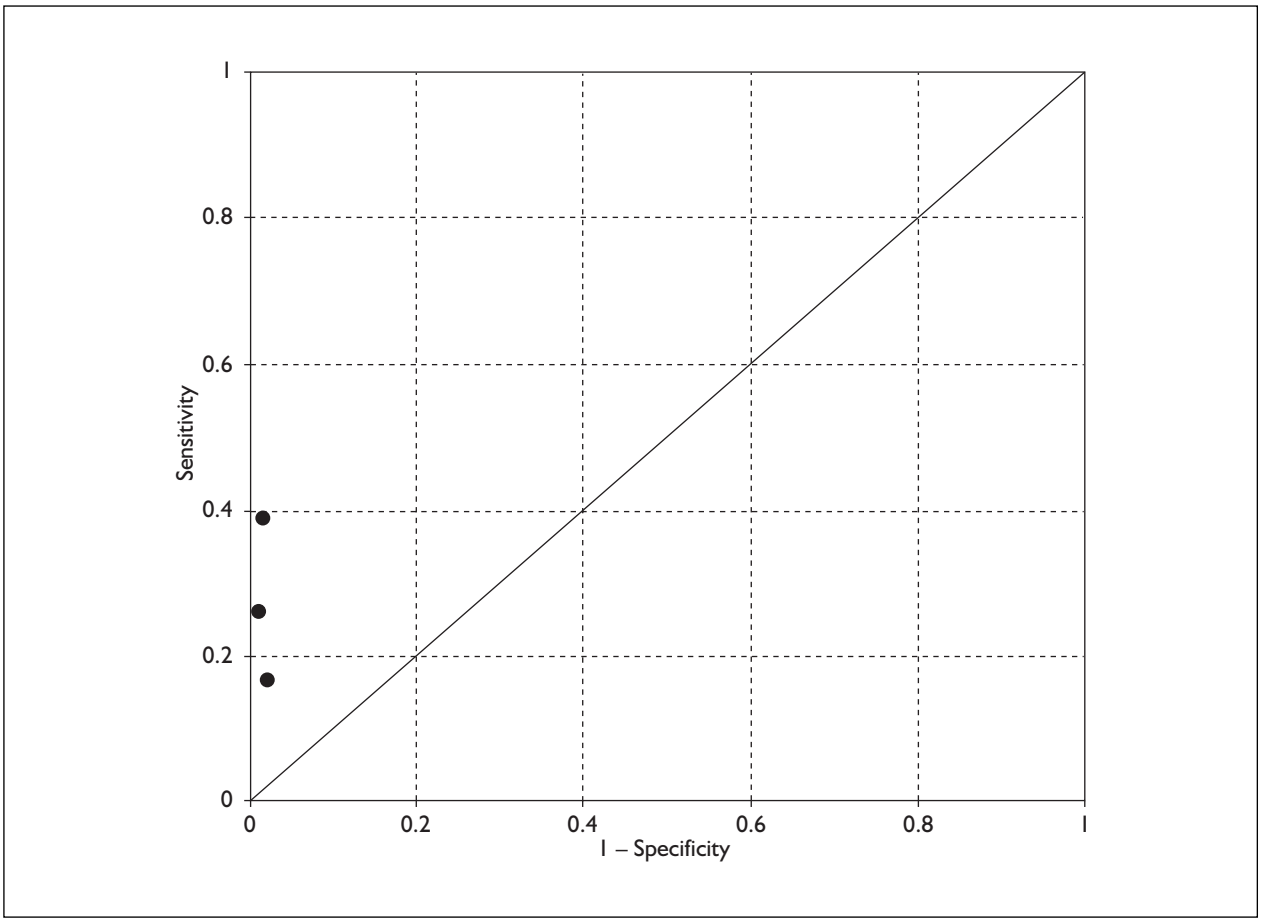

FIGURE 28 *IgG EMA SROC plot*

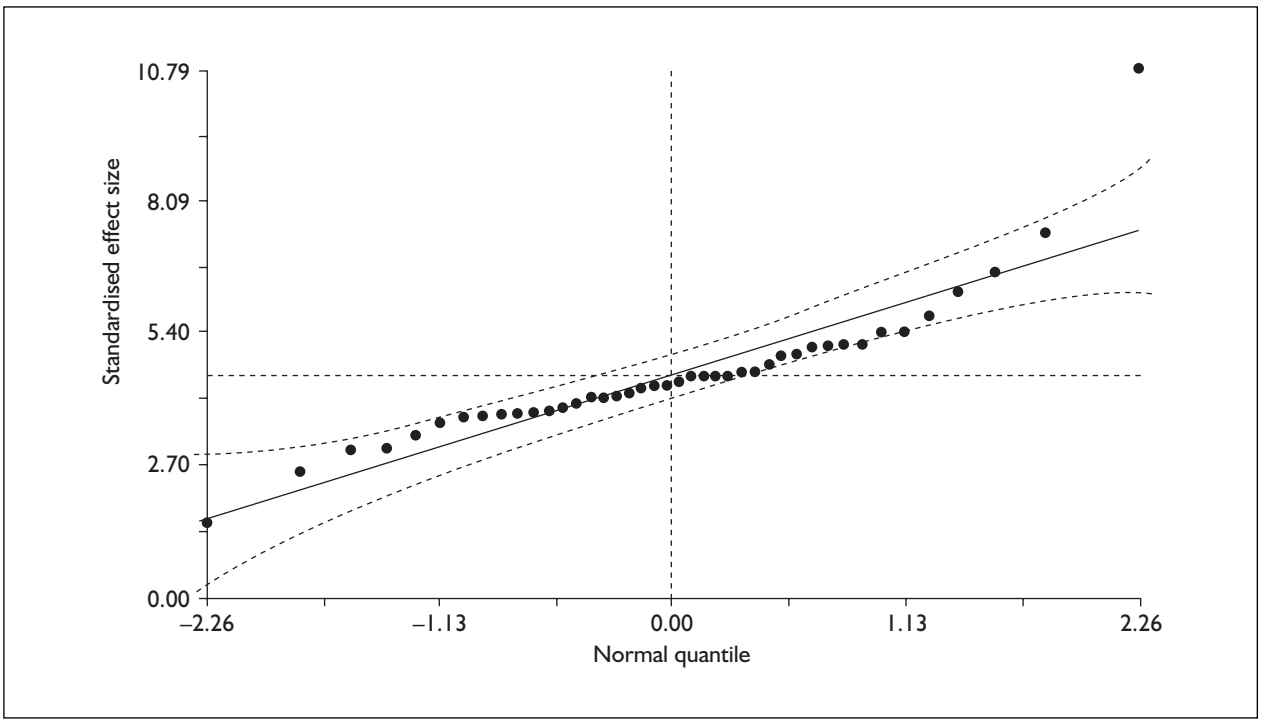

FIGURE 29 *IgA EMA normal quantile plot*

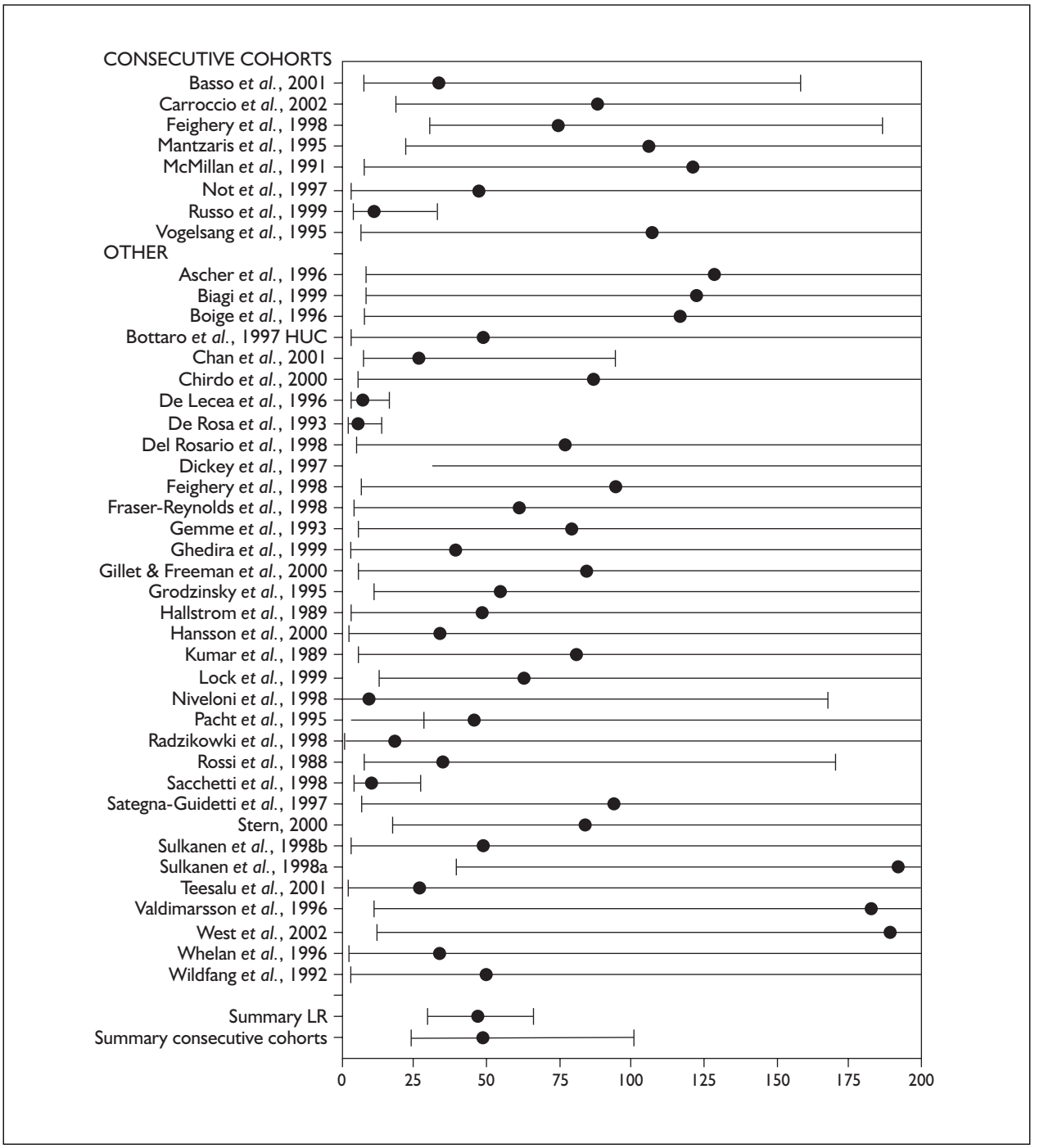

FIGURE 30 *IgA EMA positive likelihood ratio*

different populations, which is the case for the included studies. There is no obvious gap in the curve; however, the spacing between data points varies, indicating the possibility of missing studies.

The studies were then combined in meta-analyses. The DerSimonian Laird random effects method was used to estimate summary likelihood ratios (*Figures 30* and *31*). The pooled positive likelihood ratios for all IgA EMA studies and for the subgroup of well-described studies were >10, indicating a very useful test given a positive likelihood ratio, whilst the pooled negative likelihood ratios were <0.1, indicating a very useful test given a negative test result.

TTG (anti-tissue transglutaminase) antibodies

Figure 32 shows sensitivities and specificities of the included studies with 95% confidence intervals

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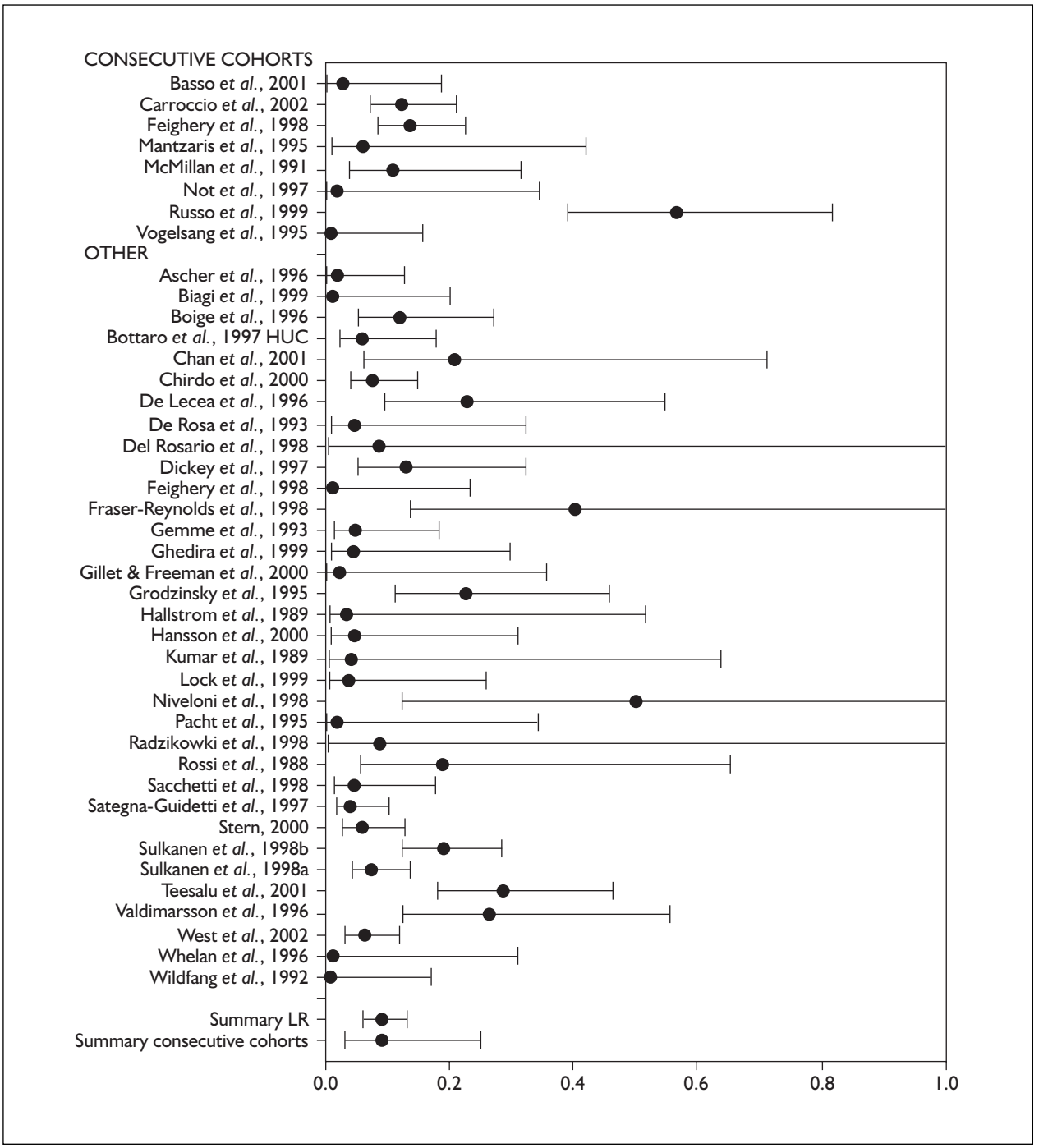

FIGURE 31 *IgA EMA negative likelihood ratio*

where availability of raw data allowed their calculation. Fourteen studies gave estimates for IgA tests. There was some variation between sensitivities, with the majority of values sensitivities lying roughly between 70 and 100% (one outlier). The sensitivities are slightly better than those for anti-gliadin antibodies and slightly below those for anti-endomysial antibodies. There was little variation between specificities, with all specificities above 90%. Full data are given in Appendix 8.

A SROC curve was calculated for IgA TTG based on 12 studies (*Figure 33*). There was no evidence that the log odds ratio was dependent on the test threshold, as in the regression analysis, the coefficient was not statistically significant. The area under the curve is 0.983 (95% CI 0.959 to 0.993), indicating good test performance. There was only one study where the selection method was well described, therefore no subgroup SROC curve is plotted.

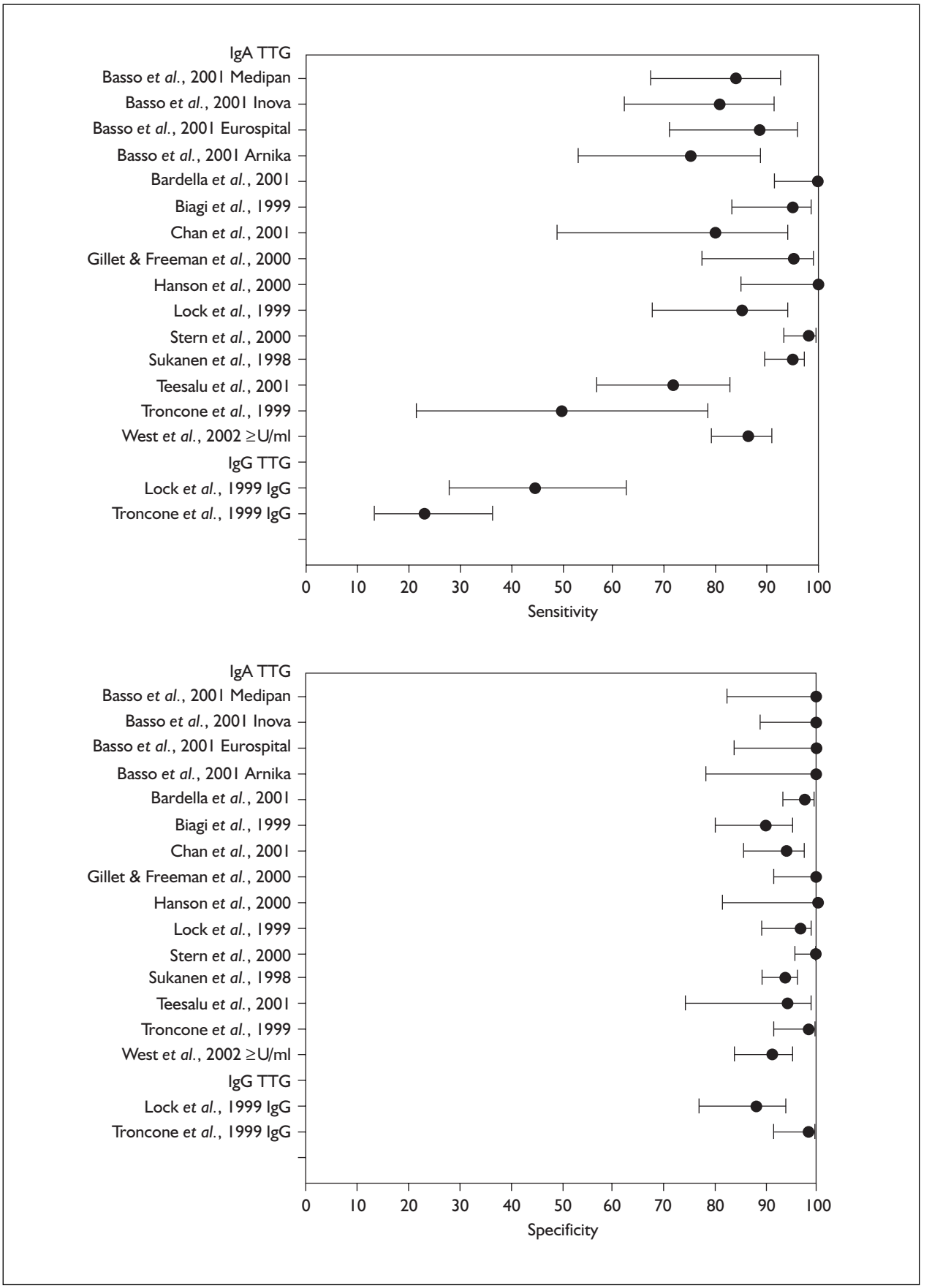

FIGURE 32 *IgA TTG sensitivity and specificity (with 95% confidence intervals)*

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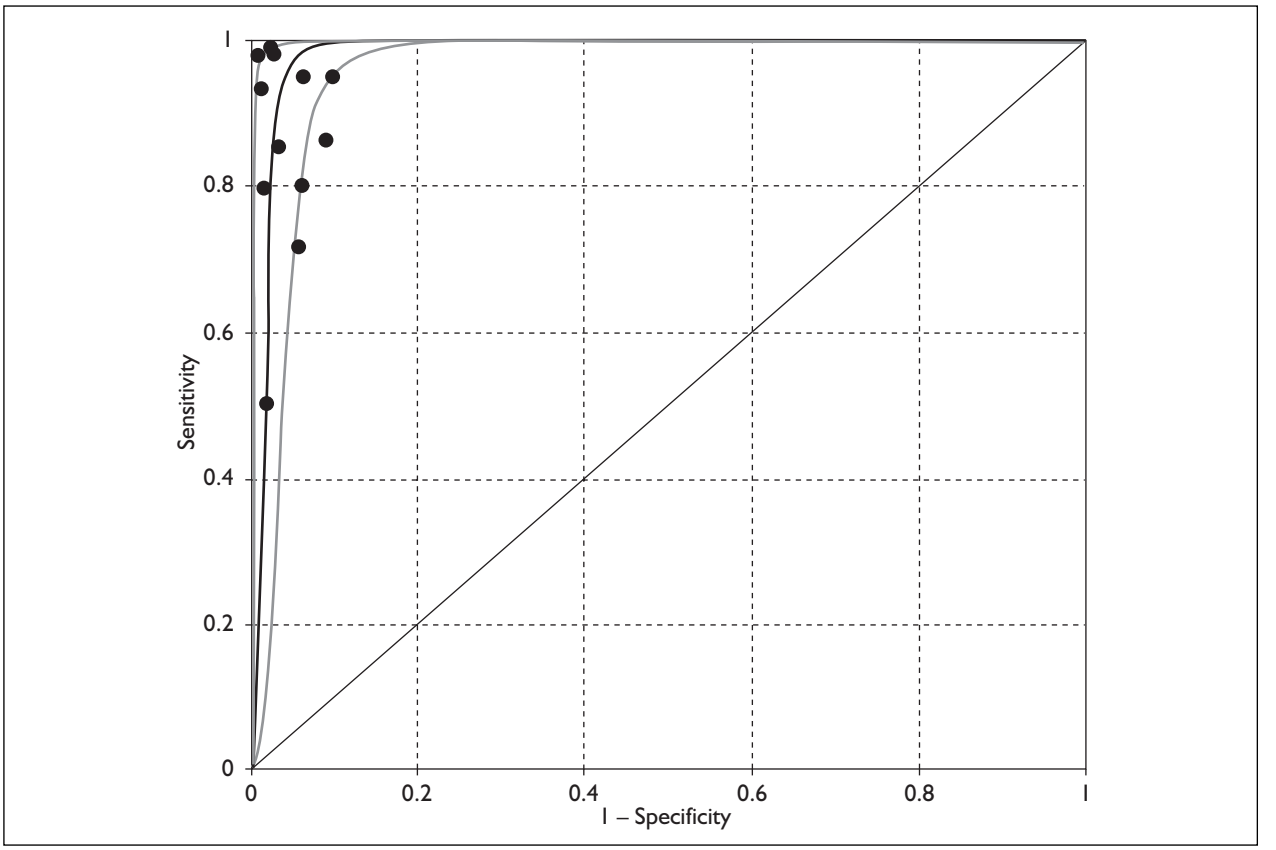

FIGURE 33 *IgA TTG SROC curve*

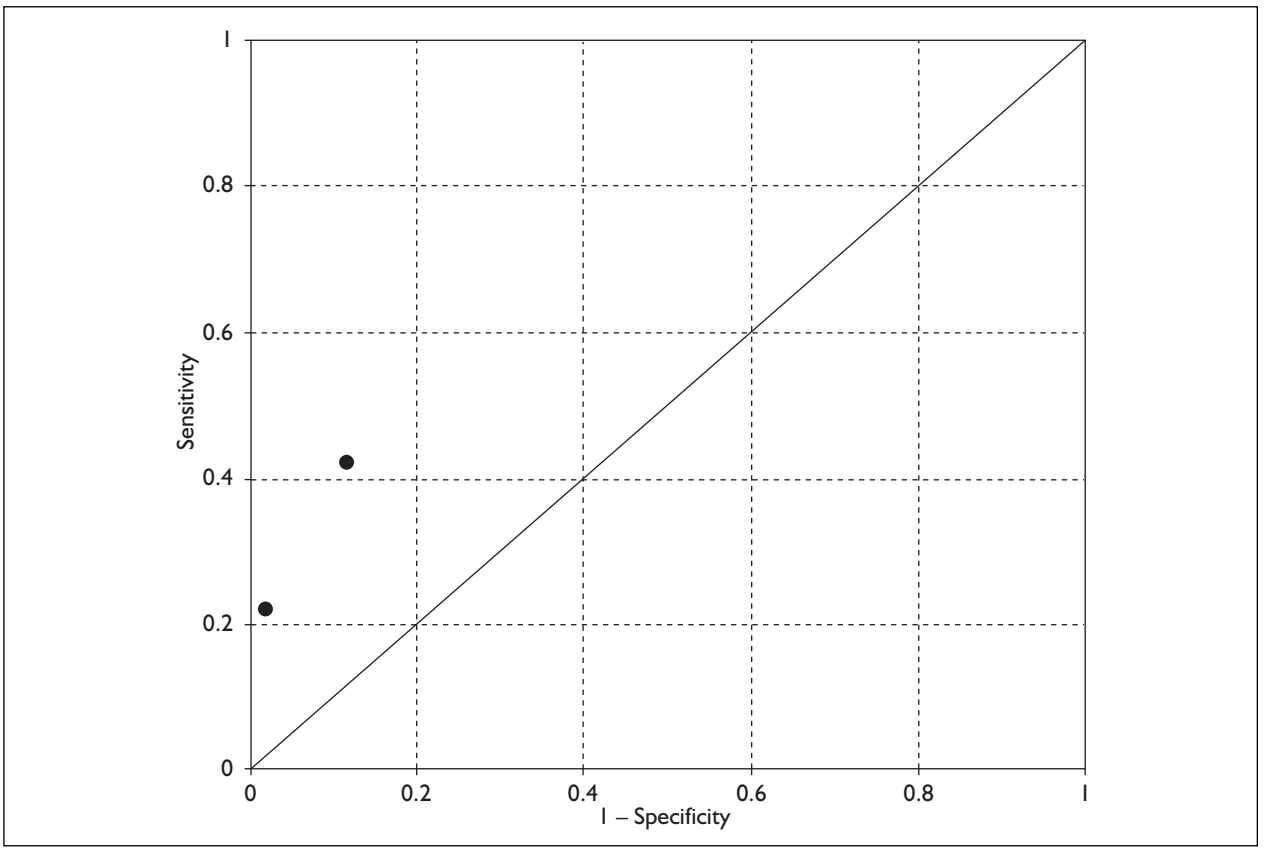

FIGURE 34 *IgG TTG SROC plot*

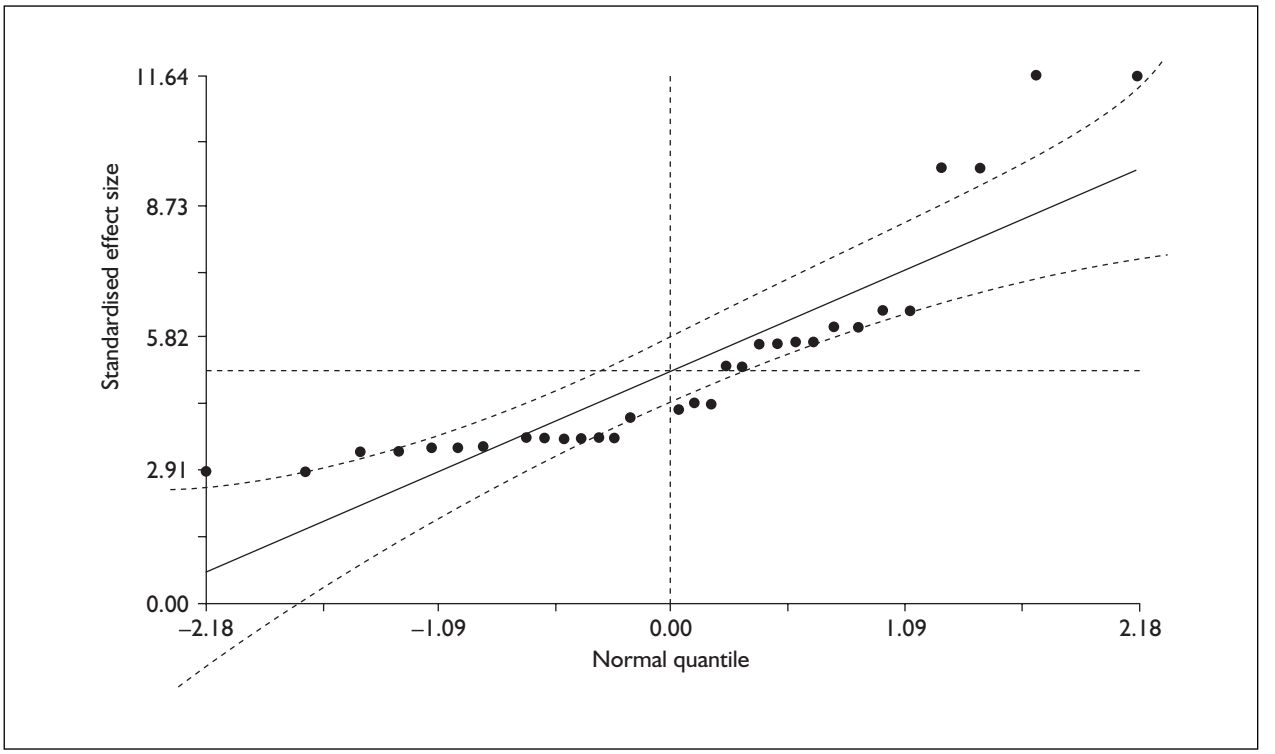

FIGURE 35 *IgA TTG normal quantile plot*

A SROC plot was drawn for IgG TTG based on two studies (*Figure 34*). Specificities were comparably high, but sensitivities were very low.

A normal quantile plot was calculated for all IgA TTG studies (*Figure 35*). It can be seen that not all data points are within the 95% confidence interval bands, suggesting that the data may not be normally distributed. The shape of the curve suggests that the studies may come from different populations, which is the case for the included studies. There are some gaps in the curve, indicating that there may be missing studies.

The studies were then combined in meta-analyses. The DerSimonian Laird random effects method was used to estimate summary likelihood ratios (*Figure 36*). The pooled positive likelihood ratios for IgA TTG was >10, indicating a very useful test given a positive likelihood ratio, whilst the pooled negative likelihood ratio was borderline (0.11), indicating a very useful test/moderately useful test given a negative test result.

Summary of test accuracy results

All antibody tests show reasonably good diagnostic test accuracy, as shown by the areas under the curve (*Table 16*). IgA EMA, IgA ARA and IgA TTG stand out as particularly good tests, followed by IgA AGA and then IgG AGA. Areas under the curve were not calculated for IgG ARA, IgG EMA or IgG TTG as there were too few studies; however, the data show that the sensitivities for IgG ARA and IgG EMA are relatively very low, and these tests do not appear to be used in practice very much. The sensitivities for IgG TTG were also low. As this a fairly recent test compared with the other antibody tests, and only two studies were identified which measured this antibody, a conclusion regarding the diagnostic efficiency of IgG TTG cannot be drawn.

Although the area under the curve gives an overall estimate of diagnostic test performance, it does not reflect the observed variations in the distribution of sensitivity and specificity between studies or the heterogeneity of effect size. For IgA ARA, for example, the sensitivities were highly variable (between 11 and 100%), which would not make it a useful test to use if the sensitivity was of importance, unless centres could consistently report sensitivities in the upper part of the curve. There is generally more variation reported for sensitivities than specificities (for ARA, EMA and TTG), although both sensitivity and specificity are similarly variable for AGA. This may be due to differences in the populations in the included studies, different tests used or different test thresholds set.

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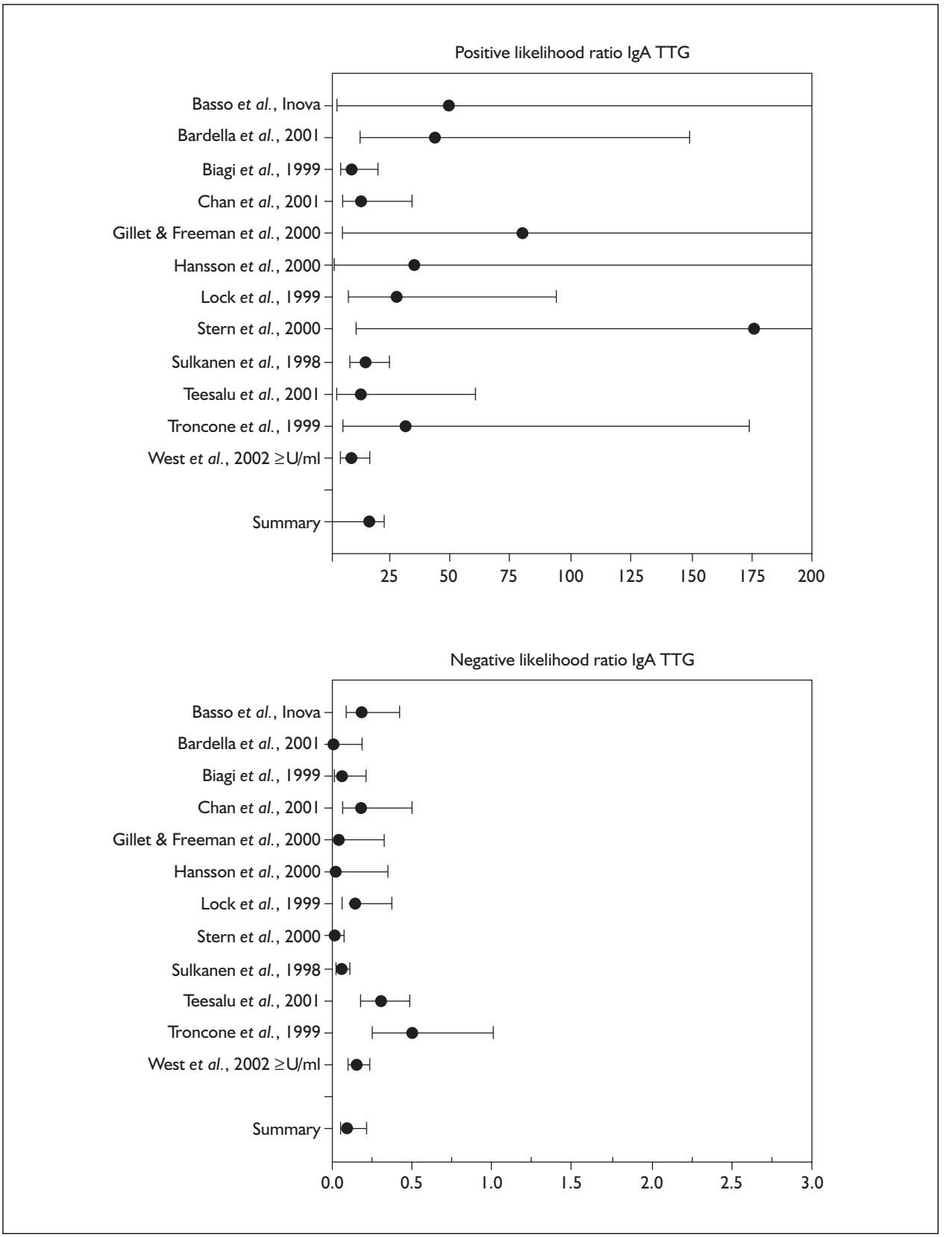

FIGURE 36 *IgA TTG likelihood ratios*

TABLE 16 *Summary of the areas under the SROC curve*

Antibody test	Area under the curve (95% CI)
IgA ARA (all)	0.982 (0.958 to 0.992)
IgA AGA (all)	0.938 (0.910 to 0.957)
IgA AGA (well-described studies)	0.957 (0.829 to 0.991)
IgG AGA (all)	0.908 (0.877 to 0.938)
IgG AGA (well-described studies)	0.845 (0.733 to 0.916)
IgA EMA (all)	0.992 (0.988 to 0.995)
IgA EMA (well-described studies)	0.987 (0.948 to 0.996)
IgA TTG (all)	0.983 (0.959 to 0.993)

TABLE 17 *Summary of Q values*

Antibody test	Equal sensitivity and specificity			Sensitivity fixed at 0.99			Specificity fixed at 0.99		
	Q	Lower 95%	Upper 95%	Specificity	Lower 95%	Upper 95%	Sensitivity	Lower 95%	Upper 95%
IgA AGA (all studies)	0.875	0.843	0.902	0.435	0.319	0.559	0.230	0.141	0.352
IgA AGA (well-described studies)	0.907	0.766	0.966	0.710	0.301	0.933	0.167	0.010	0.787
IgG AGA (all studies)	0.841	0.808	0.876	0.156	0.101	0.256	0.292	0.211	0.415
IgG AGA (well-described studies)	0.793	0.691	0.868	0.000	0.000	0.005	0.525	0.343	0.700
IgA ARA	0.946	0.907	0.969	0.860	0.705	0.941	0.512	0.181	0.832
IgA EMA (all studies)	0.972	0.961	0.981	0.952	0.919	0.972	0.842	0.654	0.937
IgA EMA (well-described studies)	0.976	0.923	0.993	0.972	0.889	0.993	0.309	0.000	0.999
IgA TTG	0.957	0.918	0.978	0.925	0.823	0.970	0.367	0.050	0.863

The value of the heterogeneity statistic *Q* calculated from the SROC curves gives the point at which sensitivity and specificity are equal (*Table 17*). It can be seen that this value is highest for EMA, followed by TTG and ARA, with AGA slightly lower. When the sensitivity is fixed at 99%, the corresponding specificity remains highest for IgA EMA, followed by IgA TTG, IgA ARA and IgA AGA. When the specificity is fixed at 99%, the corresponding sensitivity remains high only for IgA EMA.

Summary likelihood ratios were then calculated, as the regression analysis provided no evidence that test characteristics varied with test thresholds. They provide a relatively meaningful summary estimate, as they indicate by how much a test will increase the probability of a positive or negative diagnosis.

A summary of the results of the likelihood ratio meta-analyses is given in *Tables 18* and *19* and *Figure 37*. A caveat must be that in general the studies reported heterogeneous effect sizes. The heterogeneity was largely not related to a consecutive cohort design as an indicator of quality. Other possible reasons for heterogeneity include other aspects of study quality, differences in the tests (including manufacturers and substrates) and their execution in the laboratories, different populations and reference standards.

No formal statistical comparisons of the different tests have been made. The summary estimates and confidence intervals, however, suggest some conclusions. IgA ARA estimates are imprecise, but the test appears to perform well with regard to the positive likelihood ratio relative to AGA. IgA EMA tests have the highest pooled positive likelihood ratio and lowest negative likelihood ratio, making it the overall most useful test, whilst IgA TTG tests have good results for the positive likelihood ratio compared with AGAs. IgA and IgG AGA have lower pooled positive likelihood

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TABLE 18 *Summary of positive likelihood ratio meta-analysis*

Test	Studies included	No. of studies	No. of subjects	LR +ve	95% CI	Q	df	p
ARA	All	12	1390	27.98	9.53 to 82.12	66.60	11	<0.00001
	Well-described cohort	1	157	45.67	5.71 to 365.48			
IgA AGA	All	42	4750	6.72	5.13 to 8.80	245.35	41	<0.00001
	Well-described cohort	11	1482	8.96	5.60 to 14.33	28.92	10	0.0013
IgG AGA	All	35	4439	3.71	3.07 to 4.48	167.48	33	<0.00001
	Well-described cohort	11	1811	3.96	2.94 to 5.35	40.10	10	<0.00001
IgA EMA	All	42	4464	43.64	28.70 to 66.37	65.64	41	0.0086
	Well-described cohort	8	1171	48.48	23.44 to 100.29	9.34	7	0.23
IgA TTG	All	12	1473	17.00	11.19 to 25.84	15.51	11	0.16
	Well-described cohort	1	56	49.37	3.14 to 776.95			

df, Degrees of freedom; LR, likelihood ratio.

TABLE 19 *Summary of negative likelihood ratio meta-analysis*

Test	Studies included	No. of studies	No. of subjects	LR –ve	95% confidence interval	Q	df	p
ARA	All	12	1390	0.25	0.14 to 0.46	213.14	11	<0.00001
	Well-described cohort	1	152	0.67	0.47 to 0.96			
IgA AGA	All	42	4750	0.22	0.17 to 0.30	380.58	41	<0.00001
	Well-described cohort	11	1482	0.32	0.21 to 0.49	65.57	10	<0.00001
IgG AGA	All	35	4439	0.23	0.17 to 0.31	268.02	33	<0.00001
	Well-described cohort	11	1811	0.35	0.27 to 0.45	20.99	10	0.021
IgA EMA	All	42	4464	0.09	0.06 to 0.13	185.72	41	<0.00001
	Well-described cohort	8	1171	0.09	0.03 to 0.25	68.36	7	<0.00001
IgA TTG	All	12	1473	0.11	0.06 to 0.21	64.67	11	<0.00001
	Well-described cohort	1	56	0.19	0.09 to 0.42			

ratios than EMA and TTG, with IgA AGA being a moderately more useful test than IgG AGA given a positive test result. The pooled negative likelihood ratios of IgA and IgG AGA are slightly higher than those of IgA EMA and IgA TTG, making them moderately useful tests given a negative test result.

Test accuracy results in screening cohorts

Four studies were identified where the populations consisted of at-risk individuals (children with diabetes or first-degree relatives of patients with coeliac disease) compared with the other studies where the populations were symptomatic. Both of the studies of relatives and neither of the studies for children with diabetes were well-described cohorts. At least some of the sensitivities are relatively low compared with those of other studies; it is not clear, however, whether this can be attributed to population characteristics or is due to other factors. At least some of the studies with symptomatic populations also have low results for sensitivities. *Table 20* shows the sensitivities and specificities.

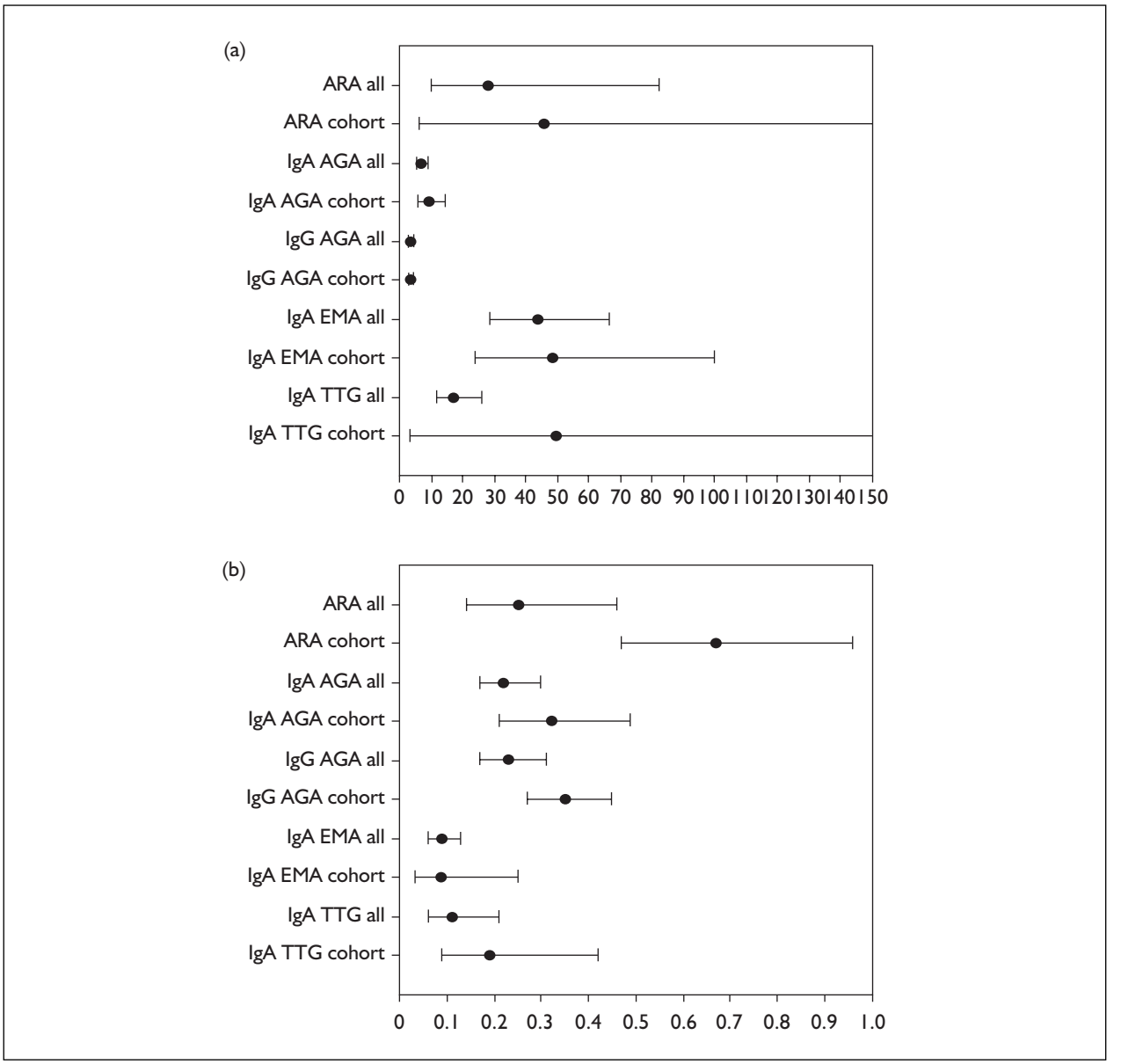

FIGURE 37 *Summary of (a) positive and (b) negative likelihood ratios*

TABLE 20 *Test accuracy results in screening cohorts*

Author, year	Type of cohort	Antibodies measured	Sensitivities (%)	Specificities (%)
Keddari *et al.*, 1989, Algeria[88]	Children with diabetes	IgA ARA IgG ARA	83.3 Data not given	Data not given Data not given
Savilahti *et al.*, 1986, Finland[89]	Children with diabetes	IgA AGA or IgG AGA or IgG ARA	100	92
Auricchio *et al.*, 1988, Italy/Finland/Spain (multicentre)[73]	1st-degree relatives of patients with coeliac disease	IgA AGA IgG AGA IgA ARA IgG ARA	46.7 66.7 33.3 93.3	92.7 81.8 99.3 97.1
Mäki *et al.*, 1991, Finland[82]	1st-degree relatives of patients with coeliac disease	IgA AGA IgG AGA IgA ARA	30.8 46.2 Data not given	87.2 89.0 Data not given

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Discussion

IgA AGA, IgG AGA, IgA ARA, IgA EMA and IgA TTG all perform well when the area under the SROC is considered with areas under the curves of >0.90. IgG AGA still has useful test performance with an area under the curve of 0.845. Taking into account both areas under the curves and LRs, IgA EMA appears to be the most useful diagnostic test, with IgA TTG also showing good test performance. IgA and IgG AGA tests are moderately useful, and while IgA ARA has a good area under the curves, it has a poor negative likelihood ratio and effect sizes were less precisely measured.

There is much heterogeneity between study results, and in particular wide ranges were described for sensitivities. In addition to bias from study design, this could be due to differences in populations or test methodologies or thresholds.

There were differences in populations in terms of symptoms and age, although all were drawn from similar settings (hospital based). The majority of populations in the studies were highly symptomatic, and thus different from a screening population. There were four studies in populations for whom screening might be considered, two studies of type 1 patients with diabetes and two of relatives of patients with coeliac disease. The limited information these studies provide means that there is still some uncertainty as to whether the tests would display the same diagnostic accuracy in a population with diabetes or another population where there may be a proportion of silent coeliac disease. It is noticeable that the two studies of relatives reported relatively low sensitivity for IgA AGA tests. As such studies involve biopsy of asymptomatic subjects, further studies are likely to present ethical and practical difficulties.

Although studies mostly overall employ the same methodologies for specific tests (ELISA for AGA and TTG and indirect immunofluorescence for EMA and ARA), there are differences in how the individual laboratories perform the tests: different in-house methods and different test kits are used, with different cut-offs for positivity. Variations in ELISA methodology include the enzyme used, the length of incubation and type of antigen preparation. Some studies also use techniques such as DIG-ELISA. The cut-off points are reported in a variety of units (for example, arbitrary units, ELISA units, optical density, millimetres for diffusion in DIG-ELISA) and quantitative comparisons are not possible. In practice, however, there may be good agreement between positive and negative results between laboratories that take part in external quality assurance schemes such as NEQAS UK. The results of studies which use identical test kits may be more comparable, as only a small amount of variation between different batches would be expected.

For indirect immunofluorescence, the interpretation of results requires expertise and can be subjective regarding the threshold for positivity, and there may be problems with interference from other antibodies.

There has been a trend towards the use of human umbilical cord instead of monkey oesophagus as a substrate for indirect immunofluorescence, which has advantages in terms of both ethical considerations and expense. Human umbilical cord is thought to be almost as good a substrate as monkey oesophagus,[90] although the same subjectivity in interpretation remains. Our results show that there is very little difference between the two substrates, although the results for human umbilical cord are based on a smaller sample size than for monkey oesophagus.

The choice of a test may depend upon factors other than test characteristics alone. Semi-automated ELISA may be preferred by laboratories. Hence, although the systematic review suggests that EMA has somewhat better performance than TTG, TTG would be preferred over gliadin, if an ELISA test were required. There is also the issue of using human tissue, which has the potential for infection, in EMA tests.

We have only been able to review systematically the use of single tests. It is not known whether obtaining a positive result in one test is independent of obtaining a positive result in a further test, except in the rare case of IgA deficiency, where it is unlikely that a patient will have a positive result in any IgA antibody test. Although this suggests the use of the generally less discriminatory IgG gliadin test, we do not know with any precision what added value this would provide from the results of studies reporting combined tests. The possible impact of combining tests is considered in the model.

Although the reviewers undertook a comprehensive database search and attempted to identify unpublished data, it remains possible that relevant studies may have been missed. The

normal quantile plots show some gaps between data points, indicating that there may be missing studies, particularly for TTG. TTG is a relatively recently developed test, and research studies may still be in progress and papers may have been published since the date of the searches on which the systematic review was based.

The study quality overall was poor, particularly in terms of study design description, with only 23.7% (n = 18) of potentially relevant studies clearly reporting the patient selection method. Reporting quality issues arose around the use of terminology by some authors. 'Cases' and 'controls' were not always used to describe an epidemiological case–control design, but often referred to a poorly described cohort design where patients were subsequently split into 'cases' and 'controls' after determination of disease status.

There was also a lack of information on whether the tests were applied independently of all other clinical information or whether patients had been selected or referred on the basis of other test results, and whether tests had been performed independently and blindly.

The reviewers were faced with the problem of either including poorly reported studies and potentially biasing the results, as it was not clear what selection methods had been operating on the study populations, or restricting the included studies to well-described ones, thus ignoring a large volume of research which may or may not have been poorly conducted. Equally, the reviewers recognise that including badly described studies on the assumption that they may have been appropriately conducted, but excluding well-described non-cohort studies, may have resulted in the inclusion of poorer quality studies, thereby potentially introducing bias into the results. Therefore, a subgroup analysis of 18 well-described cohorts was conducted and the results were compared with those of the poorly described studies. There were in fact few differences in results between well-described studies and other studies.

The studies based on well-described cohorts were no better than the other studies on other indicators of the quality of diagnostic test studies, and thus cannot be assumed to be of better quality other than having clearly described patient selection. However, this subset of well-described cohorts was scrutinised more carefully and agreement on the quality criteria was reached between three or four reviewers, and in this process the quality ratings of all studies were reduced by at least a small amount.

The ideal study design for a test accuracy study is an untreated, randomly or consecutively selected cohort with defined inclusion criteria, where all individuals prospectively undergo both the antibody test and the reference test. Both test samples should be evaluated independently and blindly and the patient should not have undergone previous antibody or other tests, which would lead to a referral for further antibody or reference tests. Retrospective evaluation of stored samples can be equally acceptable provided that it can be demonstrated that no earlier selection mechanisms had been operating. The quality of the studies included in this review is poorly reported and thus questionable, and this may have introduced bias and also may explain some of the heterogeneity in effect size.

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Chapter 5

The decision analytic model

Question considered by the model

Our survey of paediatric endocrinologists [members of British Society of Paediatric Endocrinology and Diabetes (BSPED)] demonstrates that there are significant variations in the practice of screening for autoantibodies associated with coeliac disease in children with diabetes. The ISPAD guidelines for the screening of children for coeliac disease also recognise this variation – 'Controversy exists as to the need for and frequency of screening tests to detect clinically asymptomatic cases of coeliac disease' – and make the following recommendations:

> "Consider the possibility of coeliac disease in any child or adolescent with gastrointestinal symptoms, unexplained poor growth or anaemia.
> "Immunological screening should be considered close to the time of diagnosis of diabetes and repeated if clinical circumstances suggest the possibility of coeliac disease."

ISPAD guidelines recommend definitive diagnosis by jejunal biopsy and point out that:

> "A normal mucosa in a seropositive child does not preclude later development of coeliac disease. Seropositive patients require regular reassessment."

This report utilises a decision-analytic model to quantify the costs and benefits of systematic screening for coeliac disease **at the time of diagnosis of diabetes** only, as this was what was the commissioned brief. However, coeliac disease can develop at any time after the onset of diabetes and it should be noted that the cost-effectiveness of repeat screening strategies, such as the annual screening policy adopted by ~50% of the respondents to the BSPED survey, could be evaluated by a similar model.

The decision analytic model uses the basic structure shown in *Figure 38*.

In addition to requiring information about the test characteristics (which have been systematically reviewed in this report), the prevalence of undiagnosed coeliac disease in this population, the costs and consequences of both treated and untreated coeliac disease, patterns of diagnosis in the absence of screening, estimated compliance rates with diet and the disutility of diet need estimating for this model.

This report was commissioned as a rapid review and the authors were not funded to undertake systematic reviews of these other parameters required to inform the model. Accordingly, where possible we have attempted to identify existing systematic reviews from the literature to estimate these parameters and, if no systematic reviews were identified, we have used the best individual studies identified to derive parameters (see Appendix 9 for details of final search strategies). Where we have not identified any empirical evidence about parameters, we have tried to estimate plausible ranges of values and explored these in sensitivity analyses.

The following possible screening strategies are compared:

1. no screening
2. biopsy of all children
3. single autoantibody test confirmed by biopsy in those testing positive
4. combination of autoantibody tests confirmed by biopsy in those testing positive
5. single autoantibody test without confirmatory biopsy
6. combination of autoantibody tests without confirmatory biopsy.

Neither strategy 2 (biopsy all) or strategies 5 and 6 (no biopsy confirmation of positive tests) are used in current clinical practice, but all possible screening strategies were modelled for completeness.

The tests examined in the model are AGA IgA, AGA IgG, EMA IgA, ARA IgA or TTG IgA. IgG testing using EMA, TTG and ARA were not included owing to the small number of studies identified relating to these tests.

We looked at two combination strategies: EMA IgA plus AGA IgG, and TTG IgA plus AGA IgG. From the review, EMA IgA and TTG IgA appeared to have the best test characteristics. Assuming that

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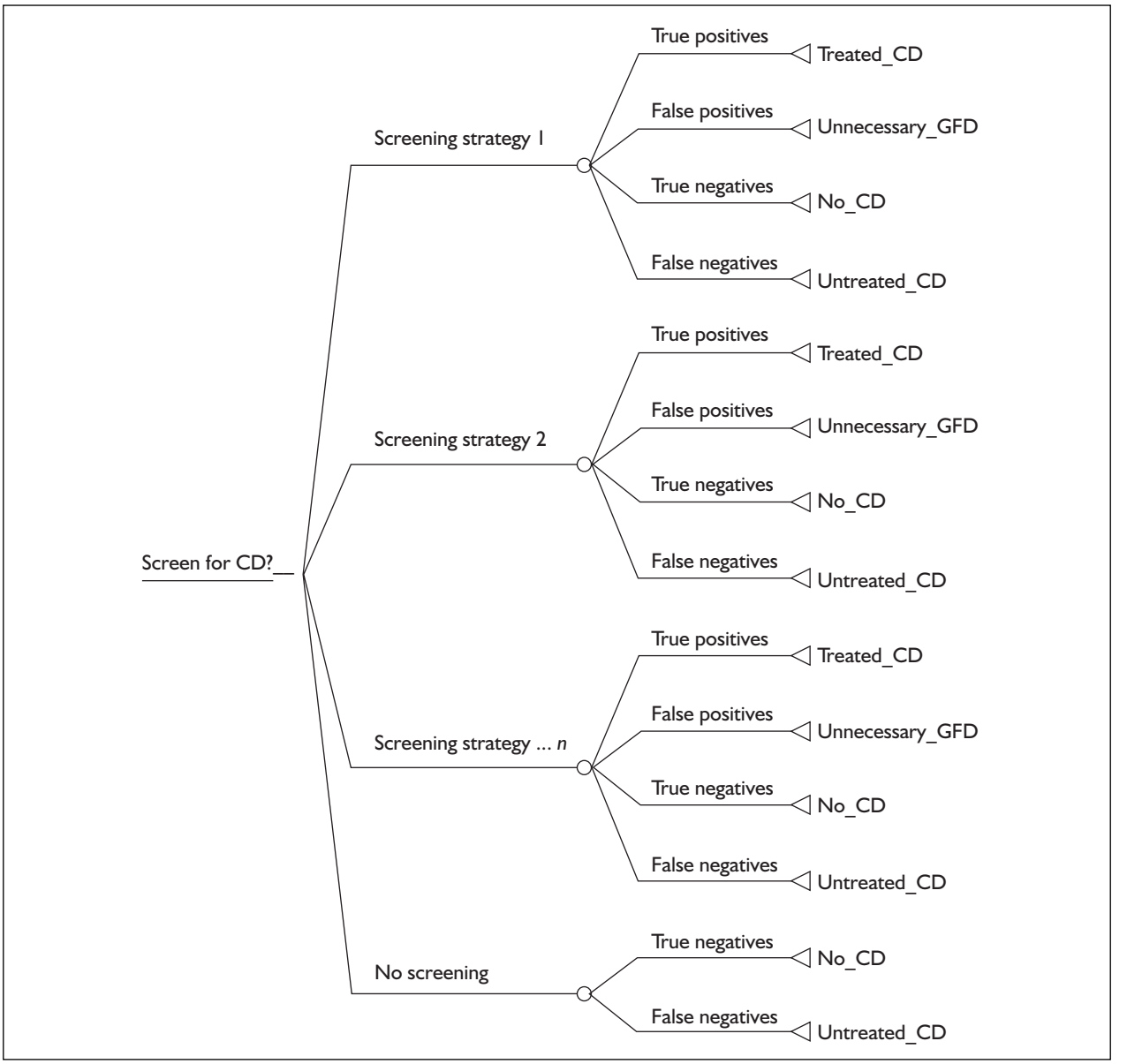

FIGURE 38 *Basic structure of decision analytic model (CD, coeliac disease; GFD, gluten-free diet)*

total IgA will not be assessed routinely, an IgG test is likely to be the most appropriate choice as the second test for these combinations as it is likely to pick up IgA-deficient patients. The AGA IgG test is used here as we have insufficient information from the review concerning alternative tests for IgG.

Basic assumptions

We have made the basic assumption that coeliac disease has a similar manifestation and clinical spectrum in children with diabetes as it has in other children despite the increased prevalence of the disease. This means that the model can equally well be applied to a general population, or to another group of children (such as those with Down's syndrome) in whom the prevalence of coeliac disease may be higher, to determine the cost-effectiveness of screening.

The model assumes that a biopsy gives a definitive diagnosis, and there are no false positives for those who go on to have an endoscopy and positive biopsy. A further simplifying assumption is that all patients will accept a biopsy if it is offered.

Perspective

In accordance with current guidance, the analysis is from an NHS perspective. It does not take into

account, therefore, the costs (e.g. of a gluten-free diet) that are borne by the patient.

Software

The model was produced in Microsoft Excel 2000.

Discounting

The costs and benefits are discounted at current treasury recommended rates of 6% for costs and 1.5% for benefits. A range of discount rates for both the costs and benefits are explored in the sensitivity analyses.

Time horizon

Because the disease is not curable, we have modelled costs and benefits over the full life expectancy of the screened population.

Parameters

The following parameters are used in the model:

- the prevalence of undiagnosed coeliac disease
- the sensitivity and specificity of the various autoantibody screening tests
- the costs of the autoantibody tests
- the cost of definitive diagnosis by endoscopy
- the cost of a gluten-free diet to the NHS
- the mean utility of the health states associated with diabetes
- the mean utility of the health states associated with treated coeliac disease
- the mean utility of the health states associated with untreated coeliac disease
- the disutility of endoscopy
- the disutility of a gluten-free diet
- the degree of compliance with a gluten-free diet
- life expectancy for childhood-onset type 1 diabetes
- the changes in life expectancy associated with both treated and untreated coeliac disease compared to the rest of the population with childhood-onset type 1 diabetes
- the proportion of individuals who would have been later diagnosed as having coeliac disease through normal clinical suspicion if they had not been picked up earlier through screening, and the mean delay to diagnosis for such individuals
- the proportion of individuals with a false-positive diagnosis of coeliac disease through screening who would discover this and abandon a gluten-free diet and the mean delay to abandonment of gluten-free diet for such individuals (only applicable to those strategies without confirmatory biopsy).

The base-case values for the above parameters are given in *Table 21*, along with the maximum and minimum values explored in the sensitivity analysis. The choice of values is explained more fully in the subsequent text.

Prevalence of undiagnosed coeliac disease

In our survey of UK clinicians, respondents provided information on numbers of children with biopsy-diagnosed coeliac disease. A total of 297 patients had coeliac disease, giving a prevalence of 2.0% (95% CI 1.8 to 2.2) for children with diabetes and with diagnosed coeliac disease. This figure underestimates the true prevalence as not all centres screen children routinely; therefore, we searched for any systematic review that estimated the true prevalence of coeliac disease in children with diabetes.

One review, by Holmes,[47] was found. Holmes collated the papers he had collected over many years and undertook a search on MEDLINE to identify papers. He found 20 papers where children with diabetes were screened via one or more autoantibody test for coeliac disease. He found that 20 of these studies reported biopsy-proven coeliac disease in children with diabetes; these are summarised in *Table 22*.

The mean prevalence estimate is 3.85% and the median is 3.45%. However, there is evidence that the sensitivity and specificity of autoantibody tests have improved over time and earlier studies may, therefore, underestimate the true prevalence of coeliac disease. Plotting the above study results by year of publication is suggestive of an increase in the estimated prevalence of coeliac disease in children with diabetes over time, as shown in *Figure 39*.

The data give an observed prevalence of coeliac disease in children with diabetes of 3.4% but extrapolation of the findings suggests that the true underlying prevalence of coeliac disease in these children may be up to 6%. Even this, we suspect, will be an underestimate as not all test-positive children were biopsied and autoantibody tests are not 100% sensitive, hence there will be children

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TABLE 21 *Parameter values*

Item	Base	Low	High	Source
Prevalence sensitivity (%)	0.033	0.01	0.08	Barera *et al*., 2002[91]
IgA AGA	91	77	97	
IgG AGA	79	69	87	
EMA	98	91	99	Systematic review in this report
IgA ARA	95	92	97	
IgA TTG	96	92	98	
Combined test				
Specificity (%)				
IgA AGA	91	77	97	
IgG AGA	79	69	87	
EMA	98	91	99	Systematic review in this report
IgA ARA	95	92	97	
IgA TTG	96	92	98	
Combined test				
Costs (£)				
IgA AGA	11.00	9.00	15.00	Coleborn P, Pathology Laboratories, Heartlands Hospital, Birmingham NHS Trust, personal communication, 2001; Mann S, Clinical Chemistry, Birmingham Children's Hospital, Birmingham NHS Trust, personal communication, 2001
IgG AGA	11.00	9.00	15.00	
EMA	10.00	8.00	11.00	
IgA ARA	14.00	12.00	16.00	
IgA TTG	11.00	9.00	15.00	
Combined test	Sum–4	Sum–4	Sum–4	
Endoscopy	500	280	800	Holmes, 2001;[47] Harewood and Murray, 2001[92]
Diet	1200	350	2000	Derived from Leicester Health Authority Prescribing Guide[93] and BNF costs[94]
Utilities				
No CD	0.90	Not varied		
Treated CD	0.88	0.85	0.90	
Untreated CD	0.82	0.79	0.85	Review of studies/assumption
Endoscopy	–0.002	–0.001	–0.003	
GFD	–0.04	–0.01	–0.08	
Compliance discount rate (%)	0.60	0.30	0.90	Review of studies
Costs	6	0	6	Treasury recommended rates
Benefits	1.5	0	6	
Life expectancy (years)				
Non-CD	52	48	56	
Treated CD	0	+1	–1	Review of studies
Untreated CD	–4	–1	–8	
Corrected diagnosis				
FN never diagnosed	0.30	0.10	0.50	
Delay to diagnose (years)	5	2	10	Review of studies/assumption
FP never corrected	0.10	0.05	0.15	
Delay to correction (years)	1	0.5	2	

with coeliac disease who remained undiagnosed in these studies. The conclusion that the true prevalence may be higher is supported by a recent high-quality inception cohort study by Barera and colleagues of 274 children with newly diagnosed diabetes in Italy, which demonstrated a period prevalence 6.2% during the study period.[91] The mean age of diagnosis was 8.3 years and the median follow-up was 2 years.

To estimate the cost-effectiveness of a programme of screening for coeliac at the time of diagnosis of diabetes, it is necessary to know the prevalence of coeliac disease at this time. Barera and colleagues[91] used repeated serological screening for 274 consecutive patients at the diagnosis of type 1 diabetes (mean age = 8.28 ± 4.65 years). One patient had a diagnosis of coeliac disease before the onset of diabetes. The

TABLE 22 *Prevalence estimates for coeliac disease in children with diabetes*

Year	Place	Sample size	Prevalence	Author
1984	Finland	215	2.3	Maki *et al.*[95]
1986	Finland	201	3.5	Savilahti *et al.*[89]
1987	Italy	146	3.4	Cacciari *et al.*[96]
1988	Germany	1032	0.97	Koletzko *et al.*[97]
1991	Italy	498	3.2	Barera *et al.*[98]
1992	Australia	180	2.2	Gadd *et al.*[99]
1993	Sweden	436	4.8	Sigurs *et al.*[100]
1993	USA	211	1.4	Rossi *et al.*[101]
1994	Australia	273	1.8	Verge *et al.*[102]
1996	Finland	776	2.4	Saukkonnen *et al.*[103]
1996	Italy	133	3.7	Lorini *et al.*[104]
1996	Italy	172	3.5	Lorini *et al.*[105]
1996	Algeria	116	16.4	Boudraa *et al.*[106]
1996	Spain	141	4.2	Calero *et al.*[107]
1997	Italy	200	4.0	Cacciari *et al.*[108]
1998	Canada	236	5.0	Fraser-Reynolds *et al.*[109]
1998	UK	167	4.8	Acerini *et al.*[110]
1999	Sweden	115	6.2	Carlsson *et al.*[52]
2000	Austria	403	1.5	Schober *et al.*[111]
2000	Germany	520	1.7	Kordonouri *et al.*[50]

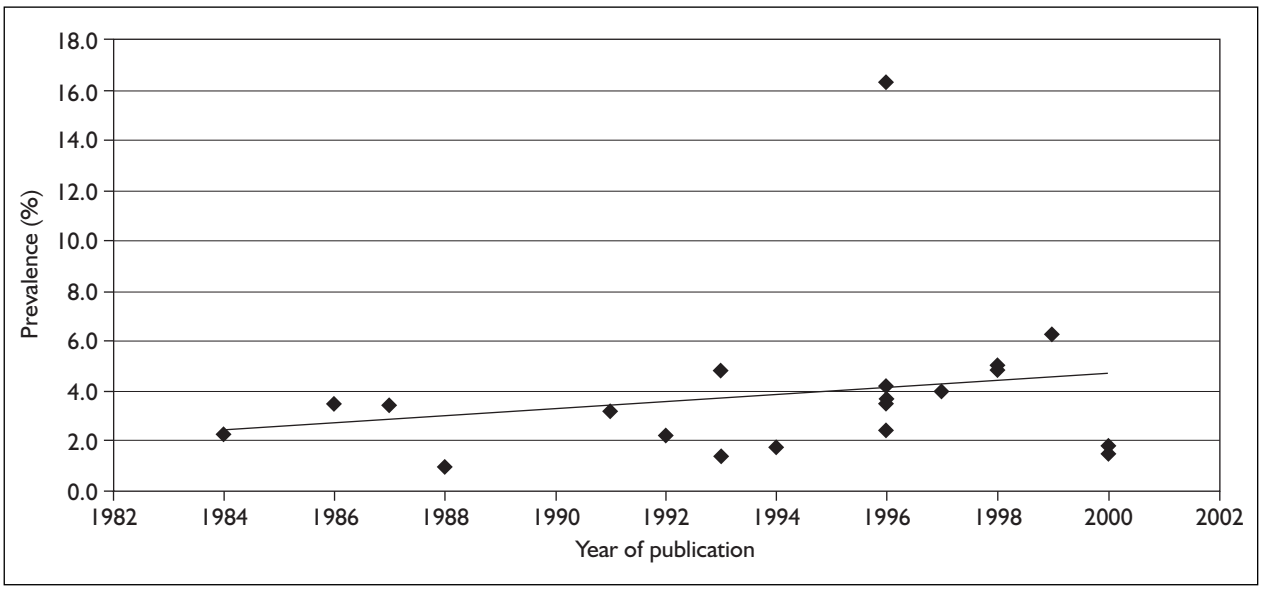

FIGURE 39 *Estimated prevalence of coeliac disease in children with diabetes by year of study publication. The Algerian data*[106] *(outlier) were excluded when fitting the line.*

IgA EMA test was used; patients with a moderate or strong positive result or two consecutive weak positive test results were biopsied. At diagnosis, 10 of 273 patients tested positive by these criteria and were referred on for jejunal biopsy; coeliac disease was diagnosed in nine. Twelve more patients, with a negative anti-endomysial antibody test at diabetes onset, tested positive within 4 years; 10 of them had biopsies performed, and seven had coeliac disease. Therefore, the overall prevalence of biopsy-confirmed coeliac disease in the entire cohort of patients was 6.2%. We have used the estimate of 3.3% (9/273) undiagnosed cases of coeliac disease at time of diabetes diagnosis from this study as our base-case prevalence. Values of 1 and 8% were used in the sensitivity analysis.

Sensitivity and specificity of autoantibody tests

Results from the systematic review conducted for this report were used. IgG tested by EMA, ARA or TTG was not considered in the model owing to the small number of studies found.

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The values used in the model were derived from the SROC curves for each test and defined at the point where sensitivity and specificity were equal. This point (Q) can be regarded as a point of 'equity' for those with and without disease, in that it is equally accurate for both groups. This gives the following estimates for use in the base case, with low and high values for the sensitivity analysis being provided by the upper and lower confidence intervals:

Antibody test	Equal sensitivity and specificity		
	Estimate (%)	Lower 95% (%)	Upper 95% (%)
IgA AGA	91	77	97
IgG AGA	81	72	87
IgA EMA	98	92	99
IgA ARA	95	91	97
IgA TTG	96	92	98

It might be preferable to use a different point on the SROC curve to optimise predictive value, but this is less straightforward, as this point will depend on the prevalence of the disease in the population being screened (which is itself a variable parameter in the model).

For the two combination regimens considered, the simplifying assumption was made that the results of the tests are independent. Sensitivity (SENS) and specificity (SPEC) of the combinations are calculated as follows:

$$SENS_{combination} = 1 - [(1-SENS_{test}\ 1) \times (1-SENS_{test}\ 2)]$$
$$SPEC_{combination} = SPEC_{test}\ 1 \times SPEC_{test}\ 2$$

Costs

Cost of auto-antibody testing

Costs of various test kits were provided by two of our clinical advisers at different centres (Coleborn P, Pathology Laboratories, Heartlands Hospital, Birmingham NHS Trust, personal communication, 2001; Mann S, Clinical Chemistry, Birmingham Children's Hospital, Birmingham NHS Trust, personal communication, 2001). A cost of £4 was added to these to cover the cost of obtaining a sample (venepuncture, etc.). The table below summarises the costs (£) obtained from the two advisers along with the base, low and high costs we use in the model.

Cost of diet

Since the economic evaluation takes an NHS perspective, the costs of a gluten-free diet borne by the NHS are included but the costs borne by individuals are not. We found no studies of the cost to the NHS of a gluten-free diet. One study from Italy showed that teenagers consumed an average of about 11.32 kg/month of gluten-free products provided by the Italian Health System. The mean cost for each patient was estimated to be ECU 1490/year.[112]

We were uncertain of the applicability of this Italian estimate to the situation in the UK and therefore we estimated a plausible range of costs of a gluten-free diet to the NHS.

In the UK, some foods suitable for a gluten-free diet are approved by the Advisory Committee on Borderline Substances and may be prescribed on FP10 prescriptions dispensed by community pharmacies. These are dietary costs thus borne by the NHS.

Foods available on prescription are approved flour mixes, plain biscuits, pizza bases, pasta and bread. There are no national guidelines on how much gluten-free food should be prescribed: however, Leicester Health Authority has produced a prescribing guide (see *Table 23*).[93] This guide should be tailored to individual patient food preferences. Gluten-free loaves are approximately one-third the size of standard loaves. Bread, and other gluten-free products, vary in taste and texture and therefore in acceptability to individuals. Some patients prefer to make their own bread using flour mixes. It is therefore likely that both the quantity and the costs of foods prescribed for individual patients vary considerably.

	Mann	Coleborn	Other costs	Base	Low	High
AGA IgA	11.74	7	4	11	9	15
AGA IgG	(IgA & IgG)	7	4	11	9	15
EMA	6.45	5–6	4	10	8	11
ARA	10.90[a]	–	4	14	12	16
TTG IgA	–	Similar to AGA	4	11	9	15

All costs in UK pounds.
[a] For IgA, IgG and IgM done together.

TABLE 23 *Prescribing guidance for a gluten-free diet, based on Andrews 2000*[93]

Age/physical activity	Approx. calorie requirement (kcal/day)	Approx. monthly requirement
Child up to 2 years	1000–1200	4–8 loaves of bread 2 pkts biscuits/crackers 1 pkt pizza bases 500 g pasta 500 g flour
3–5-year-old child	1300–1700	8–16 loaves of bread 2 pkts biscuits/crackers 1 pkt pizza bases 500 g pasta 500 g flour
6–10-year-old child Younger inactive female Older inactive male	1500–1900	8–24 loaves of bread 2 pkts biscuits/crackers 1 pkt pizza bases 500 g pasta 500 g flour
10–15-year-old child Younger active female Younger inactive male Older active male	2000–2500	16–32 loaves of bread 3 pkts biscuits/crackers 1 pkt pizza bases 500 g pasta 500 g flour
15–18 years old	2800+	20–40 loaves of bread 2 pkts biscuits/crackers 1 pkt pizza bases 500 g pasta 500 g flour

TABLE 24 *Estimated range of cost of a gluten-free diet to the NHS by age-group*

	Range of annual costs (£)		
Age group (years)	Min.	Max.	Midpoint
≤2	169	658	414
3–5	236	1018	627
6–10	236	1378	807
10–15	390	1785	1088
15–18	458	2145	1302

We used the above prescribing guide and costs of gluten-free foods taken from the BNF[113] to estimate a range of annual costs of prescriptions for patients of different ages, which are shown in *Table 24* (see Appendix 10 for full details of the calculation). In practice, wider variations in both quantities and costs of the items prescribed are likely to exist.

As a gluten-free diet is taken for life, we have used the 15–18-years age group as best representing the annual costs over the life time horizon of the model. Thus the cost of a gluten-free diet to the NHS in the base-case scenario is derived from the midpoint of the estimated range of costs in the 15–18-years age group. As adults with coeliac disease have to pay for their prescriptions, we have assumed that they will purchase annual prescription exemption certificates, and that the NHS will recoup ~£100/year of the prescribing costs. Thus the base-case estimate for cost of a gluten-free diet is £1200/year. This figure is of the same order as the Italian estimate, especially when 5 years of inflation is taken into account. We have used the similarly adjusted low and high estimates from the same age group in the sensitivity analysis, that is, £350 and £2000, respectively.

Costs of endoscopy and biopsy

Holmes[47] cites a cost of £280 for endoscopy and biopsy but does not give a source for this figure, which seems low for the childhood population where a general anaesthetic is needed. Harewood and Murray,[92] in a US study, cite a cost of US$1003, although again it is not clear whether this figure includes the cost of GA.

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For the base case we have used a cost of £500, and explored values of £280 and £800 in the sensitivity analysis.

Utility for type 1 diabetes (without concomitant coeliac disease)

No studies reporting utility weightings for type 1 diabetes were found. As the precise value is less important than the difference between this value and those for treated or untreated coeliac disease, this weighting was set arbitrarily at 0.9 for the model and was not varied in the sensitivity analysis.

Utilities for coeliac disease (treated and untreated)

Three main studies of quality of life in coeliac disease were identified.

Mustalahti and colleagues[114] used a Gastrointestinal Symptoms Rating Scale (GSRS) and the Psychological General Well-Being (PGWB) questionnaire in three adult cohorts consisting of 21 symptom-detected coeliac disease patients, 19 screen-detected coeliac disease patients and 105 non-coeliac participants. Both coeliac groups completed the questionnaire at diagnosis and 1 year after commencing a gluten-free diet (GFD); compliance with diet was recorded through a 4-day diet record at 1 year. The non-coeliac group completed baseline questionnaires only.

Both coeliac groups improved on the PGWB and GSRS scales. For both scales, the absolute improvement was approximately twice as great in the symptom-detected group, but there was clear improvement for the screen-detected group also. For both scales, scores for symptom-detected patients after 1 year of GFD were similar to the baseline scores for the non-coeliac group (no follow-up scores available for this group). Scores on both scales for screen-detected patients were similar to those of the non-coeliac population at baseline and after 1 year of GFD were slightly higher than the baseline scores for non-coeliac cohort. Neither scale is translated into utility scores. All patients reported intermediate or good compliance with GFD during the year.

Hallert and colleagues[115] studied 68 adult coeliac patients and 68 controls with type 2 diabetes; this control group was chosen to minimise the effect of diet on quality of life differences between the two groups. Patients in both groups had been treated for an average of 10 years. A Burden of Illness (BI) questionnaire and the Short Form 36 with Item (SF-36) Health Survey questionnaire were administered. Detailed results for the BI are reported, but it is not clear how these scores relate to utility. SF-36 scores can be translated into utility weightings, but the paper only reports the correlation between the two instruments and gives no values of the SF-36 scores, which could be used to derive utilities.

O'Leary and colleagues[116] asked 150 adult coeliac patients and 162 controls to complete a bowel questionnaire and the SF-36. Coeliac patients were split into several cohorts according to irritable bowel syndrome (IBS) symptoms and adherence to a gluten-free diet. Limited numerical results are given for either scale; means are plotted and median/interquartile range (IQR) reported for each of the eight subscales of the SF-36 for coeliacs on GFD and coeliacs not on GFD. Utilities cannot be derived accurately from the data available. However, it can be seen that the difference between coeliac patients on GFD and the population norms is generally small (reference values not measured in this study), with the difference between coeliac disease patients not on GFD and the population norm being 3–5 times greater.

None of these papers give data that can be used directly to derive utility values for treated and untreated coeliac disease. However, we can use the information to derive reasonable values for use in the model and sensitivity analysis. Some papers claim that there is no difference between the quality of life of treated coeliac patients and the non-coeliac population, whereas others, for example Hallert and colleagues,[117] found that after 10 years of GFD there was still a clearly lower quality of life in coeliac patients, most notably in women (who make up two-thirds of the coeliac population).

Parameter values for treated coeliac disease

Based on a value of 0.9 for the non-coeliac population with type 1 diabetes, the base-case utility for treated coeliac disease (100% compliance with GFD) will be 0.88. The sensitivity analysis will explore values of 0.9 and 0.85.

Parameter values for untreated coeliac disease

Based on values of 0.9 for the non-coeliac population with type 1 diabetes and 0.88 for treated coeliac disease, the base-case utility for untreated coeliac disease (zero compliance with GFD) will be 0.82. The sensitivity analysis will explore values of 0.85 and 0.79.

Utility of endoscopy and biopsy

We have assumed that children will have a jejunal biopsy carried out by endoscopy under general anaesthetic as a day-case procedure, which is the

overwhelmingly predominant current practice for children in the UK (Booth I, University of Birmingham, Birmingham: personal communication, 2002). The disutility for biopsy therefore is estimated as the anxiety preceding and unpleasantness of a general anaesthetic for the child and possible mild discomfort following biopsy (e.g. sore throat and vomiting). The serious risks of the procedure (e.g. perforation, bleeding, rupture, cardiac arrest, infection or severe adverse consequences of general anaesthesia) are assumed to be so rare as to be negligible.

We found no empirical evidence to inform the estimate of the disutility of endoscopy and biopsy from the patient perspective. A worst-case scenario would be that the procedure is so unpleasant that the day of the procedure carries no utility at all (i.e. is equivalent to one day of death). The best-case scenario would be that the procedure is so benign as to carry no reduction in utility. Based on these considerations, a disutility of endoscopy of –0.002 is used in the base case, with values of –0.001 and –0.003 used in the sensitivity analysis.

Disutility of gluten-free diet

A GFD is fairly restrictive, requiring the avoidance of products based on wheat, barley and rye. This includes most of the usual breads and pasta, and also many processed foods, biscuits and snack foods. Gluten-free alternatives may be difficult to find, and so the diet may be inconvenient at times as well as restrictive.

We found no literature to directly inform the value of this parameter. Hallert and colleagues,[117] note that: "The results would imply that the perception of restriction is a prominent feature of the disease burden in coeliac disease patients, being consistently greater in women than in men and conceivably brought about by the dietary restrictions".

In the absence of data relating specifically to the utility attached to the diet (and thus unconfounded by effects on health status), we have tried to come up with a reasonable range of values to use in the model. Around 10% of waking life is spent preparing and eating food, and the need to avoid gluten affects choice in the majority of meals, at least for a Western diet. Beyond lack of choice, restriction of certain foods may lead to food cravings and possibly a heightened awareness of the illness and of 'difference'.

Based on these considerations, a base case disutility of –0.04 will be used for GFD, and values of –0.01 and –0.08 explored in the sensitivity analysis.

Compliance

Twenty-three studies were identified that reported compliance. Foreign language papers were not translated but, where possible, data were taken from the English language abstract. Studies giving quantitative data about rates are given in *Table 25*.

Several factors are shown to affect compliance, for example, if diagnosis was made in less than 5 years after symptoms start compliance was higher.[118] Compliance was also associated with symptom severity,[118] sex (female > male), age[114,119,120] and patient knowledge.[118,120]

Based on these studies, we used a base-case compliance rate of 60% and used figures of 30 and 90% in the sensitivity analysis

Life expectancy

The time horizon of the model depends on the life expectancy of the population modelled.

Population with childhood onset diabetes

The mean life expectancy of the general population is currently approximately 78 years, as shown in *Figure 40*.

People who develop type 1 diabetes, especially those at an early age, have a high excess mortality compared to the rest of the population.[131] The Juvenile Diabetes Research Foundation (http://www.jdfr.org) states that even with insulin life expectancy in type 1 diabetes is shortened by around 15 years, suggesting a life expectancy of around 63 years based on the 78 years estimated above for the general population. Hart and colleagues[132] modelled cost and incidence of type 1 diabetes in Spain and estimated a life expectancy of 59.6 years. These estimates are consistent with Palmer and colleagues[133] who performed a cost-effectiveness study of management strategies for type 1 diabetes and estimated median (not mean) survival of 50–55 years under various management strategies.

The mean age of diagnosis of diabetes is ~8 years.[91] We have deducted this figure from the total life expectancy of people with type 1 diabetes to derive the time frame for the model.

We therefore used a base-case life expectancy for diabetes without coeliac disease of 52 years, and varied this from 48 to 56 years in the sensitivity analysis.

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TABLE 25 *Compliance rates*

Reference	*N*	Ages (years)	Method	Compliance (%)	Partial non-compliance (%)	Complete non-compliance (%)	Any non-compliance (%)	Comments
Ansaldi *et al.*, 1992[121]	156/335	>6 Median 14.7 Range 6–29	Survey of patients from paediatric gastroenterology clinic	89.6	9	1.4	10.4	
Sdepanian *et al.*, 2001[118]	529/584	All	Structured questionnaire survey of Brazilian Coeliac Association members	69.4		>20 years old 17.7 0–2 years old 9.9	29.5	Possibly targets a more knowledgeable subset of CD patients and may overestimate compliance in general
Lovik *et al.*, 1989[119]	28	18 adults (15–68) and 10 children (1–14)	Self-administered questionnaire	50		22 adults None detected in children	50	
Lazzari *et al.*, 1992[122]	81	Teenagers		64.1	22.3	13.6	35.9	
Westman *et al.*, 1999[123]		Children (with diabetes)	Cohort study: 3-day food record and 7-day food frequency questionnaire	30				
Mayer *et al.*, 1991[124]	123	Adolescents	Cohort of patients diagnosed <3 years of age and followed for 10 years	65	11.4	23.6	35	
Greco *et al.*, 1997[112]	306	Teenagers, young adults		73	15	12	27	
Colaco *et al.*, 1987[125]	37	Follow-up of children into adulthood	Cohort	43		27	57	

continued

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TABLE 25 *Compliance rates (cont'd)*

Reference	*N*	Ages (years)	Method	Compliance (%)	Partial non-compliance (%)	Complete non-compliance (%)	Any non-compliance (%)	Comments
Fabiani *et al.*, 1996[126]	23	Adolescents		52			48	3 patients refused to come to clinic and are therefore possibly more likely not to comply with the diet also
Cuoco *et al.*, 1998[127]	23	Adults	Direct patient questioning	69			20	
Bardella *et al.*, 1994[128]	128	Young adults	Follow-up of people diagnosed as children a mean of 11.2 years earlier	45	18	37	55	
Lamontagne *et al.*, 2001[120]	234/617	All	Questionnaire				36	
Congdon *et al.*, 1981[129]	32	Children		31	35	34	69	
Mariani *et al.*, 1998[130]	47	Adolescents	Cohort study with 3-day food record	53			47	
Kumar *et al.*, 1988[113]	102	Teenagers		56	35	9	44	

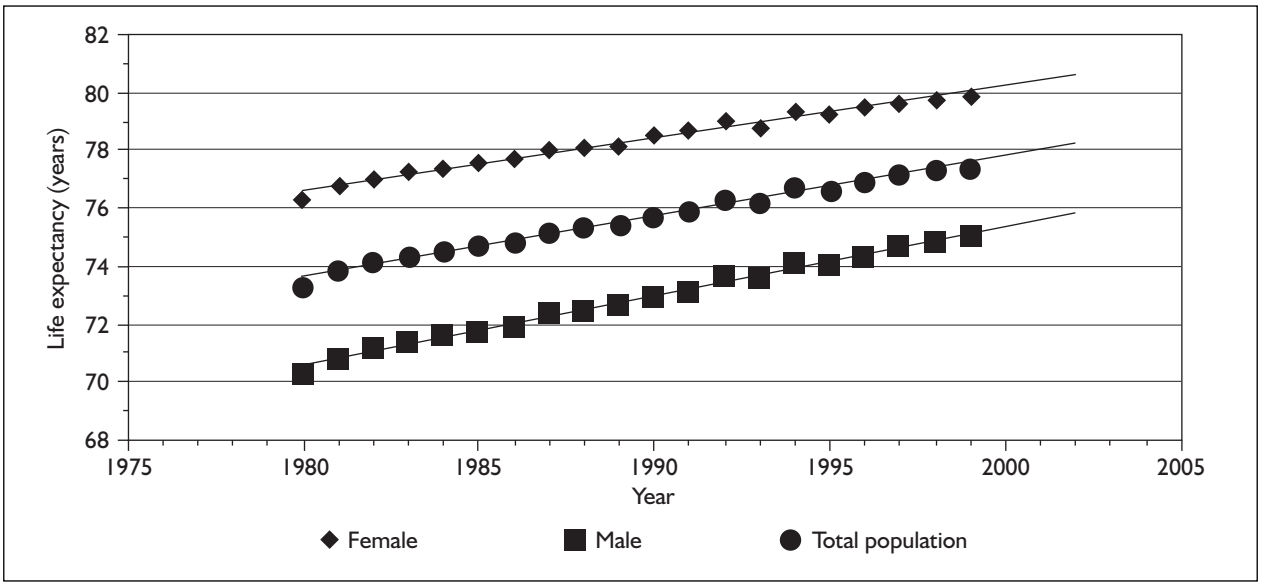

FIGURE 40 *Life expectancy at birth. Source: OECD Health Data 2002.*

Treated coeliac disease

Since the introduction of treatment with a GFD, prognosis in coeliac disease is now hugely improved. Corrao and colleagues[44] report a cohort study of patients with coeliac disease with an overall survival ratio of 0.98. Within the subgroup of patients who were compliant with a gluten-free diet, the calculated standardised mortality ratio (SMR) was 0.5 with a 95% confidence interval of 0.2 to 1.1. Collin and colleagues[134] found no excess in mortality compared with the normal population and suggested that this might be due to the high (83%) compliance with GFD in their cohort.

The base case will therefore consider a loss in life expectancy for treated coeliac disease (100% compliance with GFD) of zero, with a 1-year decrease and a 1-year increase in life expectancy explored in the sensitivity analysis. The possibility of improved life expectancy is plausible, based on both the trend toward lower mortality in the Corrao study[44] and the observation that a GFD may assist in control of diabetes.

Untreated coeliac disease

Estimating life expectancy of untreated coeliac disease is complicated by the fact that most studies identified were conducted since the introduction of GFD. The SMR for the group of coeliac patients in the Corrao study[44] with poor compliance with GFD was 6.0, indicating a much worse survival in this group.

However, it has also been observed that the excess in mortality due to coeliac disease occurs mostly in a short period just after diagnosis, making SMRs or hazard ratios clumsy tools for estimating the years of life lost due to the disease. For example, Logan and colleagues[135] reported an increase in mortality of 1.9 overall, with the highest excess in the first year after diagnosis and then steadily declining over time. In addition, they found no difference in mortality between coeliac patients diagnosed in childhood and that of the general population.

The base case will therefore consider a loss in life expectancy of 4 years in the untreated population, with values of 0 and 8 years lost in the sensitivity analysis.

Corrected diagnosis

Screening will lead to two groups with an incorrect diagnosis: those with coeliac disease but a negative test result, and those without coeliac disease and a positive test result. The latter would be corrected immediately for strategies with confirmatory biopsy, but would be treated as coeliac disease patients in strategies without confirmatory biopsy.

It is assumed that a proportion of false negatives will go on to be diagnosed through the development of symptoms and normal clinical suspicion. Similarly, it is assumed that a proportion of false positives will abandon GFD or be correctly diagnosed as non-coeliac as a result of lack of response to GFD.

Symptomatic diagnosis for false negatives

Corrao and colleagues[44] recruited a cohort of 1072 adult patients diagnosed between 1964 and

1994 in 11 gastroenterology units in Italy. For each patient, they recorded both the time of diagnosis and the time at which symptoms of coeliac disease had first appeared. They used these data to estimate the diagnostic delay for each patient. The results (ignoring 67 unknowns) were as follows:

Delay	Patients (%)
up to 12 months	34
12–119 months	32
>120 months	27
screen-detected	7

For those detected through symptoms, then, the average diagnostic delay was approximately 5 years.

The base case will use a delay to diagnosis of 5 years and values of 2 and 10 years will be used in the sensitivity analysis.

The increase in reported prevalence since the introduction of screening suggests that around two-thirds of the coeliac population may have clinically undetectable disease. It is not known how many of these patients never develop symptoms, or how many patients with coeliac disease are never diagnosed despite symptoms.

The base case will use a figure of 30% of false negatives never diagnosed, with figures of 10 and 50% explored in the sensitivity analysis.

Abandonment of diagnosis for false positives

We suspect that false positives will abandon their diet and/or their diagnosis due to lack of response within a fairly short period of time, not least because clinical follow-up is likely to include gluten challenge as a confirmatory test of the diagnosis.

The base case will use an average time to abandonment of 1 year, with values of 6 months and 2 years explored in the sensitivity analysis.

We assume that a proportion of false positives will never have their diagnosis corrected (some possibly due to perceived improvement on GFD) and will in effect remain on GFD for life; we assume that compliance for these patients is similar to that for true coeliacs. We have no information on which to base these values.

The base case will use a value of 10% lifetime false positives with values of 5 and 15% explored in the sensitivity analysis.

Structure of the model

For each strategy considered [no screening, auto-antibody test(s) with or without follow-up biopsy, biopsy for all patients] there are four possible outcomes:

- TP: true positive (does not apply to 'no screening' strategy)
- FN: false negative (does not apply to 'biopsy all patients' strategy)
- FP: false positive (does not apply to 'no screening' or 'biopsy all patients')
- TN: true negative.

For each outcome, lifetime costs and utility were calculated along with the proportion of patients in each group. Mean lifetime costs and utility were then calculated for each strategy. The cost/QALY (quality-adjusted life-year) gained for each screening strategy was calculated by comparison with the 'no screening' strategy.

Calculation of lifetime costs

Lifetime costs include the one-off costs of any screening tests and biopsies performed and annual costs of a gluten-free diet.

The one-off costs are defined by the screening strategy applied; for those strategies using a confirmatory endoscopy, costs of endoscopy were assumed to apply to the proportion of the population having a positive test result (i.e. true positives + false positives). It is assumed that a proportion of false negatives will eventually become symptomatic and be diagnosed through clinical suspicion; delayed costs of endoscopy are therefore included for this proportion.

Annual costs of a gluten-free diet apply to three groups:

- True positives – costs calculated over remaining life expectancy, including a simple adjustment for compliance.
- False negatives – it is assumed that a proportion of those with coeliac disease but not picked up by screening (or in a 'no screening' strategy) will eventually become symptomatic and be diagnosed through clinical suspicion. Costs of GFD are included for these patients. To take account of the delay to diagnosis the costs of GFD are introduced at a later time point in the model for these patients than those diagnosed through screening; these costs are thus incurred for fewer years and are more heavily discounted.

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- False positives – it is assumed that a proportion of these patients will abandon GFD completely and/or have their diagnosis corrected; for these patients the costs of GFD are calculated for the average period of time to correction/abandonment of GFD. For the remainder, costs of GFD are calculated over remaining life expectancy, including a simple adjustment for compliance. Note that the screening strategies, which used a confirmatory endoscopy, would not lead to any false positives having unnecessary GFD (as, under the simplifying assumption that biopsy is definitive, there are no treated false positives in these strategies).

Calculation of lifetime utility

Lifetime utility includes the one-off disutility of any biopsies performed, the annual utility of the health status of the individual (diabetes without coeliac disease, diabetes with treated coeliac disease, diabetes with untreated coeliac disease) and the annual (dis)utility of GFD.

In calculating lifetime utility for each group, account was taken of compliance with GFD (effects on both health status and disutility of GFD). The effect of later changes to diagnosis of false negatives and false positives was accounted for in the same way as costs, described above.

Calculation of proportions in each outcome group

The proportion of the population in each group is a function of the prevalence of coeliac disease in the population (PREV) and the sensitivity (SENS) and specificity (SPEC) of the screening tests. 'No screening' has a sensitivity of 0% and a specificity of 100%. 'Biopsy all patients' is assumed to have a sensitivity of 100% and a specificity of 100%. The calculations are as follows:

$$\%TP = PREV \times SENS$$
$$\%FN = PREV \times (1 - SENS)$$
$$\%FP = (1 - PREV) \times (1 - SPEC)$$
$$\%TN = (1 - PREV) \times SPEC$$

Calculation of life expectancy

In order to calculate lifetime costs and utilities, we needed to estimate average life expectancy. Coeliac disease is known to reduce life expectancy, and this penalty would be expected to be greater for untreated as opposed to treated coeliac disease.

Assumptions made about the degree of compliance with GFD and the late symptomatic diagnosis of coeliac disease patients not detected at screening would be expected to alter life expectancy in our model. Life expectancy for each group was therefore calculated from: life expectancy for child with diabetes but without coeliac disease; estimated reduction in life expectancy for treated coeliac disease; estimated reduction in life expectancy for untreated coeliac disease; estimated proportion of false negatives who would eventually be diagnosed symptomatically; and mean delay to diagnosis for false negatives eventually diagnosed through symptoms.

Results

Base case (compared with 'no screening')

For the base case described above, the lowest cost per QALY gained, where an antibody test with confirmatory biopsy was modelled against no screening, was for IgA EMA, with IgA TTG as the next most cost-effective option (see the table below). The least cost-effective options combining

Screening strategy		Parameters	Cost/QALY gained (£)	Cost/case detected (£)
Biopsy all patients		Base case	45170	20230
AGA IgA	+ biopsy	Base case	14770	7390
AGA IgG	+ biopsy	Base case	20160	9900
EMA IgA	+ biopsy	Base case	12250	6190
ARA IgA	+ biopsy	Base case	13500	6800
TTG IgA	+ biopsy	Base case	12970	6540
EMA IgA + AGA IgG	+ biopsy	Base case	19100	9420
TTG IgA + AGA IgG	+ biopsy	Base case	19160	9450
AGA IgA		Base case	54090	10350
AGA IgG		Base case	Dominated	18680
EMA IgA		Base case	14450	6400
ARA IgA		Base case	23950	8140
TTG IgA		Base case	19990	7490
EMA IgA + AGA IgG		Base case	Dominated	16840
TTG IgA + AGA IgG		Base case	Dominated	16870

test and biopsy were IgG AGA tests alone or in combination. The biopsy alone strategy was considerably less cost-effective than test plus biopsy combinations and test alone was less cost-effective than the same test with the addition of the biopsy. Note that 'dominated' indicated that an option was both more expensive and less effective than the no screening strategy.

Sensitivity analysis

We explored the effect of using different values for the various parameters in the model. The results in the table below are presented for TTG IgA followed by endoscopy and for TTG IgA alone compared with no screening, as the results for the different tests are broadly similar (see previous section for discussion around choice of parameter values).

Screening strategy	Parameter(s) varied	Cost/QALY gained (£)	
		Low value	High value
TTG IgA + biopsy TTG IgA alone	None (base case)	12970 19990	
TTG IgA + biopsy TTG IgA alone	Prevalence	17640 231325	11790 13230
TTG IgA + biopsy TTG IgA alone	Sensitivity	13060 20590	12930 19710
TTG IgA + biopsy TTG IgA alone	Specificity	14250 39620	12330 14630
TTG IgA + biopsy TTG IgA alone	Sensitivity and specificity	14390 42470	12310 14520
TTG IgA + biopsy TTG IgA alone	Cost of test	12840 19820	13220 20320
TTG IgA + biopsy TTG IgA alone	Cost of endoscopy	12230 20290	13980 19570
TTG IgA + biopsy TTG IgA alone	Cost of diet	5460 5990	20030 33160
TTG IgA + biopsy TTG IgA alone	Utility of treated CD	25800 60310	9740 13830
TTG IgA + biopsy TTG IgA alone	Utility of untreated CD	8810 12220	24590 54820
TTG IgA + biopsy TTG IgA alone	Disutility of endoscopy	12930 20020	13010 19950
TTG IgA + biopsy TTG IgA alone	Disutility of GFD	8660 10320	38490 DOMINATED
TTG IgA + biopsy TTG IgA alone	Compliance with GFD	15380 20050	12210 20030
TTG IgA + biopsy TTG IgA alone	LE for person with diabetes	12400 18580	19880 21410
TTG IgA + biopsy TTG IgA alone	Penalty in LE for treated CD	11130 16340	15580 25820
TTG IgA + biopsy TTG IgA alone	Penalty in LE for untreated CD	26410 63210	7510 10100
TTG IgA + biopsy TTG IgA alone	Proportion of FN never diagnosed	18590 43500	10970 14830
TTG IgA + biopsy TTG IgA alone	Delay to diagnosis for FN	11970 19940	13500 19190
TTG IgA + biopsy TTG IgA alone	Proportion of FP never corrected	12970 16090	12970 25150
TTG IgA + biopsy TTG IgA alone	Time to correction for FP	12970 18310	12970 23650
TTG IgA + biopsy TTG IgA alone	Discounting (both 0%/both 6%)	15480 24590	55110 145630

LE, life expectancy.

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Full results for the sensitivity analyses are given in Appendix 11.

Comparisons between different active screening strategies

In addition to comparing each screening strategy, we made the following comparisons.

Confirmatory biopsy versus no confirmatory biopsy

Testing strategies using a confirmatory biopsy were always cheaper and more effective than the equivalent strategies without confirmatory biopsies, and so confirmatory biopsy for those testing positive is clearly preferable.

The full results of these analyses are given in Appendix 11.

Biopsy all patients versus each antibody test strategy

Under the assumption that all patients will accept biopsy, biopsying all patients is the most expensive screening strategy, but may be more effective than testing strategies using antibody testing as a preliminary, or sole, screening tool. For each test-based screening strategy, we calculated the incremental cost-effectiveness of introducing a screening strategy of biopsying all patients instead.

Strategies using an antibody test followed by a confirmatory biopsy in those testing positive consistently gave higher utility gains than a strategy of biopsying all patients, with the exception of AGA IgG (in the base case and most sensitivity analyses) and AGA IgA (in a small number of sensitivity analyses). As the testing strategies also consistently led to lower costs than biopsying all patients, they are clearly preferable.

For strategies using antibody testing **without** confirmatory biopsy, biopsying all patients consistently led to higher gains in utility, with the exception of sensitivity analyses where the specificity of the tests were high or the disutility of diet was low. Where the cost of diet was high, AGA IgG also became more expensive than biopsying all patients (owing to the low specificity of the test). The cost/QALY of switching to 'biopsy all patients' compared with a 'test only' strategy varied considerably and depended mainly on the specificity of the testing strategy used.

The full results of these analyses are given in Appendix 11.

Combination test strategies versus single test strategies

Combination test strategies are more costly than a single test strategy. For each combination strategy, we calculated the incremental cost-effectiveness of using the combination compared with using the single best test in the combination alone. In the base case and all sensitivity analyses, combination strategies led either to a loss in utility compared with the single test (owing to the loss of specificity) or a very small gain. The cost/QALY for using a combination instead of a single test did not fall below £97,000 in any analysis and in general was substantially higher.

The full results of these analyses are given in Appendix 11.

Discussion

Screening strategies

The analyses presented above suggest that autoantibody testing may have a role in screening for coeliac disease in this population. It is clearly preferable to use a confirmatory biopsy for all positive test results than a screening strategy, which relies on antibody testing alone.

A strategy of 'biopsy all patients' may be fairly cost-effective compared with a 'no screening' strategy. However, it is clearly less cost-effective than strategies using antibody testing with confirmatory biopsy in test-positive patients only, and may also be less effective compared with such strategies where these use more accurate tests.

The use of more than one test increases the sensitivity but decreases the specificity of antibody screening, and does not appear to offer much advantage over a single test strategy.

Sensitivity of incremental cost-effectiveness ratios (ICERs) to parameters in the model

Factors having substantial impact on ICERs

The disutility of GFD is important. If the disutility is small, even strategies which allow a number of false positives to be treated unnecessarily become apparently cost-effective; for

example, in the base case AGA IgG alone was both more expensive and less effective than a 'no screening' strategy, but with a small disutility of GFD this strategy appeared more reasonable, with a cost/QALY gained of just £34,200. Other strategies became substantially cheaper with a low disutility of GFD. Conversely, if the disutility is large, the cost-effectiveness of any screening strategy is reduced.

The only cost which has any substantial impact on the results is the cost of diet, as might be expected since this is the only recurrent cost in a lifetime model. The range of costs of diet tested here was fairly wide, but even at the highest cost screening appears to be cost-effective for most screening strategies.

The utilities attached to the various health states have limited impact in themselves, but the **difference** between the utilities for non-coeliac, treated and untreated coeliac disease has a substantial effect on the estimates.

Life expectancy for the population with diabetes but without coeliac disease, that is, the time frame set for the model, has very limited impact. However, the reduction in life expectancy due to coeliac disease does have an impact, within the ranges tested here, especially for untreated disease (with a greater reduction in life expectancy).

The proportion of false negatives who would go on to be diagnosed clinically does have some impact on the results, as might be expected against a 'no screening' comparator, although the average time to symptomatic diagnosis does not have much impact within the range tested here.

Factors having limited impact on ICERs

Altering the prevalence of coeliac disease has limited impact on the results. This suggests that, if a single screen (as modelled here) were deemed worthwhile, repeat screenings might also be worthwhile, although a more complex model would be needed to check this.

Test accuracy (sensitivity and specificity) has very limited impact on any ICER estimates, with the exception of strategies not using confirmatory biopsy, which perform much better when specificity is high (as would be expected).

Compliance rates with GFD have limited impact within the (wide) range tested here. The relationship between compliance and cost-effectiveness in the model is complex, as it will affect the total cost of diet, the total disutility of diet and life expectancy for both screen- and symptom-detected coeliac disease patients.

The pattern of correction of false-positive results does have some impact on the results for strategies which do not use a confirmatory biopsy, but clearly is irrelevant to strategies which use confirmatory biopsy (as there are no treated false positives in this strategy).

The acceptance rate of biopsy has only a limited impact on the results of the model. A decrease in confirmatory biopsies would result in a lower specificity for those strategies including confirmatory biopsies, but the specificity would still remain relatively high.

Future research

In producing the model areas for further research were identified. These concern:

- What is the prevalence of coeliac disease in children with diabetes? (diagnosed and undiagnosed).
  (Systematic review of cross-sectional surveys.)
- What is the prevalence of coeliac disease in adults with diabetes? (diagnosed and undiagnosed).
  (Systematic review of cross-sectional surveys.)
- What are the consequences of coeliac disease (morbidity and mortality)? (in children and in adults, and possibly risk factors influencing these, e.g. compliance with diet).
  (Systematic review of harm studies, either prospective or retrospective cohort studies.)
- What is the natural history of 'silent' (screen-detected) coeliac disease compared to symptom-detected disease, and what is the effect of treatment for 'silent' disease?
  (Systematic review of cohort studies, RCTs.)
- What is the compliance with a GFD in general?
  (Systematic review of cross-sectional surveys or cohort studies.)
- What is the life expectancy of children with insulin-dependent (type 1) diabetes compared to the rest of the population?
  (Systematic review of cohort studies.)

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- What proportion of people picked up by screening for autoantibodies would have remained undiagnosed from clinical case-finding alone?
  (Systematic review of cohort studies.)
- What is the distribution of delay to diagnosis in those that are picked up?
  (Systematic review of retrospective symptom surveys of patients diagnosed with coeliac disease.)

Although areas for systematic review have been identified, it is likely that primary research will also be required. Sensitivity analyses helped identify areas which might influence most strongly the decision on whether to screen. These were actual costs of a gluten free diet to the NHS, life expectancy (in treated and untreated symptomatic and silent coeliac disease) and utilities of patients, including children and adolescents, with treated and untreated symptomatic and silent coeliac disease.

Chapter 6

Implications for other parties

The model has taken an NHS perspective. Patients and their families will bear some of the costs of a GFD. This will not only include the cost of prescriptions for gluten-free foods (for adults), but also other costs incurred by adaptation of the patient's diet, for example switching from processed to unprocessed foods and the purchase of gluten-free foods including items not available on prescription. Families may have to spend more time on food preparation. The social impact and perhaps even stigma of following a GFD are not easily incorporated in estimates of health-related quality of life.

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Chapter 7

Factors relevant to the NHS

Although the measurement of IgA EMA using indirect immunofluorescence results in high diagnostic accuracy, there may be an issue in terms of capacity (commercial availability of the substrate and throughput in terms of interpretation of slides by trained operators) if IgA EMA measurements were to be undertaken on a large scale for population screening, if this includes populations other than children with type 1 diabetes, for example, patients presenting in primary care with non-specific symptoms associated with coeliac disease.

The measurement of IgA TTG may be a more viable alternative, as ELISA lends itself more readily to high-throughput screening as the process can be automated and returns more objective results.

It is expected that increased screening activity would have an impact on the workload of laboratories and clinical teams, although it is beyond the scope of the current project to estimate this.

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Chapter 8
Conclusion

Antibody screening for thyroid disease

Given that definitive diagnosis of untreated thyroid disease and initiation of treatment require a TFT that is no more uncomfortable or unacceptable than an autoantibody test, the authors believe there is little value in autoantibody tests as an alternative screening test given that the predictive value (relative to that of TFTs) for thyroid disease is not very informative. This is supported by the fact that several of the NSC criteria[9] are not met. The role of antibodies in predicting future thyroid disease and potentially influencing testing schedules is uncertain. A systematic review on the test accuracy of antibody test compared with the reference standard of thyroid function tests for the identification of thyroid disease requiring treatment has not been carried out. However, the authors conclude that sufficient evidence has been presented in this report to indicate that thyroid autoantibody tests are unlikely to be cost-effective for screening purposes.

Antibody screening for coeliac disease

Systematic review of test accuracy

Seventy-six papers were included in a systematic review of antibody tests used in current practice. Many studies were of poor quality on several indicators, but 18 reported well-described cohorts. All but four studies were in symptomatic, not screening, populations.

All antibody tests show reasonably good diagnostic test accuracy, as shown by the areas under the SROC curve. IgA EMA, IgA ARA and IgA TTG stand out as particularly good tests, followed by IgA AGA and then IgG AGA. IgG TTG is a recently developed test and only two studies were identified.

In general, the studies reported heterogeneous effect sizes, largely not related to a consecutive cohort design as an indicator of quality. Other possible reasons for heterogeneity include other aspects of study quality, differences in the tests (including manufacturers and substrates) and their execution in the laboratories, different populations and reference standards.

The summary likelihood ratios indicate:

- IgA EMA tests have the highest pooled positive likelihood ratio and lowest negative likelihood ratio.
- IgA TTG tests have high positive likelihood ratio compared with AGA tests.
- IgA ARA estimates are imprecise, but the test appears to perform well with regard to the positive likelihood ratio relative to AGA.
- IgA and IgG AGA have lower pooled likelihood ratios than EMA and TTG but are moderately useful tests.

Hence IgA EMA appears to be the most accurate test, whereas if an ELISA test was required, TTG is likely to be most accurate.

Decision-analytic model

In a decision-analytic model, the lowest cost per QALY gained where an antibody test with confirmatory biopsy was modelled against no screening was for IgA EMA (£12,250 per QALY gained when compared with no screening), with IgA TTG (£12,970 per QALY gained) as the next most cost-effective option. The least cost-effective options combining test and biopsy were IgG AGA tests alone or in combination. Hence autoantibody testing may have a role in screening for coeliac disease in the population of children with type 1 diabetes.

The use of more than one test increases the sensitivity but decreases the specificity of antibody screening, and does not appear to offer much advantage over a single-test strategy.

Altering the prevalence of coeliac disease has limited impact on the model results. This suggests that repeat screenings might also be worthwhile, although a more complex model would be needed to investigate this further.

Sensitivity analyses helped identify areas which might influence most strongly the decision on whether to screen. These were actual costs of a GFD to the NHS, life expectancy (in treated and

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untreated symptomatic and silent coeliac disease) and utilities of patients, including children and adolescents, with treated and untreated symptomatic and silent coeliac disease.

Areas of uncertainty and need for further research

We have addressed questions relating to test characteristics and cost-effectiveness of screening for coeliac disease in a systematic review and health economic model. Other criteria which need to be met if screening is to take place were outside the scope of this report but are discussed briefly below.

When interpreting the results of the systematic review on test accuracy, other factors that influence the effectiveness of a diagnostic or screening test need to be taken into account. These are reliability and reproducibility of the test, acceptability to the patient, whether further test and treatment decisions are informed by the test, whether patient outcomes are improved by the test and whether the test is cost-effective. The reliability and reproducibility can be assessed through a quality assurance scheme. It is assumed that for laboratories taking part in UK NEQAS, tests results will be relatively consistent and reliable; however, no statement can be made for the studies included in this review.

Screening tests must have high acceptability to patients. A blood test is likely to be well accepted by adult patients, but may cause distress to children. Such distress can have important consequences when a child has a chronic condition such as diabetes and is likely to need repeated blood tests. Even so, a high degree of compliance might be expected, although clinicians, parents and children may well prefer to minimise invasive procedures.

As with all screening tests, informed consent should be obtained and patients and children when they are competent to consent should understand the consequences of a diagnosis of coeliac disease, of a missed diagnosis and of the harm that would result from a false-negative test, in this case the biopsy and associated costs and anxieties. The model has incorporated estimates for the harm attached to biopsy, but it was beyond the scope of this report to consider in detail the experiences of patients with a false-positive test result.

Screening programmes require a consensus on how the results of a diagnostic or screening test will inform further tests and/or treatment. There are clear criteria for diagnosis and treatment of coeliac disease. At present, however, practices differ amongst clinicians, with some following consensus guidelines (see the section 'Current practice in childhood diabetes in the UK', p. 16) and others not screening at all. In part this reflects the apparent weakness of the evidence base on silent disease, highlighted by clinicians responding to our survey.

A GFD is an effective treatment, but there is limited information on compliance with this difficult diet. There is also only limited information on the disutility attached to compliance, particularly in children and adolescents.

A criterion for screening is that the natural history of the condition be known and that there should be a latent or early phase during which intervention can prevent adverse outcomes. Further research is required regarding the long-term outcomes and complications of untreated coeliac disease, particularly silent coeliac disease. Untreated coeliac disease is known to be associated with a number of long-term complications, amongst them non-Hodgkin lymphoma, cancer of the mouth, pharynx and oesophagus and osteoporosis.[136–138] There is, however, still uncertainty regarding the strength of the association between untreated coeliac disease and malignancies, particularly in silent (asymptomatic) coeliac disease. Whilst there is evidence that adherence to a strict GFD reduces or eliminates the increased risk of lymphoma and other malignancies in coeliac disease and restores bone mineral content,[137,138] there are still uncertainties over the length of time that treatment needs to be adhered to in order to reduce the risk. Specifically with regard to children, little is known concerning the effect of delayed diagnosis on growth and development. Other outcomes where there is also limited information are those relating to the general health, well-being and utility of patients with untreated and treated coeliac disease, particularly patients with silent disease. In relation to patients with diabetes, information of the impact of treatment on glycaemic control (particularly difficult in children) and body mass index is limited. Systematic reviews and probably primary research would be informative.

The model suggests that screening is cost-effective, but has not modelled what the optimum time for screening is. Clinicians and families might want to know how much does a delay in the diagnosis of silent coeliac disease until adulthood matter. This question has not been entirely answered by the model. As patients with diabetes remain at risk of

developing coeliac disease through their lives, the appropriate interval and number of screens remains to be determined, if screening is thought to be desirable. The model has not considered the screening interval, modelling only a single screen, but it could be extended.

The focus of this report is on children with type 1 diabetes. There are other populations for whom screening for coeliac disease has been advocated, including people with Down's syndrome, first-degree relatives of patients with coeliac disease and primary care patients with symptoms that have been associated with coeliac disease. The results of the systematic review of diagnostic tests and the model are relevant to these populations, as are the areas outlined above where further research is required.

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Contributions of authors

Janine Dretzke contributed to writing the protocol, designing the survey, reviewing the searches, reviewing the literature, extracting and analysing the data on test characteristics for all studies and writing the report. Carol Cummins contributed to writing the protocol, designing and analysing the survey, reviewing the searches, reviewing the literature, extracting and analysing the data on test characteristics for all studies and writing the report. Josie Sandercock contributed to extracting the data on test characteristics for the well-designed studies, designing the decision-analytic model, reviewing the literature for the best estimates for the parameters of the model, analysing the results of the model and writing the report. Tim Barrett gave clinical advice and helped in designing the survey. Anne Fry-Smith developed and ran the literature searches and advised on information aspects of the report. Amanda Burls contributed to the writing of the protocol, designing the survey, designing the decision-analytic model, reviewing the literature for the best estimates for the parameters of the model, extracting data on test characteristics for the Spanish language and well-designed studies and writing the report.

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Appendix 1

Extract from ISPAD Guidelines

Associated conditions and other complications

Growth and development

- Impaired growth and delayed pubertal development may occur in the following circumstances:
  - poor metabolic control
  - inadequate nutritional intake
  - hypothyroidism
  - coeliac disease
  - other conditions not associated with diabetes.

Recommendation

Regular monitoring and assessment of growth are an essential part of good diabetes management.

Autoimmune disorders

- Islet cell antibodies and other autoantibodies can be found in a high proportion of children prior to the onset of type 1 diabetes.
- More children with type 1 diabetes also have other detectable organ-specific autoantibodies (e.g. thyroid, antigliadin, adrenal) than are found among the general population.
- Family members of children with diabetes are more likely to have autoantibodies and other manifestations of autoimmune disease than the general population.

Risk factors for the development of associated autoimmune disorders

- age (older)
- sex (female)
- duration of diabetes (longer)
- presence of other organ-specific autoantibodies
- family history of autoimmune disease (genetic predisposition).

Children and adolescents with diabetes have an increased risk of developing other autoimmune disorders

Thyroid disease

- Thyroid autoantibodies (TAAB), particularly microsomal antibodies, occur in up to 20–30% of young people with type 1 diabetes.
- A palpable or visible goitre may be present in 10–20%.
- Most young people with a goitre and positive TAAB have (Hashimoto's) thyroiditis but the majority are euthyroid.
- Absence of TAAB does not preclude later development of thyroid disease.

Hypothyroidism

- Overt hypothyroidism occurs in 1–5% of young people with type 1 diabetes.
- Compensated hypothyroidism – asymptomatic, normal thyroxine level, modestly raised thyroid-stimulating hormone (TSH) – occurs in 1–10%.

Diagnostic pointers

- goitre
- increased weight gain (facial fullness)
- decreased growth rate
- tiredness, lethargy.

Hypothyroidism may not significantly affect metabolic control.

Definitive diagnosis

Low total (or free) thyroxine; raised TSH.

Treatment

L-Thyroxine with TSH monitoring.

Thyrotoxicosis

- Diagnosed less frequently than hypothyroidism in association with diabetes.
- May be transient and occasionally precedes hypothyroidism (or vice versa).

Diagnostic pointers

- agitation
- tachycardia
- weight loss
- heat intolerance
- tremor
- possibly increasingly unstable metabolic control.

Definitive diagnosis

Raised total (or free) thyroxine, raised triiodothyronine, with TSH suppressed below

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normal range (raised TSH receptor-stimulating antibodies).

Treatment
Anti-thyroid drugs such as carbimazole, methimazole, propylthiouracil.

Recommendations

Regular clinical examination of the thyroid gland in all young people with diabetes for detection of goitre.

Close to the time of diagnosis of diabetes, thyroid function and thyroid antibody tests should be performed as a baseline or to uncover asymptomatic thyroid disease.

Repeat thyroid function tests should be performed if a child with diabetes develops a goitre, has slow growth velocity, has symptoms suggestive of thyroid disease or has high titres of thyroid antibodies.

Many centres repeat the thyroid function tests as part of an annual review.

Coeliac disease

- Occurs in 1–10% of children and adolescents with type 1 diabetes (prevalence is 10–50 times greater than in the general population and this varies between different geographical regions).
- Should be considered whenever a child with diabetes has gastrointestinal signs or symptoms including diarrhoea, abdominal pain, flatulence, dyspeptic symptoms or recurrent aphthous ulceration.
- Is often asymptomatic.
- Non-gastrointestinal presentations are not uncommon, for example, poor growth, iron deficiency anaemia, delayed puberty, unexplained recurrent hypoglycaemia (particularly with poor weight gain), dermatitis herpetiformis.

Immunological tests
- Antiendomysial IgA antibody (EMA) is the most specific test.
- EMA should be combined with total IgA level to exclude false-negative results (antigliadin IgG and IgA antibodies are sensitive screening tests but are less specific).
- Seroconversion to positive EMA after onset of diabetes predicts later coeliac disease but this may take months or years to develop.

Definitive diagnosis
- Jejunal biopsy showing villous atrophy.
- A normal mucosa in a seropositive child does not preclude later development of coeliac disease. Seropositive patients require regular reassessment.

Treatment
Definitive biopsy diagnosis mandates a gluten-free diet (GFD), which should reverse signs and symptoms

- GFD may improve growth and well-being in previously 'asymptomatic' patients.
- GFD may or may not alter insulin requirements.
- GFD may or may not alter metabolic control.
- GFD should be associated with disappearance of EMA.

Screening
- Controversy exists as to the need for and frequency of screening tests to detect clinically asymptomatic cases of coeliac disease.
- In some geographical areas annual screening for coeliac disease is recommended.

Recommendations

Consider the possibility of coeliac disease in any child or adolescent with gastrointestinal symptoms, unexplained poor growth or anaemia.

Immunological screening should be considered close to the time of diagnosis of diabetes and repeated if clinical circumstances suggest the possibility of coeliac disease.

Other autoimmune associations

Adrenal insufficiency
- Adrenocortical autoantibodies can be detected in 2–4% of young people with type 1 diabetes.
- Adrenal insufficiency occurs rarely in children with diabetes but must be suspected where there are decreasing insulin requirements, unexplained hypoglycaemia, weight loss, lethargy or increasing skin pigmentation.

Polyglandular autoimmune disorders
- Approximately 25% of patients with one autoimmune disease may develop another autoimmune disease during their lifetime.
- Other associated conditions include
  - vitiligo
  - alopecia
  - hypoparathyroidism
  - hypergonadotropic hypogonadism
  - pernicious anaemia.

Appendix 2

Prevalence of thyroid autoantibodies and thyroid disease in populations with diabetes

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Author, year	Population size	Method used for antibody measurements	*n* (%) of antibody positive (TPO/TMA and/or TG)	*n* (%) of antibody positive with thyroid disease (state if overt or sub-clinical disease)	*n* (%) of antibody negative with thyroid disease (state if overt or sub-clinical disease)	Test characteristics (sensitivity, specificity, PPV, NPV)	Timescale	Comments
Cerai *et al.*, 1994[34]	*n* = 144	TMA and TG by haemagglutination	15/144 (10.5%) (TPO) 6/144 (4.2%) (TG) TPO and TG: not clear Overall prevalence: 23.4% (33 or 34?)	2/144 (1.4% of total) sub-clinical hypothyroidism 2/144 (1.4% of total) overt hypothyroidism 1/144 (0.7% of total) overt hypothyroidism	Not clear how may of these patients were antibody positive or negative	Could not be calculated	No follow-up	
Court and Parkin, 1982[35]	*n* = 134 (*n* = 124 for TSH measurements)	Not stated	17/134 (13%) (not stated which antibody)	3/17 (17.6%) overt hypothyroidism 3/17 (17.6%) sub-clinical hypothyroidism	1/117 (0.85%) overt hypothyroidism 3/124 (2.4%) elevated TSH level (not defined by authors as having sub-clinical disease)	For overt hypothyroidism only: Sensitivity: 0.75 Specificity: 0.89 PPV: 0.18 NPV: 0.99 (calculated by JD)	No follow-up	
Darendeliler *et al.*, 1994[36]	*n* = 83 (*n* = 64 only for blood tests)	TMA and TG by haemagglutination	12/64 (18.8%) (not stated which antibody)	3/12 (25%) sub-clinical hypothyroidism	1/52 (2%) sub-clinical hypothyroidism	For sub-clinical hypothyroidism only: Sensitivity: 0.75 Specificity: 0.85 PPV: 0.25 NPV: 0.98 (calculated by JD)	No follow-up	

continued

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Author, year	Population size	Method used for antibody measurements	*n* (%) of antibody positive (TPO/TMA and/or TG)	*n* (%) of antibody positive with thyroid disease (state if overt or sub-clinical disease)	*n* (%) of antibody negative with thyroid disease (state if overt or sub-clinical disease)	Test characteristics (sensitivity, specificity, PPV, NPV)	Timescale	Comments
Franzese *et al.*, 2000[139]	*n* = 270	TPO and TG – method not stated	49/270 (18.1%) (not stated which antibody)	8/49 (16.3%) overt or sub-clinical hypothyroidism 2/49 (4.1%) overt or sub-clinical hyperthyroidism	No details	Could not be calculated	Mean follow-up 6.2 ± 3.8 years. Initially 7 patients with hypothyroidism and no patients with hyperthyroidism	
Frasier *et al.*, 1986[140]	*n* = 90	Not stated	Overall 31/89 (34.8%) TPO positive and 6/80 (7.5%) TG positive on at least one occasion	1 with Grave's disease – not clear if antibody positive or negative		Could not be calculated	Follow-up between 0 and 7 years	
Gilani *et al.*, 1984[37]	*n* = 58	Not stated	9/57 (16%) (TPO, measured in 57/58)	2/9 (22%) overt hypothyroidism	No details	For overt hypothyroidism only Sensitivity: 1 Specificity: 0.87 PPV: 0.22 NPV: 1 (calculated by JD)	No follow-up	12/58 patients with above normal TSH levels. Not stated if antibody positive or negative

continued

Author, year	Population size	Method used for antibody measurements	*n* (%) of antibody positive (TPO/TMA and/or TG)	*n* (%) of antibody positive with thyroid disease (state if overt or sub-clinical disease)	*n* (%) of antibody negative with thyroid disease (state if overt or sub-clinical disease)	Test characteristics (sensitivity, specificity, PPV, NPV)	Timescale	Comments
Hansen *et al.*, 1999[32]	*n* = 105	TPO and TG by RIA	13/105 (12.4%) (TPO), 14/105 (13.3%) (TG), 10/105 (9.5%) (both), overall 17/105 (16.2%)	2/17 (11.8%) sub-clinical hypothyroidism 1/17 (5.9%) overt hypothyroidism	1/88 (1.1%) sub-clinical hypothyroidism 1/88 (1.1%) overt hypothyroidism	For sub-clinical and overt hypothyroidism: Sensitivity: 0.6 Specificity: 0.14 PPV: 0.18 NPV: 0.98 For overt hypothyroidism only: Sensitivity: 0.67 Specificity: 0.15 PPV: 0.12 NPV: 0.99 (calculated by JD)	No follow-up	
Holl *et al.*, 1999[21]	*n* = 495	TPO and TG by ELISA	108/495 (21.8%) based on most recent sample TPO: 33% overall (?) TG: 16% overall (?) Both: not clear	3.3% Sub-clinical hypothyroidism (3 or 4 patients?)	3.3% Sub-clinical hypothyroidism (3 or 4 patients?)	Could not be calculated	Study length 11 years. 4.65 annual measurements per patient on average	1 patient with overt hyperthy-roidism – not clear if antibody positive or negative
Kontiainen *et al.*, 1990[141]	*n* = 131	TMA and TG by haemagglutination	29/133 (21.8%) (TPO), 4/133 (3.1%) (TG)	10/141 overt hypothyroidism 1/141overt hyperthyroidism	Not clear if patients antibody positive or negative	Could not be calculated	12-year follow-up after diagnosis of IDDM	

continued

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Author, year	Population size	Method used for antibody measurements	*n* (%) of antibody positive (TPO/TMA and/or TG)	*n* (%) of antibody positive with thyroid disease (state if overt or sub-clinical disease)	*n* (%) of antibody negative with thyroid disease (state if overt or sub-clinical disease)	Test characteristics (sensitivity, specificity, PPV, NPV)	Timescale	Comments
Lorini *et al.*, 1996[13]	*n* = 212 (cross-sectional)	TMA and TG – method not stated	35/212 (16.5%) (not stated which antibody)	No details	No details	Could not be calculated	No follow-up	
	n = 90/212 (prospective cohort)		15/90 (16.5%) (not stated which antibody)	3/15 (20%) hypothyroidism	No details	Could not be calculated	3–10 years of follow-up	
McKenna *et al.*, 1990[23]	*n* = 371	TMA and TG by haemagglutination	59/371 (15.9%) (TPO), 28/371 (7.5%) (TG), 16/371 (4.3%) (both), overall 71/371 (19.1%)	14/371 (3.8% of total) sub-clinical hypothyroidism 11/371 (3.0% of total) overt hypothyroidism 2/371 (0.5% of total) overt hyperthyroidism	Not clear how may of these patients were antibody positive or negative	For sub-clinical and overt hypo- and hyperthyroidism: Sensitivity: 0.5 Specificity: 0.84 PPV: 0.13 NPV: 0.97 Calculated by authors – could not be checked from available data	No follow-up	
Menon *et al.*, 2001[38]	*n* = 35	Not stated	19/35 (54.3%) (TPO)	1/19 (5.3%) sub-clinical hypothyroidism	0	For sub-clinical hypothyroidism: Sensitivity: 1 Specificity: 0.47 PPV: 0.05 NPV: 1 (calculated by JD)	Follow-up for each patient 1 year	

continued

Author, year	Population size	Method used for antibody measurements	*n* (%) of antibody positive (TPO/TMA and/or TG)	*n* (%) of antibody positive with thyroid disease (state if overt or sub-clinical disease)	*n* (%) of antibody negative with thyroid disease (state if overt or sub-clinical disease)	Test characteristics (sensitivity, specificity, PPV, NPV)	Timescale	Comments
Radetti *et al.*, 1995[33]	*n* = 1419	Not stated	67/1419 (4.7%) (TPO)	55 (with positive ultrasound) of 72 followed up: 26/55 (47.3%) sub-clinical hypothyroidism 1 (2%) overt hypothyroidism 1 (2%) overt hyperthyroidism	No details	Could not be calculated	Total follow-up period not clear. Sub-clinical hypothyroidism: 18 at diagnosis of Hashimoto's thyroiditis (defined by authors as antibody positivity and positive ultrasound), 8 within 1 year	
Riley *et al.*, 1981[16]	*n* = 771	Not stated	136/771 (17.6%) (TPO)	117 of 136 followed up: 45/117 (54.7%) overt or sub-clinical hypothyroidism 8/117 (6.8%) overt or sub-clinical hyperthyroidism	No details	Could not be calculated	Mean prospective follow-up: 20.6 ± 1.0 (SEM) months Hypothyroidism: 4 prior to onset of IDDM, 10 by the time of onset or within 1 year, 31 between 1 and 29 years Hyperthyroidism: 7 prior to onset of IDDM and during 3-year follow-up period	

continued

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Author, year	Population size	Method used for antibody measurements	*n* (%) of antibody positive (TPO/TMA and/or TG)	*n* (%) of antibody positive with thyroid disease (state if overt or sub-clinical disease)	*n* (%) of antibody negative with thyroid disease (state if overt or sub-clinical disease)	Test characteristics (sensitivity, specificity, PPV, NPV)	Timescale	Comments
Roldan *et al.*, 1999[142]	*n* = 204	TMA and TG by haemagglutination	36/204 (17.6%) (TPO), 12/204 (5.9%) (TG and both)	4/36 (11%) sub-clinical hypothyroidism 1/36 (3%) sub-clinical hyperthyroidism 1/36 (3%) overt hypothyroidism 2/36 (6%) overt hyperthyroidism	No details	Could not be calculated	Length of follow-up between 0 and 18.5 years (from diagnosis of diabetes)	
Sanchez-Lugo, 1991[39]	*n* = 78 (*n* = 65 for antibody tests)	Not stated	10/65 (15.4%)	1/10 (10%) hypothyroid (overt or sub-clinical not stated)	0	For hypothyroidism: Sensitivity: 1 Specificity: 0.86 PPV: 0.1 NPV: 1 (calculated by JD)	No follow-up	
Wong, 1993[143]	*n* = 26	Not stated	0/26 (0%)	0	0	N/A	Length of follow-up period not clear	
Wong 1994[40]	*n* = 33	Not stated	1/33 (3%) (TPO)	0	0	For any thyroid disease: Sensitivity: 0 Specificity: 0.97 PPV: 0 NPV: 1 (calculated by JD)	Results for mean duration of 5.2 ± 1.9 years follow-up	

Appendix 3

Search strategies for main systematic review

Database: EMBASE (1980 to March 2002)

Search strategy

1. celiac disease/ (4492)
2. celiac disease$.mp. (4645)
3. coeliac disease$.mp. (2167)
4. celiac sprue.mp. (188)
5. coeliac sprue.mp. (34)
6. gluten sensitive enteropath$.mp. (262)
7. gluten enteropath$.mp. (62)
8. or/1-7 (4939)
9. sensitiv$.tw. (368291)
10. specificit$.tw. (126444)
11. predictive value$.mp. (21278)
12. exp serology/ (29437)
13. or/9-12 (481280)
14. reticulin.mp. (823)
15. gliadin.mp. (1019)
16. (endomysial or endomysium).mp. (739)
17. tissue transglutaminase.mp. (541)
18. antireticulin.mp. (73)
19. antigliadin.mp. (328)
20. antiendomysial.mp. (108)
21. antiendomysium.mp. (109)
22 . or/14-21 (2980)
23. 22 and 13 and 8 (477)
24. limit 23 to human (445)
25. from 24 keep 1-200 (200)

Database: MEDLINE (1966 to March 2002)

Search strategy

1. celiac disease/ (8198)
2. coeliac disease$.mp. (2773)
3. celiac disease$.mp. (8432)
4. celiac sprue.mp. (244)
5. coeliac sprue.mp. (36)
6. gluten sensitive enteropath$.mp. (320)
7. gluten enteropath$.mp. (116)
8. or/1-7 (8864)
9. exp "sensitivity and specificity"/ (111380)
10. sensitiv$.mp. (464194)
11. specificit$.mp. (154393)
12. predictive value$.mp. (54768)
13. serological tests/ (10251)
14. or/9-13 (605330)
15. reticulin.mp. (1322)
16. gliadin.mp. (1379)
17. (endomysial or endomysium).mp. (785)
18. tissue transglutaminase.mp. (520)
19. antireticulin.mp. (81)
20. antigliadin.mp. (359)
21. antiendomysial.mp. (92)
22. antiendomysium.mp. (114)
23. or/15-22 (3713)
24. 8 and 14 and 23 (502)
25. limit 24 to human (486)
26. from 25 keep 1-200 (200)

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Coeliac
(CELIAC next DISEASE*)
(COELIAC and DISEASE*)
(CELIAC next SPRUE)
(COELIAC next DISEASE*)
(COELIAC next SPRUE)
CELIAC-DISEASE*:ME
(GLUTEN next (SENSITIVE next ENTEROPATH*))
(GLUTEN next ENTEROPATH*)
((((((#1 or #3) or #4) or #5) or #6) or #7) or #8)
RETICULIN
GLIADIN
ENDOMYSI*
(TISSUE next TRANSGLUTAMINASE)
ANTIRETICULIN
ANTIGLIADIN
ANTIENDOMYSI*
((((((#10 or #11) or #12) or #13) or #14) or #15) or #16)
(#9 and #17)

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Appendix 4

Excluded studies

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Appendix 5

Main study characteristics [cohorts where the selection method is described (*n* = 18) are in bold]

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Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Altuntas *et al.*, 1998, Turkey[144]	Paediatric endocrinology outpatient clinic	Prospective evaluation, selection of patients not described	Children with short stature (no gastrointestinal symptoms)	4–16 years; 29 M, 18 F	47
Artan, 1998, Turkey[60]	University hospital, outpatient paediatric clinic	Retrospective evaluation, selection of patients not described	Children with gastrointestinal symptoms, abnormal growth, anaemia, family history of CD or other symptoms	0.5–18 years; 31 M, 32 F	63
Ascher *et al.*, 1996, Sweden[145]	University hospital, department of paediatrics	Appears to be prospective evaluation, selection method not described	Children and adults, no further details	<5 years (40), 5–18 years (41), adults (39)	120
Ascher *et al.*, 1990, Sweden[72]	**Hospital, department of paediatrics**	**Prospective cohort, consecutive patients**	**Children with symptoms suggestive of CD**	**6 months–16.5 years (median 17 months)**	**130**
Auricchio *et al.*, 1988, Italy/Finland/ Spain (multicentre)[73]	**(University) hospitals**	**Prospective cohort of 1st-degree relatives giving informed consent**	**1st-degree relatives (adults and children) of patients with CD**	**Adults and children**	**152**
Bardella *et al.*, 2001, Italy[146]	University hospital, department of gastroenterology	Prospective consecutive cohort, but additional non-consecutive patient group included with disease controls	Adults with gastrointestinal symptoms, anaemia, osteoporosis or dermatitis herpetiformis	17–79 years (mean 39); 24 M, 56 F	150
Bardella *et al.*, 1991, Italy[74]	**Not stated**	**Prospective cohort, consecutive patients**	**Adults and children with gastrointestinal symptoms, anaemia, tiredness or weight loss**	**15–69 years (median 28); 19 M, 41 F**	**60**
Basso *et al.*, 2001, Italy[63]	**University hospital, department of paediatrics**	**Consecutive biopsies, retrospective evaluation of sera**	**Children with suspected CD**	**1–16 years; 25 M, 47 F**	**72**
Biagi *et al.*, 1999, UK/Italy[147]	Hospital gastroenterology clinic	Selection of case and control sera not described	Symptoms not stated	15–88 years; 40 M, 60 F	100
Bode *et al.*, 1993, Denmark[75]	**Hospital, paediatric department**	**Prospective cohort, consecutive patients**	**Children with gastrointestinal symptoms, failure to thrive, short stature or other symptoms**	**0.33–15.5 years (median 2.75); 117 M, 74 F**	**191**

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Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Bode and Gudmand-Hoyer, 1994, Denmark[76]	**University hospital, department of medical gastroenterology**	**Cohort (not clear if pro- or retrospective), consecutive patients**	**Adults with suspicion of CD**	**17–81 years (median age 51); 36 M, 64 F**	**100**
Boige *et al.*, 1996, France[148]	Hospital gastroenterology units	Sera selected from register, selection method not described	No details	14–82 years	108
Bonamico *et al.*, 1992, Italy[149]	Paediatric endocrinology outpatient clinic	Prospective evaluation, selection method not described	Children with short stature and no gastrointestinal problems	Mean 9.3 years [±39 months (SD)]; 22 M, 27 F	49
Bottaro *et al.*, 1997, Italy[150]	Paediatric hospital	Selection of cases/controls not described	Not stated	7 months–15 years; 28 M, 47 F	75
Bottaro *et al.*, 1995, Italy[77]	**University paediatric hospital**	**Retrospective cohort; all patients with biopsy 1991–93**	**Children with gastrointestinal problems, short stature or anaemia**	**Range from <1 to >10 years**	**245**
Bürgin-Wolff *et al.*, 1983, Switzerland/ Germany[151]	Children's hospitals	Prospective evaluation, selection method not described	Children with malabsorption symptoms	2 months–18 years	190
Cacciari *et al.*, 1985, Italy[152]	University hospital, department of paediatrics	Prospective evaluation, selection method not described	Children with short stature	2.8–16.7 years	104
Carroccio *et al.*, 2002, Italy[78]	**University hospitals**	**Cohort (unable to determine if pro- or retrospective); consecutive patients**	**Children and adults with gastrointestinal symptoms, anaemia or poor growth/weight loss**	**7 months–84 years; 84 M; 107 F**	**191**
Castro *et al.*, 1987, Italy[153]	Children's hospital, gastroenterology unit	Selection of cases/controls not described	Suspected CD (controls), not stated for cases	9 months–15 years (cases), no details for controls	106
Chan *et al.*, 2001, Canada[49]	Children's hospital gastrointestinal clinic	Prospective evaluation, not clear how patients selected	Children with gastrointestinal symptoms, failure to thrive/short stature, family history of CD or trisomy-21	2 months–16 years	77

continued

Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Chartrand *et al.*, 1997, Canada[154]	Hospital, division of paediatric gastroenterology	Prospective cohort, selection method not stated	Children with gastrointestinal symptoms, weight loss, failure to thrive	0.5–18.1 years (mean 5.2)	176
Chirdo *et al.*, 2000, Argentina[155]	Paediatric hospital, gastroenterology service	Selection of cases/controls not described	Controls: children with gastrointestinal symptoms, short stature; cases: no details	Controls: 1.5–14 years (mean 5.2); cases: no details	151
Chirdo *et al.*, 1999, Argentina[66]	Paediatric hospital, gastrointestinal department	Selection of cases/controls not described	Controls: children with gastrointestinal symptoms, short stature; cases: no details	13 months–14 years; 31 M, 28 F	59
Corazza *et al.*, 1997, Italy[79] *(research letter)*	**University hospital**	**Cohort (unable to determine if pro- or retrospective); consecutive patients**	**No details**	**No details**	**78**
de Lecea *et al.*, 1996, Spain[156]	Children's hospital, gastroenterology unit	Prospective evaluation, selection method not described	Children with short stature	11 months–14 years (mean 6.47, SD 0.24)	65
De Rosa *et al.*, 1993, Argentina[157]	Children's hospital, gastroenterology unit	Prospective cohort, selection method not described	Symptoms of CD or malabsorption	6 months–12 years; 29 M, 27 F	43
Del Rosario *et al.*, 1998, USA[158]	Children's hospital	Selection method not described	Children with gastrointestinal symptoms and/or failure to gain weight	5 months–16.7 years	46
Dickey *et al.*, 1997, UK[159]	Gastroenterology clinics	Selection method not described	Adults and children with gastrointestinal symptoms, anaemia, fatigue, weight loss, abnormal liver biochemistry, dermatitis herpetiformis or family history of CD	11–88 years (mean 42); 126 M, 192 F	318
Fälth-Magnusson *et al.*, 1994, Sweden[61]	University hospital	Selection method not described	Children with gastrointestinal symptoms, short stature	0.7–16.8 years	Results appear to be based on 262

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Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Feighery *et al.*, 1998, Ireland[80]	**Gastroenterology clinic**	**Retrospective cohort; consecutive patients**	**Adults and children with gastrointestinal symptoms, anaemia, weight loss, short stature, failure to thrive or recurrent oral ulceration**	**1–84 years**	**441**
Feighery *et al.*, 1998, Ireland/UK[160]	Hospital	Selection method not described	Gastrointestinal symptoms	No details	80
Fraser-Reynolds *et al.*, 1998, Canada[109]	Paediatric hospital, gastrointestinal clinic	Prospective cohort, selection method not described	Children with gastrointestinal symptoms	2 months–16 years	56
Gemme *et al.*, 1993, Italy[161]	University paediatric hospital	Selection method not described	Children with suspected CD	6 months–18 years	92
Ghedira *et al.*, 1999, Tunisia[162]	Not stated	Retrospective evaluation, selection method not described	Adults with gastrointestinal symptoms, anaemia, weight loss or short stature	16–65 years; 14 M, 29 F	43
Gillett and Freeman, 2000, Canada[163]	University hospital, division of gastroenterology	Selection of cases/controls not described	No details	No details	63
Grodzinsky *et al.*, 2001, Sweden[62]	University hospitals (multicentre)	Retrospective (incomplete) cohort, selection method not described	Children with suspected CD	9 months–16.7 years	133
Grodzinsky *et al.*, 1995, Sweden[164]	Hospital paediatric departments	Prospective cohort, selection method not described	Children with suspected CD	10 months–18 years (median 1.7)	97
Hällström *et al.*, 1989, Finland[165]	University hospital, department of microbiology/ immunology	Appears to be case–control study, selection of cases/controls not described	Controls (children): abdominal symptoms, no details for cases/adults	1–16 years	38 (children only)
Hansson *et al.*, 2000, Sweden[166]	University hospital, department of paediatrics	Appears to be case–control study, selection of cases/controls not described	Controls: gastrointestinal symptoms; no details for cases	1–17 years	39

continued

Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Juto *et al.*, 1985, Sweden[167]	University hospital, department of paediatrics	Selection method not described	Children or infants with symptoms of malabsorption or short stature	No details	69
Keddari *et al.*, 1989, Algeria[88]	Children's hospital	Prospective evaluation, selection method not described	Children (duration of diabetes 3.5 ± 0.6 years)	2–21 years (mean 12.5)	54
Kelly *et al.*, 1987, Ireland[81]	**Children's hospital**	**Prospective cohort, consecutive patients**	**Children with symptoms suggestive of CD**	**9 months–15 years (median 6)**	**77**
Kumar *et al.*, 1989, USA[168]	Hospital and children's hospital	Retrospective evaluation, selection method not described	Children and infants with gastrointestinal symptoms	No further details	52
Lerner *et al.*, 1994, Israel[64]	Paediatric gastroenterology unit, hospital department of paediatrics	Prospective evaluation, selection method not described	Children with gastrointestinal symptoms or failure to thrive	1–17 years	75
Lindberg *et al.*, 1985, Sweden[65]	Children's hospitals	Selection method not described	Children with gastrointestinal symptoms, failure to thrive and/or short stature	7 months–16 years	234
Lock *et al.*, 1999, UK[169]	Hospitals	Retrospective evaluation, selection method not described	Adults with suspected CD, anaemia, malabsorption, tiredness, IDDM, family history	No details	92
Mäki *et al.*, 1991, Finland[82]	**Not stated**	**Prospective cohort of 1st-degree relatives giving consent**	**1st-degree healthy relatives (adults and children) from coeliac families**	**No symptoms**	**122**
Mantzaris *et al.*, 1995, Greece[83]	**Hospital department of gastroenterology**	**Cohort, consecutive patients; unable to determine if pro- or retrospective**	**Not clearly stated**	**No details**	**129**
McMillan *et al.*, 1991, UK[84]	**Hospital gastroenterology clinic**	**Retrospective cohort, consecutive patients**	**Children and adults with gastrointestinal symptoms, tiredness, weight loss or short stature**	**26–80 years (mean 40); 36 M, 60 F**	**96**

continued

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Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Meini *et al.*, 1996, Italy[68]	**University hospital, department of paediatrics**	**Prospective cohort, consecutive IgA-deficient patients**	**IgA-deficient children referred to immunology department due to recurrent respiratory tract infections or low IgA levels**	**2–15 years; 32 M, 33 F**	**65**
Murr *et al.*, 1992, Austria[170]	University children's hospital	Selection of patients not described	Children with gastrointestinal symptoms, failure to gain weight, abnormal growth, anaemia	0.6–7.1 years	44
Niveloni *et al.*, 1998, Argentina[171]	Gastroenterology hospital	Prospective cohort, selection method not described	Adults with primary biliary cirrhosis (high risk)	33–72 years (median 49); 1 M, 9 F	10
Not *et al.*, 1997, Italy[85]	**Paediatric clinic**	**Prospective cohort, consecutive patients**	**Children with symptoms indicative of CD, including failure to thrive and recurrent gastrointestinal problems**	**1–20 years**	**45**
Not *et al.*, 1993, Italy[67]	Children's hospital	Prospective evaluation, selection method not described	Children with gastrointestinal symptoms, failure to thrive or short stature	2–20 years	114
Pacht *et al.*, 1995, Israel[172]	Paediatric gastroenterology nutrition unit	Cohort, not clear whether pro- or retrospective	Children with gastrointestinal symptoms or failure to thrive	2–16 years	44
Radzikowski *et al.*,1988, Poland/USA[173]	Department of paediatric gastroenterology and dermatology	Selection method not described	Children with short stature and suspicion of CD	3.5–14 years	14
Rich and Christie, 1990, USA[174]	Department of paediatrics, University hospital and children's hospital and medical centre	Prospective cohort, selection method not described	Children with gastrointestinal symptoms, failure to thrive or short stature	14 months–16 years (mean 7)	60
Rossi *et al.*, 1988, USA/Israel[175]	Hospital and children's hospital	Selection of patients not described	Infants and children with gastrointestinal symptoms	No details	53

continued

Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Russo *et al.*, 1999, Canada[86]	**University hospital, paediatric gastroenterology clinic**	**Prospective cohort, consecutive patients**	**Children with suspicion of CD**	**7 months–18.1 years (mean 5.2); 63 M, 32 F**	**95**
Sacchetti *et al.*, 1998, Italy[176]	University department of paediatrics, centre for the study of gastrointestinal disorders	Selection of patients not described	Children with clinical symptoms of CD or suggestive laboratory test results (not clear what was tested)	Mean 6 years	80
Sategna-Guidetti *et al.*, 1997, Italy[177]	University department of medicine	Selection of cases/ controls not described	Controls: gastrointestinal disorders; no details for cases	17–79 (cases); no details for controls	152
Savilahti *et al.*, 1986, Finland[89]	University children's hospital	Prospective cohort, selection method not described	Children with diabetes (high risk)	No details	110
Signer *et al.*, 1979, Switzerland[178]	University children's hospital	Prospective evaluation, selection method not described	Children with gastrointestinal symptoms	2 months–17 years	48
Sommer and Eitelberger, 1992, Austria[69]	Children's hospital	Prospective cohort, selection method not described	Children with dystrophy, gastrointestinal symptoms, failure to thrive or short stature	5 months – 14 years (median 1.36); 40 M, 30 F	70
Stenhammar *et al.*, 1984, Sweden[179]	Hospital, department of paediatrics	Selection of cases/controls not described	Children with symptoms of CD, gastrointestinal symptoms or short stature	0.2–16.5 years; 30 M, 42 F	72
Stern, 2000, Germany[180]	Hospital	Selection not described	No details	Adults and children	192
Stern and Grüttner, 1981, Germany[181]	University paediatric hospital	Selection not described	Children with non-specific enteropathy or gastrointestinal symptoms	No details	120
Sulkanen *et al.*, 1998, Finland[182]	University hospital	Appears to be case–control study, selection of controls not described	Adults with gastrointestinal symptoms, malabsorption, heredity, extraintestinal symptoms (cases); no details for controls	19–72 years	125

continued

Author, year, country	Setting	Study design	Sample source/population	Population characteristics (age)/prevalence if known	Sample size (only relevant subgroups where patients had both tests)
Sulkanen *et al.*, 1998, Finland[183]	University (children's) hospital	Appears to be case–control study, selection of controls not described	Controls: suspected CD, IDDM; no details for cases	0.8–76 years	343
Teesalu *et al.*, 2001, Finland/USA[184]	University children's hospital	Retrospective evaluation of sera, selection method not described	Controls: suspected CD; no details for cases	0.5–15 years for cases; no details for biopsied controls	60
Troncone *et al.*, 1999, Italy[185]	University hospital, department of paediatrics	Selection method not clearly described	Children with suspected CD	0.9–20 years; 52 M, 59 F	111
Valdimarsson *et al.*, 1996, Sweden[186]	University hospital	Prospective cohort, selection method not described	Adults with symptoms of CD or other gastrointestinal symptoms	For 156: 17–84 years [mean 45 (M), 46 (F)]; 70 M, 86 F	144
Vogelsang *et al.*, 1995, Austria[87]	**Departments of internal medicine and paediatrics, University Hospital**	**Prospective cohort, consecutive patients**	**Children and adults with gastrointestinal symptoms, weight loss or joint/bone pain**	**15–79 years (median 33); 41 M, 61 F**	**102**
West *et al.*, 2002, UK[187]	Hospitals and gastroenterology outpatient clinic	Selection not described	Adults; no further details	15–88 years	230
Whelan *et al.*, 1996, Ireland[188]	Gastroenterology clinic	Selection of cases/controls not described	Controls: non-specific symptoms; no details for cases	No details	41
Wildfang *et al.*, 1992, Germany[189]	University children's hospital	Retrospective evaluation, selection not described	Children with gastrointestinal symptoms, failure to thrive, short stature, suspected CD	2 months–13.9 years	70

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Appendix 6

Description of reference test standard and biopsy method [cohorts where the selection method is described (n = 18) are in bold]

Author, year	Biopsy method	Description of reference test standard
Altuntas *et al.*, 1998[144]	Endoscopic duodenal biopsy	Total or subtotal villous atrophy, crypt hyperplasia and intraepithelial lymphocytic infiltration
Artan 1998[60]	Carey capsule or endoscope	Crypt hyperplastic villous atrophy or flat mucosa and intraepithelial lymphocyte infiltration
Ascher *et al.*, 1996[145]	Not stated	ESPGAN criteria
Ascher *et al.*, 1990[72]	**Watson capsule**	**Histology according to ESPGAN criteria, verification in some patients**
Auricchio *et al.*, 1988[73]	**Not stated**	**Severe partial or subtotal villous atrophy**
Bardella *et al.*, 2001[146]	Endoscope	Histological diagnosis according to Marsh's criteria
Bardella *et al.*, 1991[74]	**Endoscope or Watson capsule**	**Not stated**
Basso *et al.*, 2001[63]	**Endoscope**	**On basis of histology and subsequent improvement on GFD**
Biagi *et al.*, 1999[147]	Not stated	ESPGAN criteria
Bode *et al.*, 1993[75]	**Not stated**	**ESPGAN criteria**
Bode and Gudmand-Hoyer, 1994[76]	**Not stated**	**Crypt hypertrophic villous atrophy and increased numbers of inflammatory cells**
Boige *et al.*, 1996[148]	Endoscope	Total villous atrophy with remission on GFD
Bonamico *et al.*, 1992[149]	Watson or Kilby capsule	Sub- or total mucosal atrophy with normal diet and improvement of weight/height growth with normalisation of biological data on GFD
Bottaro *et al.*, 1997[150]	Not stated	ESPGAN criteria
Bottaro *et al.*, 1995[77]	**Watson capsule**	**Severe partial or subtotal villous atrophy**
Bürgin-Wolff *et al.*, 1983[151]	Not stated	Total or sub-total villous atrophy, response to GFD, relapse after gluten challenge (second biopsies not performed in all)
Cacciari *et al.*, 1985[152]	Paediatric Watson capsule	ESPGAN
Carroccio *et al.*, 2002[78]	**Children: multipurpose Crosby capsule Adults: biopsy during gastroduodenoscopy**	**Clinical symptoms and intestinal histology damage (inflammatory infiltration of the mucosa with enlarged crypts and/or intestinal villous atrophy on GCD, disappearance on GFD and reappearance on gluten challenge)**
Castro *et al.*, 1987[153]	No details	No details
Chan *et al.*, 2001[49]	Carey capsule or endoscopy	Increased number of intraepithelial lymphocytes with associated sub-total or total villous atrophy
Chartrand *et al.*, 1997[154]	Paediatric video endoscope	Flat intestinal mucosa on GCD, clinical remission on GFD (ESPGAN criteria)

continued

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Author, year	Biopsy method	Description of reference test standard
Chirdo *et al.*, 2000[155]	Not stated	ESPGAN
Chirdo *et al.*, 1999[66]	Not stated	Not stated
Corazza *et al.*, 1997[79] *(research letter)*	**Not stated**	**Not stated**
de Lecea *et al.*, 1996[156]	Not stated	Sub-total villous atrophy (and follow-up)
De Rosa *et al.*, 1993[157]	Crosby Kugler capsule	Histology grade I–IV; III and IV correspond to severe or total villous atrophy
Del Rosario *et al.*, 1998[158]	Endoscope	Diagnosis of CD supported by absent or blunted villi, crypt hyperplasia, increased intraepithelial lymphocytes, plasma cells in the lamina propria and damaged absorptive cells
Dickey *et al.*, 1997[159]	Endoscope	Villous atrophy
Fälth-Magnusson *et al.*, 1994[61]	Watson or Storz capsule	Alexander's classification and ESPGAN
Feighery et al., 1998[80]	**Endoscope (adults) or Crosby capsule (children)**	**Improvement of symptoms and small intestinal lesion on GFD**
Feighery *et al.*, 1998[160]	Not stated	Typical histological lesion
Fraser-Reynolds *et al.*, 1998[109]	Carey capsule	Intraepithelial lymphocytes in combination with partial or total villous atrophy
Gemme *et al.*, 1993[161]	Not stated	Original or amended ESPGAN criteria
Ghedira *et al.*, 1999[162]	Not stated	Sub-total or total villous atrophy
Gillett and Freeman, 2000[163]	Not stated	Not stated
Grodzinsky *et al.*, 2001[62]	Watson or Storz capsule	Mucosal lesions grade III or IV Alexander's classification
Grodzinsky *et al.*, 1995[164]	Watson or Storz capsule	Mucosal lesions grade III or IV Alexander's classification
Hällström *et al.*, 1989[165]	Not stated	Not stated
Hansson *et al.*, 2000[166]	Not stated	Subtotal or total villous atrophy
Juto *et al.*, 1985[167]	Standard paediatric suction biopsy instruments	Subtotal or partial villous atrophy
Keddari *et al.*, 1989[88]	Endoscope	Villous atrophy
Kelly *et al.*, 1987[81]	**Not stated**	**Sub-total or partial villous atrophy and clinical improvement on GFD**
Kumar *et al.*, 1989[168]	Crosby–Kugler capsule	ESPGAN
Lerner *et al.*, 1994[64]	Crosby capsule or endoscope	Grades I–IV according to Townley criteria, modified by Ingkaran
Lindberg *et al.*, 1985[65]	Watson capsule	Evaluation according to Alexander or Perera *et al.*
Lock *et al.*, 1999[169]	Not stated	Typical histological features
Mäki *et al.*, 1991[82]	**Not stated**	**Severe partial villous atrophy with crypt hyperplasia or flat mucosa**
Mantzaris *et al.*, 1995[83]	**Not stated**	**Not stated**
McMillan *et al.*, 1991[84]	**Crosby capsule**	**ESPGAN**
Meini *et al.*, 1996[68]	**Watson capsule**	**Severe or partial villous atrophy**
Murr *et al.*, 1992[170]	Watson capsule	ESPGAN criteria 1978 or 1989

continued

Author, year	Biopsy method	Description of reference test standard
Niveloni *et al.*, 1998[171]	Endoscopy	Villous atrophy graded I (normal)–IV (total villous atrophy), grades II–IV classified as CD
Not *et al.*, 1997[85]	**Endoscopy**	**ESPGAN criteria**
Not *et al.*, 1993[67]	Endoscopy	ESPGAN criteria
Pacht *et al.*, 1995[172]	Crosby–Kugler capsule or endoscopy	ESPGAN criteria
Radzikowski *et al.*,1988[173]	Not stated	Flattened mucosa, normalisation on GFD
Rich and Christie, 1990[174]	Standard paediatric suction biopsy technique	Flat small bowel biopsy and response to GFD
Rossi *et al.*, 1988[175]	Crosby–Kugler capsule or endoscopy	Total villous atrophy
Russo *et al.*, 1999[86]	**Endoscopy**	**ESPGAN criteria**
Sacchetti *et al.*, 1998[176]	Not stated	ESPGAN criteria
Sategna-Guidetti *et al.*, 1997[177]	Endoscope	Typical histological appearance of mucosa and positive response on GFD
Savilahti *et al.*, 1986[89]	Not stated	Total villous atrophy
Signer *et al.*, 1979[178]	Watson paediatric capsule	Total or subtotal villous atrophy
Sommer and Eitelberger 1992[69]	Watson capsule	Total villous atrophy
Stenhammar *et al.*, 1984[179]	Watson capsule	ESPGAN
Stern, 2000[180]	Not stated	ESPGAN
Stern and Grüttner, 1981[181]	Not stated	ESPGAN or flat mucosa with improvement on GFD
Sulkanen *et al.*, 1998[182]	Not stated	Subtotal or severe villous atrophy with crypt hyperplasia and recovery on GFD
Sulkanen *et al.*, 1998[183]	Watson capsule or endoscope	Children: ESPGAN; adults: severe VA and crypt hyperplasia, mucosal healing confirmed on biopsy
Teesalu *et al.*, 2001[184]	Not stated	ESPGAN
Troncone *et al.*, 1999[185]	Not stated	ESPGAN
Valdimarsson *et al.*, 1996[186]	Watson capsule or endoscope	Mucosal lesions grade III or IV Alexander's classification plus two of following criteria: morphological improvement on GFD; biochemical signs of malabsorption; symptoms suggestive of CD
Vogelsang *et al.*, 1995[87]	**Baumgartner–Classen capsule**	**Modified ESPGAN criteria (mainly typical flat small bowel mucosa, crypt hyperplasia, elevated intraepithelial lymphocyte counts; symptomatic recovery after GFD)**
West *et al.*, 2002[187]	Not stated	Severe partial or subtotal villous atrophy
Whelan *et al.*, 1996[188]	Not stated	Subtotal villous atrophy
Wildfang *et al.*, 1992[189]	Not stated	ESPGAN criteria of 1989

GFD, gluten-free diet; GCD, gluten-containing diet.

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Appendix 7

Quality assessment [cohorts where the selection method is described (*n* = 18) are in bold]

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Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Altuntas *et al.*, 1998[144]	×	CT	CT	✓	CT	✓	
Artan 1998[60]	×	✓	✓	✓	CT	✓	
Ascher *et al.*, 1996[145]	×	CT	✓	✓	CT	✓	
Ascher *et al.*, 1990[72]	✓	**CT**	✓	✓	**CT**	✓	
Auricchio *et al.*, 1988[73]	✓	**CT**	**CT**	**CT**	**CT**	✓	**Reference test performed in 152/170**
Bardella *et al.*, 2001[146]	✓	CT	CT	✓	CT	✓	
Bardella *et al.*, 1991[74]	✓	**CT**	**CT**	✓	**CT**	**CT**	
Basso *et al.*, 2001[63]	✓	✓	**CT**	**CT**	**CT**	✓	**Not every test performed in all patients**
Biagi *et al.*, 1999[147]	×	CT	CT	CT	CT	✓	
Bode *et al.*, 1993[75]	✓	✓	✓	✓	**CT**	✓	**Biopsies in 4 patients performed on basis of positive test result**
Bode and Gudmand-Hoyer, 1994[76]	✓	**CT**	**CT**	✓	**CT**	✓	

continued

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Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Boige *et al.*, 1996[148]	×	CT	CT	CT	CT	✓	Reference test performed in all, antibody test in 27/49 (methodology not available at beginning of study)
Bonamico *et al.*, 1992[149]	×	CT	✓	✓	CT	✓	
Bottaro *et al.*, 1997[150]	×	✓	✓	✓	CT	CT	
Bottaro *et al.*, 1995[77]	✓	**CT**	**CT**	✓	**CT**	✓	
Bürgin-Wolff *et al.*, 1983[151]	×	✓	✓	✓	CT	✓	
Cacciari *et al.*, 1985[152]	×	CT	CT	✓	✓	✓	
Carroccio *et al.*, 2002[78]	✓	**CT**	**CT**	✓	**CT**	**CT**	
Castro *et al.*, 1987[153]	×	CT	CT	CT	CT	CT	
Chan *et al.*, 2001[49]	×	✓	✓	✓	CT	✓	2 IgA-deficient children subsequently excluded from analysis
Chartrand *et al.*, 1997[154]	×	✓	✓	✓	CT	✓	Reference test performed in all, cannot tell for antibody tests

continued

Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Chirdo *et al.*, 2000[155]	×	CT	CT	CT	CT	✓	
Chirdo *et al.*, 1999[66]	×	CT	CT	✓	CT	✓	
Corazza *et al.*, 1997[79] *(research letter)*	✓	✓	✓	✓	**CT**	✓	
de Lecea *et al.*, 1996[156]	×	CT	CT	CT	×	✓	
De Rosa *et al.*, 1993[157]	×	✓	✓	✓	CT	✓	
Del Rosario *et al.*, 1998[158]	×	CT	CT	✓/×	CT	CT	Antibody test results known for 22/46 (positive) patients before referral for biopsy; antigliadin tests carried out in 43/46 only
Dickey *et al.*, 1997[159]	×	CT	CT	✓	CT	✓	
Fälth-Magnusson *et al.*, 1994[61]	×	CT	CT	✓	CT	✓	
Feighery *et al.*, 1998[80]	✓	**CT**	**CT**	**CT**	**CT**	✓	**Patients included for whom concurrent biopsies and serology were available**

continued

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Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Feighery *et al.*, 1998[160]	×	CT	CT	✓	CT	✓	
Fraser-Reynolds *et al.*, 1998[109]	×	✓	✓	✓	CT	✓	
Gemme *et al.*, 1993[161]	×	CT	CT	CT	CT	✓	
Ghedira *et al.*, 1999[162]	×	CT	CT	✓	CT	✓	
Gillett and Freeman, 2000[163]	×	CT	CT	CT	CT	✓	
Grodzinsky *et al.*, 2001[62]	×	CT	✓	✓	CT	✓	
Grodzinsky *et al.*, 1995[164]	×	✓	✓	✓	CT	✓	
Hällström *et al.*, 1989[165]	×	CT	CT	✓	CT	✓	
Hansson *et al.*, 2000[166]	×	CT	✓	✓	CT	✓	
Juto *et al.*, 1985[167]	×	CT	CT	✓	CT	✓	
Keddari *et al.*, 1989[88]	×	✓	✓	✓	CT	✓	
Kelly *et al.*, 1987[81]	✓	**CT**	✓	✓	**CT**	✓	

continued

Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Kumar *et al.*, 1989[168]	×	✓	CT	CT	CT	✓	
Lerner *et al.*, 1994[64]	×	✓	✓	✓	CT	✓	Reference test performed in all, antibody tests in 70–100%
Lindberg *et al.*, 1985[65]	×	CT	✓	✓	CT	✓	Reference test performed in all, antibody test in 190/234
Lock *et al.*, 1999[169]	×	×	CT	✓	✓	✓	
Mäki *et al.*, 1991[82]	✓	**CT**	**CT**	**CT✓**	**CT (for children)**	✓	**Antibody test in all, 122/148 biopsied**
Mantzaris *et al.*, 1995[83]	✓	**CT**	✓	**CT**	**CT**	✓	
McMillan *et al.*, 1991[84]	✓	✓	✓	✓	**CT**	✓	
Meini *et al.*, 1996[68]	✓	✓	✓	✓	**CT**	✓	**Reference test performed in all, antibody test in 60/65**
Murr *et al.*, 1992[170]	×	CT	CT	CT	CT	✓	
Niveloni *et al.*, 1998[171]	×	CT	✓	✓	✓	✓	
Not *et al.*, 1997[85]	✓	✓	**CT**	✓	**CT**	✓	

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Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Not *et al.*, 1993[67]	×	CT	CT	✓	CT	✓	
Pacht *et al.*, 1995[172]	×	CT	✓	✓	CT	✓	
Radzikowski *et al.*,1988[173]	×	CT	✓	✓	CT	✓	
Rich and Christie, 1990[174]	×	CT	CT	CT	CT	✓	
Rossi *et al.*, 1988[175]	×	CT	✓	CT	CT	✓	
Russo *et al.*, 1999[86]	✓	**CT**	✓	✓	**CT**	✓	
Sacchetti *et al.*, 1998[176]	×	CT	CT	CT	×	CT	Preliminary laboratory tests carried out before antibody tests and biopsy
Sategna-Guidetti *et al.*, 1997[177]	×	✓	CT	✓	CT	✓	
Savilahti *et al.*, 1986[89]	×	CT	CT	✓	✓	✓	Biopsy in 110/122
Signer *et al.*, 1979[178]	×	CT	CT	✓	CT	✓	
Sommer and Eitelberger, 1992[69]	×	✓	✓	✓	CT	CT	Test for IgA in all, IgG only in 29/70 (data not extracted)

continued

Author, year	Was the selection method described?	Was the test measured independently (blindly) of the reference standard?	Was the reference standard measured independently (blindly) of the test?	Was the choice of patient assessed by the reference standard independent of the test?	Was the test measured independently of all other clinical information?	Were the reference standard and the test performed before any treatment was given?	Comments
Stenhammar *et al.*, 1984[179]	×	CT	CT	✓	CT	✓	
Stern, 2000[180]	×	✓	✓	CT	CT	✓	
Stern and Grüttner, 1981[181]	×	CT	CT	CT	CT	✓	
Sulkanen *et al.*, 1998[182]	×	CT	CT	CT	CT	✓	
Sulkanen *et al.*, 1998[183]	×	CT	✓	✓	CT	✓	
Teesalu *et al.*, 2001[184]	×	CT	✓	✓	CT	✓	
Troncone *et al.*, 1999[185]	✓	CT	CT	✓	CT	✓	
Valdimarsson *et al.*, 1996[186]	×	CT	✓	✓	CT	CT	Reference test performed in all, antibody test in 144/156
Vogelsang *et al.*, 1995[87]	✓	**CT**	**CT**	✓	**CT**	✓	
West *et al.*, 2002[187]	×	×	✓	✓	CT	✓	
Whelan *et al.*, 1996[188]	×	✓	✓	✓	CT	✓	
Wildfang *et al.*, 1992[189]	×	CT	CT	CT	CT	✓	Some patients selected for antibody tests if biopsy confirmed CD; stated that IgA EMA test carried out if IgA/G antigliadin was positive (though appear to have EMA results for all)

CT, cannot tell.

Appendix 8

Autoantibody test methods and results [cohorts where the selection method is described (n = 18) are in bold]

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TABLE 26 *Studies including IgA AGA tests*

Author, year	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Altuntas *et al.*, 1998[144]	ELISA	Euroimmun kit, Lübeck, Germany	25-50 RU/ml weakly positive; >50 RU/ml strongly positive	None
Artan 1998[60]	ELISA	Labmaster, Turku, Finland	>25 AU, >25 AU for >2 years and >50 AU for <2 years (manufacturer's instructions), >50 AU, >20 AU	None
Ascher *et al.*, 1990[72]	**ELISA**	**Pharmacia Diagnostics, Uppsala, Sweden**	**>35 AU**	**5 samples run in 8 replicates on 10 different occasions by 7 persons and variation calculated [total coefficient of variation (CV) = 8.3–11.5%]**
Ascher *et al.*, 1996[145]	ELISA	Pharmacia Gluten EIA kit	20 AU for ≥5 years, 35 AU for <5 years	None
Ascher *et al.*, 1996[145]	DIG-ELISA	Described elsewhere	IgA >13mm, IgG >16 mm for <5 years; IgA >11mm, IgG >14mm for ≥5 years	None
Auricchio *et al.*, 1988[73]	**ELISA**	**In-house methods, some Pharmacia kits**	**Values above the 90th percentile of a healthy age-matched population**	**Good correlation between in-house and commercial tests**
Bardella *et al.*, 1991[74]	**Solid-phase enzyme immunoassay**	**Pharmacia Gluten IgA EIA kit**	**>25 AU**	**None**
Bardella *et al.*, 2001[146]	ELISA	ORGenTec Diagnostika, Germany kit	>12 AU/ml	Intra- and inter-assay CV 6.5 and 8.7%
Basso *et al.*, 2001[63]	**ELISA**	**Pharmacia & Upjohn, Sweden**	**3.66 U/ml**	**All tests performed in duplicate**
Bode and Gudmand-Hoyer 1994[76]	**DIG-ELISA**	**Described elsewhere**	**IgA >10.5 mm (borderline 9.5 ≤ IgA ≤10.5mm**	**Each serum sample analysed twice (difference never exceeded 1 mm)**
Bode *et al.*, 1993[75]	**DIG-ELISA**	**Described elsewhere**	**IgA ≥10.5 mm**	**Each serum sample analysed twice (difference never exceeded 1 mm)**
Bode *et al.*, 1993[75]	**DIG-ELISA**	**Described elsewhere**	**IgA ≥10 mm**	**Each serum sample analysed twice (difference never exceeded 1 mm)**
Bonamico *et al.*, 1992[149]	Micro-ELISA	Described elsewhere	Not stated	None
Bottaro *et al.*, 1997[150]	ELISA	Immunopharmacology Research kit, Italy	IgA >10%	None
Bottaro *et al.*, 1995[77]	**ELISA**	**IPR-Immuno Pharmacology Research Catania**	**IgA >10%**	**None**

continued

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TABLE 26 *Studies including IgA AGA tests (cont'd)*

Author, year	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Cacciari *et al.*, 1985[152]	Micro-ELISA	No details	No details	None
Cacciari *et al.*, 1985[152]	Immunofluorescence	No details	No details	None
Carroccio *et al.*, 2002[78]	**ELISA**	**Alpha-Gliatest, Eurospital Pharma, Trieste, Italy)**	**10% of reference serum = upper normal limit**	**None**
Chartrand *et al.*, 1997[154]	ELISA	Falcon 3915, Becton Dickinson Lab Ware, Lincoln Park, NJ, USA	OD of 0.25	Reproducibility of tests on different days confirmed
Chirdo *et al.*, 1999[66]	ELISA 7 antigenic preparations (commercial gliadin, ethanolic extract, ω-gliadin, O1, O2, LP1, LP2)	In-house	Not stated	None
Chirdo *et al.*, 2000[155]	ELISA (ω-gliadin, commercial gliadin and wheat extract)	Described elsewhere	Not stated	None
de Lecea *et al.*, 1996[156]	ELISA	Described elsewhere	Reference value 0.3 (mean + 2SD of control population)	None
De Rosa *et al.*, 1993[157]	ELISA	In-house	>25 units	All tests performed twice
Del Rosario *et al.*, 1998[158]	ELISA	All tests carried out by IMMCO Diagnostics	No details	None
Fälth-Magnusson *et al.*, 1994[61]	ELISA	In-house	Various cut-offs (see results)	None
Fälth-Magnusson *et al.*, 1994[61]	DIG-ELISA	In-house	Various cut-offs (see results)	None
Gemme *et al.*, 1993[161]	ELISA	No details	No details	None
Ghedira *et al.*, 1999[162]	ELISA	In-house	EI>1.6	None
Grodzinsky *et al.*, 1995[164]	ELISA	In house method	40 units (96.8th percentile for blood donor group described elsewhere)	None
Grodzinsky *et al.*, 2001[62]	ELISA (Linkoping)	In house method	≥30 U	CV <15%
Grodzinsky *et al.*, 2001[62]	ELISA (Umea)	In house method	OD ≥0.1	CV for low positive control 19.8% and for high positive control 13.6%

continued

TABLE 26 *Studies including IgA AGA tests (cont'd)*

Author, year	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Grodzinsky *et al.*, 2001[62]	ELISA UNICAP-100 (Linkoping)	Pharmacia & Upjohn Diagnostics, Uppsala, Sweden	3 mg litre/antigen	CV 4–11%
Grodzinsky *et al.*, 2001[62]	ELISA Pharmacia CAP System Gliadin IgA FEIA (CAP) (Orebro)	Pharmacia & Upjohn Diagnostics, Uppsala, Sweden	3 mg litre/antigen	CV 5–7%
Grodzinsky *et al.*, 2001[62]	ELISA Pharmacia CAP System Gliadin IgA FEIA (CAP) (Umea)	Pharmacia & Upjohn Diagnostics, Uppsala, Sweden	3 mg litre/antigen	Interassay CV for low and high positive controls (CV) 5–7%
Grodzinsky *et al.*, 2001[62]	DIG-ELISA (Orebro)	In-house method	Zone diameter >11mm	CV <15%
Hansson *et al.*, 2000[166]	ELISA	Described elsewhere	No details	None
Juto *et al.*, 1985[167]	ELISA	In-house	Mean OD +3SD (OD test serum/OD cut-off, values >1)	Intrassay CV <5% at beginning of study, subsequently not done in duplicate
Lerner *et al.*, 1994[64]	ELISA	Immco Diagnostic Buffalo, NY, USA	Absorbance >2SD of the mean of normal values	None
Lindberg *et al.*, 1985[65]	DIG-ELISA	Sigma Chemical, St Louis, MO, USA and Dako, Copenhagen, Denmark	Appearance of brown, circular areas ≥11 mm (IgA) and ≥14 mm (IgG)	None
Lock *et al.*, 1999[169]	ELISA	Described elsewhere	OD>0.12	None
Mäki *et al.*, 1991[82]	**ELISA**	**Not described**	**0.20 ELISA units/ml**	**Sera blind tested in another laboratory**
McMillan *et al.*, 1991[84]	**ELISA**	**Labmaster, Turku, Finland**	**Titre ≥20**	**None**
McMillan *et al.*, 1991[84]	**Indirect immunofluorescence**	**Rat liver, kidney and mouse stomach sections; Biodiagnostics UK**	**Titre ≥20**	**None**
Meini *et al.*, 1996[68]	**ELISA**	**Eurospital**	**>25 AU/dl**	**None**
Murr *et al.*, 1992[170]	Enzyme immunoassay	Pharmacia Gluten IgA EIA	> 25 AU	Within-assay CV 6.0–7.7%; between-assay CV 11.0–11.6%
Niveloni *et al.*, 1998[171]	Micro-ELISA	Described elsewhere	>25 AU/ml	None
Not *et al.*, 1993[67]	ELISA	Described elsewhere	ELISA index >3	None
Not *et al.*, 1993[67]	Strip AGA test (dot immunobinding assay)	Described elsewhere	Subjective colorimetric evaluation (+ to +++)	None

continued

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TABLE 26 *Studies including IgA AGA tests (cont'd)*

Author, year	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Rich and Christie, 1990[174]	ELISA	Sigma Chemicals, St Louis, MO, USA	Antibody level >2 SD above the mean of the reference standard of the control group	None
Russo *et al.*, 1999[86]	**ELISA**	**Described elsewhere**	**0.25 ELISA units**	**None**
Sacchetti *et al.*, 1998[176]	ELISA	No details	No details	None
Savilahti *et al.*, 1986[89]	ELISA	No details	Mean + 2SD of internal control sera	None
Sommer and Eitelberger, 1992[69]	Enzyme immunoassay	'Gluten IgA-EIA', Pharmacia Diagnostics, Uppsala, Sweden	>25 AU, >50AU and >100 AU	Each series of analyses included the same patient serum sample in addition to the commercial control
Stenhammar *et al.*, 1984[179]	DIG-ELISA	Described elsewhere	>11.5 mm	None
Stern, 2000[180]	ELISA	Method described elsewhere	>5 AU	All tests carried out in duplicate; intra-laboratory CVs calculated
Sulkanen *et al.*, 1998[182]	ELISA	Described elsewhere	>0.2 EU/ml	None
Sulkanen *et al.*, 1998[183]	ELISA	In-house		None
Valdimarsson *et al.*, 1996[186]	ELISA	Described elsewhere	30 units	None
Vogelsang *et al.*, 1995[87]	**ELISA**	**No details**	**IgA ≥0.21 AU/ml**	**None**
West *et al.*, 2002[187]	ELISA	In-house	No details	None
Wildfang *et al.*, 1992[188]	No details	No details	No details	None

TABLE 27 *IgA AGA sensitivity and specificity*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Altuntas *et al.*, 1998[144]	IgA AGA	6	2	19	20	23.1	11.0	42.1	90.5	71.1	97.3	75.0	48.7
Artan 1998[60]	IgA AGA (>20 AU)	17	22	17	7	70.8	50.8	85.1	43.6	29.3	59.0	43.6	70.8
Artan 1998[60]	IgA AGA (>25 AU)	17	23	18	7	70.8	50.8	85.1	43.9	29.9	59.0	42.5	72.0
Artan 1998[60]	IgA AGA (>50 AU)	7	7	32	17	29.2	14.9	49.2	82.1	67.3	91.0	50.0	65.3
Artan 1998[60]	IgA AGA (Manufacturer's cut-off)	14	19	20	10	58.3	38.8	75.5	51.3	36.2	66.1	42.4	66.7
Ascher *et al.*, 1990[72]	**IgA AGA**	**35**	**7**	**85**	**1**	**97.2**	**85.8**	**99.5**	**92.4**	**85.1**	**96.3**	**83.3**	**998.8**
Ascher *et al.*, 1996[145]	IgA AGA (DIG-ELISA)	50	2	63	5	90.9	80.4	96.1	96.9	89.5	99.2	96.2	92.6
Ascher *et al.*, 1996[145]	IgA AGA (ELISA)	50	1	64	5	90.9	80.4	96.1	98.5	91.8	99.7	98.0	92.8
Auricchio *et al.*, 1988[73]	**IgA AGA**	**7**	**10**	**127**	**8**	**46.7**	**24.8**	**69.9**	**92.7**	**87.1**	**96.0**	**41.2**	**94.1**
Bardella *et al.*, 1991[74]	**IgA AGA**	**17**	**1**	**33**	**9**	**65.4**	**46.2**	**80.6**	**97.1**	**85.1**	**99.5**	**94.4**	**78.6**
Bardella *et al.*, 2001[146]	IgA AGA	38	12	98	2	95.0	83.5	98.6	89.1	81.9	93.6	76.0	98.0
Basso *et al.*, 2001[63]	**IgA AGA**	**CT**	**CT**	**CT**	**CT**								
Bode and Gudmand-Hoyer, 1994[76]	**IgA AGA**	**6**	**3**	**84**	**7**	**46.2**	**23.2**	**70.9**	**96.6**	**90.3**	**98.8**	**66.7**	**92.3**
Bode *et al.*, 1993[75]	**IgA AGA (threshold 1)**	**9**	**1**	**176**	**5**	**64.3**	**38.8**	**83.7**	**99.4**	**96.9**	**99.9**	**90.0**	**97.2**
Bode *et al.*, 1993[75]	**IgA AGA (threshold 2)**	**CT**	**CT**	**CT**	**CT**								
Bonamico *et al.*, 1992[149]	IgA AGA	13	1	8	5	72.2	49.1	87.5	88.9	56.5	98.0	92.9	61.5
Bottaro *et al.*, 1995[77]	**IgA AGA**	**106**	**8**	**107**	**24**	**81.5**	**74.0**	**87.3**	**93.0**	**86.9**	**96.4**	**93.0**	**81.7**
Bottaro *et al.*, 1997[150]	IgA AGA	46	8	17	4	92.0	81.2	96.8	68.0	48.4	82.8	85.2	81.0
Cacciari *et al.*, 1985[152]	IgA AGA (ELISA)	5	3	92	4	55.6	26.7	81.1	96.8	91.1	98.9	62.5	95.8
Cacciari *et al.*, 1985[152]	IgA AGA (immunofluorescence)	5	3	92	4	55.6	26.7	81.1	96.8	91.1	98.9	62.5	95.8
Carroccio *et al.*, 2002[78]	**IgA AGA adults**	**CT**	**CT**	**CT**	**CT**								

continued

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TABLE 27 *IgA AGA sensitivity and specificity (cont'd)*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Carroccio *et al.*, 2002[78]	**IgA AGA all**	**61**	**10**	**90**	**30**	**67.0**	**56.9**	**75.8**	**90.0**	**82.6**	**94.5**	**85.9**	**75.0**
Carroccio *et al.*, 2002[78]	**IgA AGA children**	**CT**	**CT**	**CT**	**CT**								
Chartrand *et al.*, 1997[154]	IgA AGA	24	6	140	6	80.0	62.7	90.5	95.9	91.3	98.1	80.0	95.9
Chirdo *et al.*, 1999[66]	IgA AGA (commercial gliadin)	21	4	27	7	75.0	56.6	87.3	87.1	71.1	94.9	84.0	79.4
Chirdo *et al.*, 1999[66]	IgA AGA (ethanolic extract)	18	3	28	10	64.3	45.8	79.3	90.3	75.1	96.7	85.7	73.7
Chirdo *et al.*, 1999[66]	IgA AGA (LP1)	22	2	29	6	78.6	60.5	89.8	93.5	79.3	98.2	91.7	82.9
Chirdo *et al.*, 1999[66]	IgA AGA (LP2)	22	3	28	6	78.6	60.5	89.8	90.3	75.1	96.7	88.0	82.4
Chirdo *et al.*, 1999[66]	IgA AGA (O1)	16	2	29	12	57.1	39.1	73.5	93.5	79.3	98.2	88.9	70.7
Chirdo *et al.*, 1999[66]	IgA AGA (O2)	17	4	27	11	60.7	42.4	76.4	87.1	71.1	94.9	81.0	71.1
Chirdo *et al.*, 1999[66]	IgA AGA (ω-gliadin)	24	1	30	4	85.7	68.5	94.3	96.8	83.8	99.4	96.0	88.2
Chirdo *et al.*, 2000[155]	IgA AGA (ω-gliadin)	94	5	41	11	89.5	82.2	94.0	89.1	77.0	95.3	94.9	78.8
de Lecea *et al.*, 1996[156]	IgA AGA	17	3	31	3	85.0	64.0	94.8	91.2	77.0	97.0	85.0	91.2
De Rosa *et al.*, 1993[157]	IgA AGA	26	1	16	0	100.0	87.1	100.0	94.1	73.0	99.0	96.3	100.0
Del Rosario *et al.*, 1998[158]	IgA AGA	4	3	36	0	100.0	51.0	100.0	92.3	79.7	97.3	57.1	100.0
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, DIG-ELISA, cut-off 12 mm	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, DIG-ELISA, cut-off 4 mm	60	193	68	3	95.2	86.9	98.4	26.1	21.1	31.7	23.7	95.8
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, DIG-ELISA, cut-off 6 mm	56	28	171	7	88.9	78.8	94.5	85.9	80.4	90.1	66.7	96.1
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, DIG-ELISA, cut-off 8 mm	52	10	189	11	82.5	71.4	90.0	95.0	91.0	97.2	83.9	94.5

continued

TABLE 27 *IgA AGA sensitivity and specificity (cont'd)*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, ELISA, cut-off 0.15 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, ELISA, cut-off 0.20 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, ELISA, cut-off 0.25 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, ELISA, cut-off 0.30 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, ELISA, cut-off 0.35 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgA AGA, DIG-ELISA, cut-off 10 mm	43	2	19	19	69.4	57.0	79.4	99.0	96.4	99.7	95.6	91.2
Gemme *et al.*, 1993[161]	IgA AGA	49	6	35	2	96.1	86.8	98.9	85.4	71.6	93.1	89.1	94.6
Ghedira *et al.*, 1999[162]	IgA AGA	19	7	13	4	82.6	62.9	93.0	65.0	43.3	81.9	73.1	76.5
Grodzinsky *et al.*, 1995[164]	IgA AGA	24	12	58	3	88.9	71.9	96.1	82.9	72.4	89.9	66.7	95.1
Grodzinsky *et al.*, 2001[62]	IgA AGA (DIG-ELISA Orebro)	57	19	39	18	76.0	65.2	84.2	67.2	54.4	77.9	75.0	68.4
Grodzinsky *et al.*, 2001[62]	IgA AGA (ELISA Linkoping)	65	19	39	10	86.7	77.2	92.6	67.2	54.4	77.9	77.4	79.6
Grodzinsky *et al.*, 2001[62]	IgA AGA (ELISA Umea)	66	14	44	9	88.0	78.7	93.6	75.9	63.5	85.0	82.5	83.0
Grodzinsky *et al.*, 2001[62]	IgA AGA (CAP Orebro)	61	15	43	14	81.3	71.1	88.5	74.1	61.6	83.7	80.3	75.4
Grodzinsky *et al.*, 2001[62]	IgA AGA (CAP Umea)	66	18	40	9	88.0	78.7	93.6	69.0	56.2	79.4	78.6	81.6
Grodzinsky *et al.*, 2001[62]	IgA AGA (UniCAP Linkoping)	53	21	47	7	88.3	77.8	94.2	69.1	57.4	78.8	71.6	87.0
Juto *et al.*, 1985[167]	IgA AGA	26	2	39	2	92.9	77.4	98.0	95.1	83.9	98.7	92.9	95.1
Lerner *et al.*, 1994[64]	IgA AGA	CT	CT	CT	CT								
Lindberg *et al.*, 1985[65]	IgA AGA	CT	CT	CT	CT								

continued

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TABLE 27 *IgA AGA sensitivity and specificity (cont'd)*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Lock *et al.*, 1999[169]	IgA AGA	25	3	62	2	92.6	76.6	97.9	95.4	87.3	98.4	89.3	96.9
Mäki *et al.*, 1991[82]	**IgA AGA**	**4**	**14**	**95**	**9**	**30.8**	**12.7**	**57.6**	**87.2**	**79.6**	**92.2**	**22.2**	**91.3**
McMillan *et al.*, 1991[84]	**IgA AGA (ELISA)**	**28**	**0**	**68**	**0**	**100.0**	**87.9**	**100.0**	**100.0**	**94.7**	**100.0**	**100.0**	**100.0**
McMillan *et al.*, 1991[84]	**IgA AGA (immuno-fluorescence)**	**21**	**0**	**68**	**7**	**75.0**	**56.6**	**87.3**	**100.0**	**94.7**	**100.0**	**100.0**	**90.7**
Meini *et al.*, 1996[68]	**IgA AGA**	**0**	**0**	**55**	**5**	**0.0**	**0.0**	**43.4**	**100.0**	**93.5**	**100.0**		**91.7**
Murr *et al.*, 1992[170]	IgA AGA	21	3	20	1	95.5	78.2	99.2	87.0	67.9	95.5	87.5	95.2
Niveloni *et al.*, 1998[171]	IgA AGA	2	1	7	0	100.0	34.2	100.0	87.5	52.9	97.8	66.7	100.0
Not *et al.*, 1993[67]	IgA AGA (ELISA)	0	0	114	0				100.0	96.7	100.0		100.0
Not *et al.*, 1993[67]	IgA AGA (strip AGA)	0	0	11	0				100.0	96.7	100.0		100.0
Rich and Christie, 1990[174]	IgA AGA	8	3	42	7	53.3	30.1	75.2	93.3	82.1	97.7	72.7	85.7
Russo *et al.*, 1999[86]	**IgA AGA**	**20**	**10**	**61**	**4**	**83.3**	**64.1**	**93.3**	**85.9**	**76.0**	**92.2**	**66.7**	**93.8**
Sacchetti *et al.*, 1998[176]	IgA AGA	43	17	14	5	89.6	77.8	95.5	45.2	29.2	62.2	71.7	73.7
Sommer and Eitelberger, 1992[69]	IgA AGA (>100 AU)	15	2	53	0	100.0	79.6	100.0	96.4	87.7	99.0	88.2	100.0
Sommer and Eitelberger, 1992[69]	IgA AGA (>25 AU)	15	21	34	0	100.0	79.6	100.0	61.8	48.6	73.5	41.7	100.0
Sommer and Eitelberger, 1992[69]	IgA AGA (>50 AU)	15	10	45	0	100.0	79.6	100.0	81.8	69.7	89.8	60.0	100.0
Stern, 2000[180]	IgA AGA	95	16	73	8	92.2	85.4	96.0	82.0	72.8	88.6	85.6	90.1
Sulkanen *et al.*, 1998[182]	IgA AGA	74	2	27	22	77.1	67.7	84.4	93.1	78.0	98.1	97.4	55.1
Sulkanen *et al.*, 1998[183]	IgA AGA	115	38	169	21	84.6	77.5	89.7	81.6	75.8	86.3	75.2	88.9
Valdimarsson *et al.*, 1996[186]	IgA AGA	15	38	87	4	78.9	56.7	91.5	69.6	61.1	77.0	28.3	95.6
Vogelsang *et al.*, 1995[87]	**IgA AGA**	**40**	**9**	**44**	**9**	**81.6**	**68.6**	**90.0**	**83.0**	**70.8**	**90.8**	**81.6**	**83.0**
West *et al.*, 2002[187]	IgA AGA	99	5	9	31	76.2	68.1	82.7	95.0	88.8	97.8	95.2	75.4
Wildfang *et al.*, 1992[189]	IgA AGA	6	0	46	18	25.0	12.0	44.9	100.0	92.3	100.0	100.0	71.9

CT, cannot tell; where raw data were not available, calculations were not performed; LCI, lower 95% confidence interval; NPV, negative predictive value; UCI, upper 95% confidence interval.

TABLE 28 *Studies including IgG AGA tests*

Author, year	Antibody tested	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Altuntas *et al.*, 1998[144]	IgG AGA	ELISA	Euroimmun kit, Lübeck, Germany	25–50 RU/ml weakly positive; >50 RU/ml strongly positive	None
Artan 1998[60]	IgG AGA	ELISA	Labmaster, Turku, Finland	>25 AU, >25 AU for >2 years and >50 AU for < 2 years (manufacturer's instructions), >50 AU, >20 AU	None
Ascher *et al.*, 1996[145]	IgG AGA	ELISA	Pharmacia Gluten EIA kit	20 AU for ≥5 years, 35 AU for <5 years	None
Ascher *et al.*, 1996[145]	IgG AGA	DIG-ELISA	Described elsewhere	IgA >13 mm, IgG >16 mm for <5 years; IgA >11 mm, IgG >14 mm for ≥5 years	None
Auricchio *et al.*, 1988[73]	**IgG AGA**	**ELISA**	**In-house methods, some Pharmacia kits**	**Values above the 90th percentile of a healthy age-matched population**	**Good correlation between in-house and commercial tests**
Basso *et al.*, 2001[63]	**IgG AGA**	**ELISA**	**Pharmacia & Upjohn, Sweden**	**40 U/ml**	**All tests performed in duplicate**
Bode and Gudmand-Hoyer, 1994[76]	**IgG AGA**	**DIG-ELISA**	**Described elsewhere**	**IgG >14 mm (borderline 13 ≤ IgG ≤ 14 mm**	**Each serum sample analysed twice (difference never exceeded 1 mm)**
Bode *et al.*, 1993[75]	**IgG AGA**	**DIG-ELISA**	**Described elsewhere**	**IgG >14 mm**	**Each serum sample analysed twice (difference never exceeded 1 mm)**
Bode *et al.*, 1993[75]	**IgG AGA**	**DIG-ELISA**	**Described elsewhere**	**IgG ≥13 mm**	**Each serum sample analysed twice (difference never exceeded 1 mm)**
Bonamico *et al.*, 1992[149]	IgG AGA	Micro-ELISA	Described elsewhere	Not stated	None
Bottaro *et al.*, 1997[150]	IgG AGA	ELISA	Immunopharmacology Research kit, Italy	IgG >25%	None
Bottaro *et al.*, 1995[77]	**IgG AGA**	**ELISA**	**IPR-Immuno Pharmacology Research, Catania**	**IgG >25%**	**None**
Bürgin-Wolff *et al.*, 1983[151]	IgG AGA	Fluorescent immunosorbent test	In-house	Titre >1:20	None
Carroccio *et al.*, 2002[78]	**IgG AGA**	**ELISA**	**Alpha-Gliatest, Eurospital Pharma, Trieste, Italy**	**20% of reference serum = upper normal limit**	**None**
Castro *et al.*, 1987[153]	IgG AGA	Indirect immuno-fluorescence	Method of Bürgin-Wolff; no details on substrate	Not stated	None

continued

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TABLE 28 *Studies including IgG AGA tests (cont'd)*

Author, year	Antibody tested	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Chartrand *et al.*, 1997[154]	IgG AGA	ELISA	Falcon 3915, Becton Dickinson Lab Ware, Lincoln Park, NJ, USA	OD of 0.30	Reproducibility of tests on different days confirmed
Chirdo *et al.*, 1999[66]	IgG AGA	ELISA	In-house	Not stated	None
Chirdo *et al.*, 2000[155]	IgG AGA (ω-gliadin commercial gliadin and wheat extract)	ELISA	Described elsewhere	Not stated	None
Del Rosario *et al.*, 1998[158]	IgG AGA	ELISA	Labmaster, Turku, Finland	>100 EU	None
Dickey *et al.*, 1997[159]	IgG AGA	ELISA	Labmaster, Turku, Finland	100 EU	None
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA	ELISA and DIG ELISA	In-house	Various cut-offs (see results)	None
Feighery *et al.*, 1998[80]	**IgG AGA**	**Immunoassay**	**DELFIA system**	**3 AU**	**None**
Grodzinsky *et al.*, 1995[164]	IgG AGA	ELISA	In house method	Cut-off dependent on age (97.5th percentile in healthy children)	None
Hansson *et al.*, 2000[166]	IgG AGA	ELISA	Described elsewhere	No details	None
Juto *et al.*, 1985[167]	IgG AGA	ELISA	In-house	Mean OD + 3SD	Intra-assay CV <5% at beginning of study, subsequently not done in duplicate
Kelly *et al.*, 1987[81]	**IgG AGA**	**ELISA**	**In-house method**	**ELISA index above that of control group range**	**None**
Lerner *et al.*, 1994[64]	IgG AGA	ELISA	Immco Diagnostic, Buffalo, NY, USA	Absorbance >2SD of the mean of normal values	None
Lindberg *et al.*, 1985[65]	IgG AGA	DIG-ELISA	Sigma Chemical, St Louis, MO, USA and Dako, Copenhagen, Denmark	Appearance of brown, circular areas ≥11 mm (IgA) and ≥14 mm (IgG)	None
Lock *et al.*, 1999[169]	IgG AGA	ELISA	Described elsewhere	OD>0.20	None
Mäki *et al.*, 1991[82]	**IgG AGA**	**ELISA**	**Not described**	**0.20 ELISA units/ml**	**Sera blind tested in another laboratory**
McMillan *et al.*, 1991[84]	**IgG AGA**	**Indirect immuno-fluorescence**	**As above**	**Titre ≥20**	**None**

continued

TABLE 28 *Studies including IgG AGA tests (cont'd)*

Author, year	Antibody tested	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
McMillan *et al.*, 1991[84]	**IgG AGA**	**ELISA**	**As above**	**Titre ≥20**	**None**
Meini *et al.*, 1996[68]	**IgG AGA**	**ELISA**	**Eurospital**	**>25 AU/dl**	**None**
Niveloni *et al.*, 1998[171]	IgG AGA	Micro-ELISA	Described elsewhere	>28 AU/ml	None
Not *et al.*, 1993[67]	IgG AGA	Strip AGA test (dot immunobinding assay	Described elsewhere	ELISA index >1.3	None
Not *et al.*, 1993[67]	IgG AGA	ELISA	Described elsewhere	ELISA index >3	None
Rich and Christie, 1990[174]	IgG AGA	ELISA	Sigma Chemical, St Louis, MO, USA	Antibody level > 2 SD above the mean of the reference standard of the control group	None
Russo *et al.*, 1999[86]	**IgG AGA**	**ELISA**	**Described elsewhere**	**0.30 ELISA units**	**None**
Sacchetti *et al.*, 1998[176]	IgG AGA	ELISA	No details	No details	None
Savilahti *et al.*, 1986[89]	IgG AGA	ELISA	No details	Mean + 2SD of internal control sera	None
Signer *et al.*, 1979[178]	IgG AGA	Fluorescent immunosorbent test	Not described	Titre >1:20	None
Stenhammar *et al.*, 1984[179]	IgG AGA	DIG-ELISA	Described elsewhere	>14.4 mm	None
Stern, 2000[180]	IgG AGA	ELISA	Method described elsewhere	>16 AU	All tests carried out in duplicate; intra-laboratory CVs calculated
Stern and Grüttner, 1981[181]	IgG AGA	Indirect immuno-fluorescence	No details on substrate	Titre ≥16	None
Sulkanen *et al.*, 1998[182]	IgG AGA	ELISA	Described elsewhere	>10.0 EU/ml	None
Sulkanen *et al.*, 1998[183]	IgG AGA	ELISA	In-house	Concentration +2SD compared with controls	Intra-assay CV 10.8%, inter-assay CV 10.6%
Vogelsang *et al.*, 1995[87]	**IgG AGA**	**ELISA**	**No details**	**IgG ≥0.23 AU/ml**	**None**
Wildfang *et al.*, 1992[189]	IgG AGA	No details	No details	No details	None

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TABLE 29 *IgG AGA sensitivity and specificity*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Altuntas *et al.*, 1998[144]	IgG AGA	26	21	0	0	100.0	87.1	100.0	0.0	0.0	15.5	55.3	N/A
Artan 1998[60]	IgG AGA (>20 AU)	20	23	18	4	83.3	64.1	93.3	43.9	29.9	59.0	46.5	81.8
Artan 1998[60]	IgG AGA (>25 AU)	20	18	21	4	83.3	64.1	93.3	53.8	38.6	68.4	52.6	84.0
Artan 1998[60]	IgG AGA (>50 AU)	15	5	34	9	62.5	42.7	78.8	87.2	73.3	94.4	75.0	79.1
Artan 1998[60]	IgG AGA (Manufacturer's cut-off)	20	16	23	4	83.3	64.1	93.3	59.0	43.4	72.9	55.6	85.2
Ascher *et al.*, 1996[145]	IgG AGA (DIG-ELISA)	48	9	56	7	87.3	76.0	93.7	86.2	75.7	92.5	84.2	88.9
Ascher *et al.*, 1996[145]	IgG AGA (ELISA)	53	20	45	2	96.4	87.7	99.0	69.2	57.2	79.1	72.6	95.7
Auricchio *et al.*, 1988[73]	**IgG AGA**	**10**	**25**	**112**	**5**	**66.7**	**41.7**	**84.8**	**81.8**	**74.4**	**87.3**	**28.6**	**95.7**
Basso *et al.*, 2001[63]	**IgG AGA**	**CT**	**CT**	**CT**	**CT**								
Bode and Gudmand-Hoyer, 1994[76]	**IgG AGA**	**10**	**5**	**82**	**3**	**76.9**	**49.7**	**91.8**	**94.3**	**87.2**	**97.5**	**66.7**	**96.5**
Bode *et al.*, 1993[75]	**IgG AGA (threshold 1)**	**10**	**0**	**177**	**4**	**71.4**	**45.4**	**88.3**	**100.0**	**97.9**	**100.0**	**100.0**	**97.8**
Bode *et al.*, 1993[75]	**IgG AGA (threshold 2)**	**CT**	**CT**	**CT**	**CT**								
Bonamico *et al.*, 1992[149]	IgG AGA	16	2	7	2	88.9	67.2	96.9	77.8	45.3	93.7	88.9	77.8
Bottaro *et al.*, 1995[77]	**IgG AGA**	**113**	**40**	**75**	**17**	**86.9**	**80.1**	**91.7**	**65.2**	**56.1**	**73.3**	**73.9**	**81.5**
Bottaro *et al.*, 1997[150]	IgG AGA	50	16	9	0	100.0	92.9	100.0	36.0	20.2	55.5	75.8	100.0
Bürgin-Wolff *et al.*, 1983[151]	IgG AGA	72	18	100	0	100.0	94.9	100.0	94.7	77.2	90.1	54.1	100.0
Cacciari *et al.*, 1985[152]	IgG AGA (ELISA)	7	13	82	2	77.8	45.3	93.7	86.3	78.0	91.8	35.0	97.6
Cacciari *et al.*, 1985[152]	IgG AGA(immuno-fluorescence)	7	9	86	2	77.8	45.3	93.7	90.5	83.0	94.9	43.8	97.7
Carroccio *et al.*, 2002[78]	**IgG AGA adults**	**CT**	**CT**	**CT**	**CT**								
Carroccio *et al.*, 2002[78]	**IgG AGA all**	**69**	**25**	**75**	**22**	**75.8**	**66.1**	**83.5**	**75.0**	**65.7**	**82.5**	**73.4**	**77.3**

continued

TABLE 29 *IgG AGA sensitivity and specificity (cont'd)*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Carroccio *et al.*, 2002[78]	**IgG AGA children**	**CT**	**CT**	**CT**	**CT**								
Castro *et al.*, 1987[153]	IgG AGA	63	0	28	15	80.8	70.7	88.0	100.0	87.9	100.0	100.0	65.1
Chartrand *et al.*, 1997[154]	IgG AGA	25	31	45	5	83.3	66.4	92.7	59.2	48.0	69.6	44.6	90.0
Chirdo *et al.*, 1999[66]	IgG AGA (commercial gliadin)	24	6	25	4	85.7	68.5	94.3	80.6	63.7	90.8	80.0	86.2
Chirdo *et al.*, 1999[66]	IgG AGA (ethanolic extract)	23	8	23	5	82.1	64.4	92.1	74.2	56.8	86.3	74.2	82.1
Chirdo *et al.*, 1999[66]	IgG AGA (LP1)	24	7	24	4	85.7	68.5	94.3	77.4	60.2	88.6	77.4	85.7
Chirdo *et al.*, 1999[66]	IgG AGA (LP2)	24	8	23	4	85.7	68.5	94.3	74.2	56.8	86.3	75.0	85.2
Chirdo *et al.*, 1999[66]	IgG AGA (O1)	23	5	26	5	82.1	64.4	92.1	83.9	67.4	92.9	82.1	83.9
Chirdo *et al.*, 1999[66]	IgG AGA (O2)	23	8	23	5	82.1	64.4	92.1	74.2	56.8	86.3	74.2	82.1
Chirdo *et al.*, 1999[66]	IgG AGA (ω-gliadin)	25	5	26	3	89.3	72.8	96.3	83.9	67.4	92.9	83.3	89.7
Chirdo *et al.*, 2000[155]	IgG AGA (ω-gliadin)	100	9	37	5	95.2	89.3	97.9	80.4	66.8	89.3	91.7	88.1
Del Rosario *et al.*, 1998[158]	IgG AGA	4	24	15	0	100.0	51.0	100.0	38.5	24.9	54.1	14.3	100.0
Dickey *et al.*, 1997[159]	IgG AGA	20	47	240	11	64.5	46.9	78.9	83.6	78.9	87.5	29.9	95.6
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, DIG-ELISA, cut-off 10 mm	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, DIG-ELISA, cut-off 12 mm	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, DIG-ELISA, cut-off 14 mm	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, DIG-ELISA, cut-off 6 mm	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, DIG-ELISA, cut-off 8 mm	CT	CT	CT	CT								

continued

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TABLE 29 *IgG AGA sensitivity and specificity (cont'd)*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, ELISA, cut-off 0.6 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, ELISA, cut-off 0.70 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, ELISA, cut-off 0.8 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, ELISA, cut-off 0.9 AU/ml	CT	CT	CT	CT								
Fälth-Magnusson *et al.*, 1994[61]	IgG AGA, ELISA, cut-off 1.0 AU/ml	CT	CT	CT	CT								
Feighery *et al.*, 1998[80]	**IgG AGA**	**67**	**101**	**243**	**30**	**69.1**	**59.3**	**77.4**	**70.6**	**65.6**	**75.2**	**39.9**	**89.0**
Juto *et al.*, 1985[167]	IgG AGA	28	13	28	0	100.0	87.9	100.0	68.3	53.0	80.4	68.3	100.0
Kelly *et al.*, 1987[81]	**IgG AGA**	**19**	**7**	**1**	**50**	**27.5**	**18.4**	**39.0**	**12.5**	**2.2**	**47.1**	**73.1**	**2.0**
Lerner *et al.*, 1994[64]	IgG AGA	CT	CT	CT	CT								
Lindberg *et al.*, 1985[65]	IgG AGA	CT	CT	CT	CT								
Lock *et al.*, 1999[169]	IgG AGA	22	6	59	5	81.5	63.3	91.8	90.8	81.3	95.7	78.6	92.2
Mäki *et al.*, 1991[82]	**IgG AGA**	**6**	**12**	**97**	**7**	**46.2**	**23.2**	**70.9**	**89.0**	**81.7**	**93.6**	**33.3**	**93.3**
McMillan *et al.*, 1991[84]	**IgG AGA (ELISA)**	**16**	**9**	**59**	**12**	**57.1**	**39.1**	**73.5**	**86.8**	**76.7**	**92.9**	**64.0**	**83.1**
McMillan *et al.*, 1991[84]	**IgG AGA (immuno-fluorescence)**	**21**	**4**	**64**	**7**	**75.0**	**56.6**	**87.3**	**94.1**	**85.8**	**97.7**	**84.0**	**90.1**
Meini *et al.*, 1996[68]	**IgG AGA**	**5**	**11**	**44**	**0**	**100.0**	**56.6**	**100.0**	**80.0**	**67.6**	**88.4**	**31.3**	**100.0**
Niveloni *et al.*, 1998[171]	IgG AGA	1	0	8	1	50.0	9.5	90.5	100.0	67.6	100.0	100.0	88.9
Not *et al.*, 1993[67]	IgG AGA (ELISA)	0	5	109	0				95.6	90.1	98.1	0.0	100.0
Not *et al.*, 1993[67]	IgG AGA (strip AGA)	0	2	112	0				98.2	93.8	99.5	0.0	100.0
Rich and Christie, 1990[174]	IgG AGA	15	19	26	0	100.0	79.6	100.0	57.8	43.3	71.0	44.1	100.0
Russo *et al.*, 1999[86]	**IgG AGA**	**20**	**11**	**60**	**4**	**83.3**	**64.1**	**93.3**	**84.5**	**74.3**	**91.1**	**64.5**	**93.8**

continued

TABLE 29 *IgG AGA sensitivity and specificity (cont'd)*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Sacchetti *et al.*, 1998[176]	IgG AGA	42	6	26	6	87.5	75.3	94.1	81.3	64.7	91.1	87.5	81.3
Signer *et al.*, 1979[178]	IgG AGA	20	4	24	0	100.0	83.9	100.0	85.7	68.5	94.3	83.3	100.0
Stern, 2000[180]	IgG AGA	96	31	68	7	93.2	86.6	96.7	68.7	59.0	77.0	75.6	90.7
Stern and Grüttner, 1981[181]	IgG AGA	68	7	43	2	97.1	90.2	99.2	86.0	73.8	93.0	90.7	95.6
Sulkanen *et al.*, 1998[182]	IgG AGA	35	0	29	61	36.5	27.5	46.4	100.0	88.3	100.0	100.0	32.2
Sulkanen *et al.*, 1998[183]	IgG AGA	94	55	152	42	69.1	60.9	76.3	73.4	67.0	79.0	63.1	78.4
Vogelsang *et al.*, 1995[87]	**IgG AGA**	**36**	**14**	**39**	**13**	**73.5**	**59.7**	**83.8**	**73.6**	**60.4**	**83.6**	**72.0**	**75.0**
Wildfang *et al.*, 1992[189]	IgG AGA	23	20	1	26	46.9	33.7	60.6	4.8	0.8	22.7	53.5	3.7

CT, cannot tell; where raw data were not available, calculations were not performed.

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TABLE 30 *Studies including IgA ARA tests*

Author, year	Antibody tested	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Ascher *et al.*, 1996[145]	IgA ARA	Indirect immunofluorescence	Rat stomach	Not stated	None
Auricchio *et al.*, 1988[73]	**IgA ARA**	**ELISA**	**In-house methods, some Pharmacia kits**	**Values above the 90th percentile of a healthy age-matched population**	**Good correlation between in-house and commercial tests**
Bardella *et al.*, 2001[146]	IgA ARA	Indirect immunofluorescence	Monkey oesophagus	Titre >1:10	None
Boige *et al.*, 1996[148]	IgA ARA	Indirect immunofluorescence	Rat liver/stomach/kidney	Not stated	2 independent reviewers
Bottaro *et al.*, 1997[150]	IgA ARA	Indirect immunofluorescence	Rat liver and kidney	Not stated	Reproducibility checked by 2 independent operators
Cacciari *et al.*, 1985[152]	IgA ARA	Not stated	No details	Not stated	None
Ghedira *et al.*, 1999[162]	IgA ARA	Indirect immunofluorescence	Rat kidney, liver and stomach	Fluorescence	None
Hällström *et al.*, 1989[165]	IgA ARA	Indirect immunofluorescence	Rat liver/kidney/stomach	Not stated	None
Keddari *et al.*, 1989[88]	IgA ARA	Indirect immunofluorescence	Not stated	≥40	None
Lerner *et al.*, 1994[64]	IgA ARA	Indirect immunofluorescence	Mouse or rat kidney	Not stated	None
Lock *et al.*, 1999[169]	IgA ARA	Indirect immunofluorescence	Rat liver, kidney and stomach	Not stated	None
Mäki *et al.*, 1991[82]	**IgA ARA**	**Indirect immunofluorescence**	**Not described**	**Titre ≥5**	**Sera blind tested in another laboratory**
Savilahti *et al.*, 1986[89]	ARA	Indirect immunofluorescence	No details	Antibody in serum dilution ≥1:10	None
Sulkanen *et al.*, 1998[182]	IgA ARA	Indirect immunofluorescence	Rat liver, kidney, stomach, heart	Not stated	None
Sulkanen *et al.*, 1998[183]	IgA ARA	Indirect immunofluorescence	Rat liver/kidney/heart	Not stated	None
Whelan *et al.*, 1996[188]	IgA ARA	Indirect immunofluorescence	Rat liver	Not stated	None

TABLE 31 *IgA ARA sensitivity and specificity*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Ascher *et al.*, 1996[145]	IgA ARA	48	18	47	6	88.9	77.8	94.8	72.3	60.4	81.7	72.7	88.7
Auricchio *et al.*, 1988[73]	**IgA ARA**	**5**	**1**	**136**	**10**	**33.3**	**15.2**	**58.3**	**99.3**	**96.0**	**99.9**	**83.3**	**93.2**
Bardella *et al.*, 2001[146]	IgA ARA	40	3	107	0	100.0	91.2	100.0	97.3	92.3	99.1	93.0	100.0
Boige *et al.*, 1996[148]	IgA ARA	21	0	66	21	50.0	35.5	64.5	100.0	94.5	100.0	100.0	75.9
Bottaro *et al.*, 1997[150]	IgA ARA	37	0	25	13	74.0	60.4	84.1	100.0	86.7	100.0	100.0	65.8
Cacciari *et al.*, 1985[152]	IgA ARA	1	0	95	8	11.1	2.0	43.5	100.0	96.1	100.0	100.0	92.2
Ghedira *et al.*, 1999[162]	IgA ARA	18	0	20	5	78.3	58.1	90.3	100.0	83.9	100.0	100.0	80.0
Hällström, 1989[165]	IgA ARA	14	0	24	0	100.0	78.5	100.0	100.0	86.2	100.0	100.0	100.0
Keddari *et al.*, 1989[88]	IgA ARA	5	CT	CT	1	83.3	43.6	97.0					
Lock *et al.*, 1999[169]	IgA ARA	16	0	65	11	59.3	40.7	75.5	100.0	94.4	100.0	100.0	85.5
Mäki *et al.*, 1991[82]	**IgA ARA**	**12**	**1**	**CT**	**CT**							**92.3**	
Sulkanen *et al.*, 1998[182]	IgA ARA	72	0	24	29	71.3	61.8	79.2	100.0	86.2	100.0	100.0	45.3
Sulkanen *et al.*, 1998[183]	IgA ARA	125	8	199	11	91.9	86.1	95.4	96.1	92.6	98.0	94.0	94.8
Lerner *et al.*, 1994[64]	IgA ARA (mouse kidney)	CT	CT	CT	CT								
Lerner *et al.*, 1994[64]	IgA ARA (rat kidney)	CT	CT	CT	CT								
Whelan *et al.*, 1996[188]	IgA ARA	21	0	16	4	84.0	65.3	93.6	100.0	80.6	100.0	100.0	80.0

CT, cannot tell; where raw data were not available, calculations were not performed.

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TABLE 32 *Studies including IgG ARA tests*

Author, year	Method	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Auricchio *et al.*, 1988[73]	**ELISA**	**In-house methods, some Pharmacia kits**	**Values above the 90th percentile of a healthy age-matched population**	**'Good correlation' between in-house and commercial tests, not verified**
Cacciari *et al.*, 1985[152]	Not stated	No details	No details	None
Hällström, 1989[165]	Indirect immunofluorescence	Rat liver, kidney, stomach	Fluorescence	None
Keddari *et al.*, 1989[88]	Indirect immunofluorescence	Not stated	≥40	None
Sulkanen *et al.*, 1998[182]	Indirect immunofluorescence	Rat liver, kidney, stomach, heart	Fluorescence	None

TABLE 33 *IgG ARA sensitivity and specificity*

Author, year	Antibody tested	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Auricchio *et al.*, 1988[73]	**IgG ARA**	**14**	**4**	**133**	**1**	**93.3**	**70.2**	**98.8**	**97.1**	**92.7**	**98.9**	**77.8**	**99.3**
Cacciari *et al.*, 1985[152]	IgG ARA	1	1		8	11.1	2.0	43.5	98.9	94.3	99.8	50.0	92.2
Hällström, 1989[165]	IgG ARA	9	0	24	5	64.3	38.8	83.7	100.0	86.2	100.0	100.0	82.8
Keddari *et al.*, 1989[88]	IgG ARA	CT	CT	CT	CT								
Sulkanen *et al.*, 1998[182]	IgG ARA	16	0	29	80	16.7	10.5	25.4	100.0	88.3	100.0	100.0	26.6

CT, cannot tell; where raw data were not available, calculations were not performed.

TABLE 34 *Studies including IgA EMA tests*

Author, year	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Ascher *et al.*, 1996[145]	Monkey oesophagus	Fluorescence	None
Biagi *et al.*, 1999[147]	Human umbilical cord	Fluorescence	None
Boige *et al.*, 1996[148]	Monkey oesophagus	Fluorescence	2 independent reviewers
Bottaro *et al.*, 1997[150]	Monkey oesophagus	Fluorescence	Reproducibility checked by 2 independent operators
Bottaro *et al.*, 1997[150]	Human umbilical cord	Fluorescence	Reproducibility checked by 2 independent operators
Carroccio *et al.*, 2002[78]	**Monkey oesophagus; Anti-Endomisio, Eurospital Pharma, Trieste, Italy**	**1 = titre positive at dilutions of 1:5–1:20 2 = 1:40–1:80, 3 = 1:100 4 = 1:200, 5 = >1:200**	**None**
Chan *et al.*, 2001[49]	Monkey oesophagus; SCIMEDX, Denville, NJ, USA	Staining of the endomysium at titres of 1:10 or higher	Slides examined by 2 technicians
Chirdo *et al.*, 1999[66]	Monkey oesophagus	Fluorescence	None
Chirdo *et al.*, 2000[155]	Monkey oesophagus	Fluorescence	None
de Lecea *et al.*, 1996[156]	Biosystem	Fluorescence	None
De Rosa *et al.*, 1993[157]	Monkey oesophagus	Fluorescence	All tests performed twice
Del Rosario *et al.*, 1998[158]	Monkey oesophagus	Fluorescence	None
Del Rosario *et al.*, 1998[158]	Monkey oesophagus (Biodiagnostics, UK)	Titre ≥1:5	None
Dickey *et al.*, 1997[159]	Monkey oesophagus	Titre ≥1:5	None
Feighery *et al.*, 1998[160]	Monkey oesophagus, human umbilical cord, cell line derived from human umbilical endothelial cells	Fluorescence	None
Feighery *et al.*, 1998[80]	**Monkey oesophagus**	**Staining in reticulin type pattern**	**None**
Fraser-Reynolds *et al.*, 1998[109]	Monkey oesophagus	Fluorescence	Slides reviewed by 2 independent examiners
Gemme *et al.*, 1993[161]	Byosystem kit; monkey oesophagus	Fluorescence	None
Ghedira *et al.*, 1999[162]	Human umbilical cord	Fluorescence	None
Gillett and Freeman, 2000[163]	Human umbilical cord	Fluorescence	None
Grodzinsky *et al.*, 1995[164]	Monkey oesophagus; SCIMEDX, Denville, NJ, USA	Fluorescence	None

continued

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TABLE 34 *Studies including IgA EMA tests (cont'd)*

Author, year	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Hällström, 1989[165]	Monkey oesophagus	Fluorescence	None
Hansson *et al.*, 2000[166]	Monkey oesophagus	Fluorescence	None
Kumar *et al.*, 1989[168]	Monkey oesophagus	Fluorescence	None
Lerner *et al.*, 1994[64]	Monkey oesophagus	Fluorescence	None
Lock *et al.*, 1999[169]	Monkey oesophagus	Fluorescence	None
Lock *et al.*, 1999[169]	Human umbilical cord	Fluorescence	None
Mantzaris *et al.*, 1995[83]	**Monkey oesophagus**	**Fluorescence**	**None**
McMillan *et al.*, 1991[84]	**Monkey oesophagus; Biodiagnostics, UK**	**Titre ≥20**	**None**
Niveloni *et al.*, 1998[171]	Monkey oesophagus	Fluorescence	None
Not *et al.*, 1997[85]	**EMA, Eurospital, Trieste, Italy; monkey oesophagus and human umbilical cord**	**Honeycomb-like fluorescence**	**Slides evaluated by 2 independent operators**
Pacht *et al.*, 1995[172]	Monkey oesophagus	Fluorescence	None
Radzikowski *et al.*, 1988[173]	Letter. Limited method details	Fluorescence	None
Rossi *et al.*, 1988[175]	Monkey oesophagus	Fluorescence	None
Russo *et al.*, 1999[86]	**Monkey oesophagus; in-house method**	**Characteristic pattern**	**Immunofluorescence sections read on two separate occasions by blinded observer (no discrepancies)**
Russo *et al.*, 1999[86]	**Human umbilical cord; in-house method**	**Characteristic pattern**	**Immunofluorescence sections read on two separate occasions by blinded observer (no discrepancies)**
Sacchetti *et al.*, 1998[176]	No details	Fluorescence	None
Sategna-Guidetti *et al.*, 1997[177]	Monkey oesophagus	Fluorescence	None
Sategna-Guidetti *et al.*, 1997[177]	Human umbilical cord	Fluorescence	None
Stern, 2000[180]	Human umbilical cord	Fluorescence	All tests carried out in duplicate; intra-laboratory CVs calculated
Sulkanen *et al.*, 1998[182]	Human umbilical cord	Fluorescence	None
Sulkanen *et al.*, 1998[183]	Human umbilical cord	Fluorescence	None
Teesalu, *et al.*, 2001[184]	Human umbilical cord	Fluorescence	None

continued

TABLE 34 *Studies including IgA EMA tests (cont'd)*

Author, year	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Troncone *et al.*, 1999[185]	Monkey oesophagus	Fluorescence	None
Valdimarsson *et al.*, 1996[186]	Monkey oesophagus; SCIMEDX, Denville, NJ, USA	Fluorescence	None
Vogelsang *et al.*, 1995[87]	**Monkey oesophagus; Bios, Barcelona, Spain**	**Fluorescence**	**None**
West *et al.*, 2002[187]	Monkey oesophagus	Fluorescence	None
Whelan *et al.*, 1996[188]	Monkey oesophagus	Fluorescence	None
Wildfang *et al.*, 1992[189]	Monkey oesophagus	Fluorescence	All tests (for EMA) carried out in duplicate. 45% deviated by 0 titre levels, 50% by 1 and one serum by 2

TABLE 35 *IgA EMA sensitivity and specificity*

Author, year	Antibody tested[a,b]	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Ascher *et al.*, 1996[145]	IgA EMA	54	0	65	1	98.2	90.4	99.7	100.0	94.4	100.0	100.0	98.5
Biagi *et al.*, 1999[147]	IgA EMA	39	0	61	0	100.0	91.0	100.0	100.0	94.1	100.0	100.0	100.0
Boige *et al.*, 1996[148]	IgA EMA	37	0	66	5	88.1	75.0	94.8	100.0	94.5	100.0	100.0	93.0
Chan *et al.*, 2001[49]	IgA EMA	8	2	64	1	88.9	56.5	98.0	97.0	89.6	99.2	80.0	98.5
Chan *et al.*, 2001[49]	IgA EMA	8	2	65	2	80.0	49.0	94.3	97.0	89.8	99.2	80.0	97.0
Chirdo *et al.*, 2000[155]	IgA EMA	97	0	46	8	92.4	85.7	96.1	100.0	92.3	100.0	100.0	85.2
De Rosa *et al.*, 1993[157]	IgA EMA	25	3	14	1	96.2	81.1	99.3	82.4	59.0	93.8	89.3	93.3
Del Rosario *et al.*, 1998[158]	IgA EMA	5	0	41	0	100.0	56.6	100.0	100.0	91.4	100.0	100.0	100.0
Dickey *et al.*, 1997[159]	IgA EMA	27	0	287	4	87.1	71.1	94.9	100.0	98.7	100.0	100.0	98.6
Feighery *et al.*, 1998[160]	IgA EMA	33	0	47	0	100.0	89.6	100.0	100.0	92.4	100.0	100.0	100.0
Fraser-Reynolds *et al.*, 1998[109]	IgA EMA	3	0	51	2	60.0	23.1	88.2	100.0	93.0	100.0	100.0	96.2
Ghedira *et al.*, 1999[162]	IgA EMA	22	0	20	1	95.7	79.0	99.2	100.0	83.9	100.0	100.0	95.2
Gillett and Freeman, 2000[163]	IgA EMA	21	0	42	0	100.0	84.5	100.0	100.0	91.6	100.0	100.0	100.0

continued

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TABLE 35 *IgA EMA sensitivity and specificity (cont'd)*

Author, year	Antibody tested[a,b]	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Grodzinsky *et al.*, 1995[164]	IgA EMA	21	1	69	6	77.8	59.2	89.4	98.6	92.3	99.7	95.5	92.0
Hällström, 1989[165]	IgA EMA	14	0	24	0	100.0	78.5	100.0	100.0	86.2	100.0	100.0	100.0
Hansson *et al.*, 2000[166]	IgA EMA	21	0	17	1	95.5	78.2	99.2	100.0	81.6	100.0	100.0	94.4
Kumar *et al.*, 1989[168]	IgA EMA	11	0	41	0	100.0	74.1	100.0	100.0	91.4	100.0	100.0	100.0
Lerner *et al.*, 1994[64]	IgA EMA	CT	CT	CT	CT								
Mantzaris *et al.*, 1995[83]	**IgA EMA**	**15**	**1**	**112**	**1**	**93.8**	**71.7**	**98.9**	**99.1**	**95.2**	**99.8**	**93.8**	**99.1**
McMillan *et al.*, 1991[84]	**IgA EMA**	**25**	**0**	**68**	**3**	**89.3**	**72.8**	**96.3**	**100.0**	**94.7**	**100.0**	**100.0**	**95.8**
Niveloni *et al.*, 1998[171]	IgA EMA	1	0	8	1	50.0	9.5	90.5	100.0	67.6	100.0	100.0	88.9
Not *et al.*, 1997[85]	**IgA EMA**	**22**	**0**	**23**	**0**	**100.0**	**85.1**	**100.0**	**100.0**	**85.7**	**100.0**	**100.0**	**100.0**
Pacht *et al.*, 1995[172]	IgA EMA	22	0	22	0	100.0	85.1	100.0	100.0	85.1	100.0	100.0	100.0
Radzikowski *et al.*, 1988[173]	IgA EMA	5	0	9	0	100.0	56.6	100.0	100.0	70.1	100.0	100.0	100.0
Rossi *et al.*, 1988[175]	IgA EMA	9	1	41	2	81.8	52.3	94.9	97.6	87.7	99.6	90.0	95.3
Sacchetti *et al.*, 1998[176]	IgA EMA	46	3	29	2	95.8	86.0	98.8	90.6	75.8	96.8	93.9	93.5
Stern, 2000[180]	IgA EMA	97	1	88	6	94.2	87.9	97.3	98.9	93.9	99.8	99.0	93.6
Sulkanen *et al.*, 1998[182]	IgA EMA	78	0	29	18	81.3	72.3	87.8	100.0	88.3	100.0	100.0	61.7
Sulkanen *et al.*, 1998[183]	IgA EMA	126	1	206	10	92.6	87.0	96.0	99.5	97.3	99.9	99.2	95.4
Teesalu *et al.*, 2001[184]	IgA EMA	30	0	18	12	71.4	56.4	82.8	100.0	82.4	100.0	100.0	60.0
Valdimarsson *et al.*, 1996[186]	IgA EMA	14	0	125	5	73.7	51.2	88.2	100.0	97.0	100.0	100.0	96.2
	IgA EMA	**49**	**0**	**53**	**0**	**100.0**	**92.7**	**100.0**	**100.0**	**93.2**	**100.0**	**100.0**	**100.0**
West *et al.*, 2002[187]	IgA EMA	122	0	100	8	93.8	88.3	96.8	100.0	96.3	100.0	100.0	92.6
Whelan *et al.*, 1996[188]	IgA EMA	25	0	16	0	100.0	86.7	100.0	100.0	80.6	100.0	100.0	100.0
Wildfang *et al.*, 1992[189]	IgA EMA	46	0	24	0	100.0	92.3	100.0	100.0	86.2	100.0	100.0	100.0
Carroccio *et al.*, 2002[78]	**IgA EMA Adults**	**CT**	**CT**	**CT**	**CT**								
Bottaro *et al.*, 1997[150]	IgA EMA (huc)	47	0	25	3	94.0	83.8	97.9	100.0	86.7	100.0	100.0	89.3
Lock *et al.*, 1999[169]	IgA EMA (huc)	26	1	64	1	96.3	81.7	99.3	98.5	91.8	99.7	96.3	98.5
Russo *et al.*, 1999[86]	**IgA EMA (huc)**	**11**	**3**	**68**	**13**	**45.8**	**27.9**	**64.9**	**95.8**	**88.3**	**98.6**	**78.6**	**84.0**

continued

TABLE 35 *IgA EMA sensitivity and specificity (cont'd)*

Author, year	Antibody tested[a,b]	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Sategna-Guidetti *et al.*, 1997[177]	IgA EMA (huc)	100	0	48	4	96.2	90.5	98.5	100.0	92.6	100.0	100.0	92.3
Bottaro *et al.*, 1997[150]	IgA EMA (mo)	48	1	24	2	96.0	86.5	98.9	96.0	80.5	99.3	98.0	92.3
Lock *et al.*, 1999[169]	IgA EMA (mo)	27	0	65	0	100.0	87.5	100.0	100.0	94.4	100.0	100.0	100.0
Russo *et al.*, 1999[86]	**IgA EMA (mo)**	**18**	**8**	**63**	**6**	**75.0**	**55.1**	**88.0**	**88.7**	**79.3**	**94.2**	**69.2**	**91.3**
Sategna-Guidetti *et al.*, 1997[177]	IgA EMA (mo)	100	0	48	4	96.2	90.5	98.5	100.0	92.6	100.0	100.0	92.3
Feighery *et al.*, 1998[80]	**IgA EMA (with IgA-deficient patients)**	**84**	**4**	**340**	**13**	**86.6**	**78.4**	**92.0**	**98.8**	**97.0**	**99.5**	**95.5**	**96.3**
Feighery *et al.*, 1998[80]	**IgA EMA (without IgA-deficient patients)**	**84**	**4**	**340**	**11**	**88.4**	**80.4**	**93.4**	**98.8**	**97.0**	**99.5**	**95.5**	**96.9**
Carroccio *et al.*, 2002[78]	**IgA EMA all**	**80**	**1**	**99**	**11**	**87.9**	**79.6**	**93.1**	**99.0**	**94.6**	**99.8**	**98.8**	**90.0**
Carroccio *et al.*, 2002[78]	**IgA EMA children**	**CT**	**CT**	**CT**	**CT**								
Gemme *et al.*, 1993[161]	IgA EMA	40	0	41	2	95.2	84.2	98.7	100.0	91.4	100.0	100.0	95.3
de Lecea *et al.*, 1996[156]	EMA	16	4	30	4	80.0	58.4	91.9	88.2	73.4	95.3	80.0	88.2
Basso *et al.*, 2001[63]	**IgA EMA**	**37**	**1**	**33**	**1**	**97.4**	**86.5**	**99.5**	**97.1**	**85.1**	**99.5**	**97.4**	**97.1**

[a] All tests for IgG EMA used indirect immunofluorescence.
[b] mo, monkey oesophagus; huc, human umbilical cord.
CT, cannot tell; where raw data were not available, calculations were not performed.

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TABLE 36 *Studies including IgG EMA tests*

Author, year	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Basso *et al.*, 2001[63]	**Eurospital**	**Fluorescence**	**All tests performed in duplicate**
Boige *et al.*, 1996[148]	Monkey oesophagus	Fluorescence	2 independent reviewers
Grodzinsky *et al.*, 1995[164]	Monkey oesophagus; SCIMEDX, Denville, NJ, USA	Fluorescence	None
McMillan *et al.*, 1991[84]	**Monkey oesophagus; Biodiagnostics, UK**	**Titre in 20 or above**	**None**
Sulkanen *et al.*, 1998[182]	Human umbilical cord	Fluorescence	None
Sulkanen *et al.*, 1998[183]	Human umbilical cord	Fluorescence	None

TABLE 37 *IgG EMA sensitivity and specificity*

Author, year	Antibody tested[a]	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Boige *et al.*, 1996[148]	IgG EMA	11	0	66	31	26.2	15.3	41.1	100.0	94.5	100.0	100.0	68.0
McMillan *et al.*, 1991[84]	**IgG EMA**	**11**	**1**	**67**	**17**	**39.3**	**23.6**	**57.6**	**98.5**	**92.1**	**99.7**	**91.7**	**79.8**
Sulkanen *et al.*, 1998[182]	IgG EMA	15	0	29	81	15.6	9.7	24.2	100.0	88.3	100.0	100.0	26.4

[a] All IgA anti-tissue transglutaminase tests were ELISA tests.

***TABLE 38** Studies including IgA TTG tests*

Author, year	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity	Information on reproducibility
Chan *et al.*, 2001[49]	Quantalite, INOVA, San Diego, CA, USA	Standardised OD >20	None
Bardella *et al.*, 2001[146]	Genesis Diagnostics, UK kit	>10 AU/ml	Intra-and inter-assay CV 5.8 and 10.5%
Basso et *al.*, 2001[63]	**Eurospital, Trieste, Italy; Medipan Diagnostics, Selchow, Germany; Inova Diagnostics, San Diego, CA, USA; Arnika, Milan, Italy**	**5 AU 40 U/ml 20 units 0 U/ml**	**All tests performed in duplicate**
Basso et *al.*, 2001[63]	**Eurospital, Trieste, Italy; Medipan Diagnostics, Selchow, Germany; Inova Diagnostics, San Diego, CA, USA; Arnika, Milan, Italy**	**5 AU 40 U/ml 20 units 0 U/ml**	**All tests performed in duplicate**
Basso et *al.*, 2001[63]	**Eurospital, Trieste, Italy; Medipan Diagnostics, Selchow, Germany; Inova Diagnostics, San Diego, CA, USA; Arnika, Milan, Italy**	**5 AU 40 U/ml 20 units 0 U/ml**	**All tests performed in duplicate**
Basso et *al.*, 2001[63]	**Eurospital, Trieste, Italy; Medipan Diagnostics, Selchow, Germany; Inova Diagnostics, San Diego, CA, USA; Arnika, Milan, Italy**	**5 AU 40 U/ml 20 units 0 U/ml**	**All tests performed in duplicate**
Biagi *et al.*, 1999[147]	In-house	Negative <0.4 OD; positive >0.6 OD; 0.4–0.6 borderline	Intra-assay CV <5% for positive results; 20–30% for negative results Inter-assay CV <5% for OD >1.0; ~20% for OD >0.4–1.0; 20–30% for negative results
Chirdo *et al.*, 2000[155]	Procedure according to Sulkanen *et al.*, 1998[192]	Not stated	None
Gillett and Freeman, 2000[163]	Method by Dieterich, modified	>400 AU	None
Lock *et al.*, 1999[169]	Method by Dieterich	Not stated	None
Stern, 2000[180]	Methods described elsewhere	> 8AU	All tests carried out in duplicate; intra-laboratory CVs calculated
Sulkanen *et al.*, 1998[183]	In-house	>10AU	Intra-assay CV 10.8%, inter-assay CV 10.6%
Teesalu, *et al.*, 2001[184]	In-house, guinea pig liver	>18 AU	Intra-assay CV 4.9%, inter-assay CV 8.9%
Troncone *et al.*, 1999[185]	In-house	97th percentile of control group	None
West *et al.*, 2002[187]	Kit Binding Site, UK	≥4 U/ml and ≥9 U/ml	TTG: within- and between-batch CV 5 and 12% at 2–3 U/ml and 5 and 7% at 6 U/ml
Hansson *et al.*, 2000[166]	In-house (human erythrocyte, sigma and guinea pig liver)	Cut-off determined by SROC curves (0.06 AU)	None

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TABLE 39 *IgA TTG sensitivity and specificity*

Author, year	Antibody tested[a]	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Bardella *et al.*, 2001[146]	IgA TTG	40	2	108	0	100.0	91.2	100.0	98.2	93.6	99.5	95.2	100.0
Basso *et al.*, 2001[63]	**IgA TTG (Arnika)**	**15**	**0**	**14**	**5**	**75.0**	**53.1**	**88.8**	**100.0**	**78.5**	**100.0**	**100.0**	**73.7**
Basso *et al.*, 2001[63]	**IgA TTG (Eurospital)**	**23**	**0**	**20**	**3**	**88.5**	**71.0**	**96.0**	**100.0**	**83.9**	**100.0**	**100.0**	**87.0**
Basso *et al.*, 2001[63]	**IgA TTG (Inova)**	**21**	**0**	**30**	**5**	**80.8**	**62.1**	**91.5**	**100.0**	**88.6**	**100.0**	**100.0**	**85.7**
Basso *et al.*, 2001[63]	**IgA TTG (Medipan)**	**26**	**0**	**18**	**5**	**83.9**	**67.4**	**92.9**	**100.0**	**82.4**	**100.0**	**100.0**	**78.3**
Biagi *et al.*, 1999[147]	IgA TTG	37	6	55	2	94.9	83.1	98.6	90.2	80.2	95.4	86.0	96.5
Chan *et al.*, 2001[49]	IgA TTG	8	4	62	1	88.9	56.5	98.0	93.9	85.4	97.6	66.7	98.4
Chan *et al.*, 2001[49]	IgA TTG	8	4	63	2	80.0	49.0	94.3	94.0	85.6	97.7	66.7	96.9
Gillett and Freeman, 2000[163]	IgA TTG	20	0	42	1	95.2	77.3	99.2	100.0	91.6	100.0	100.0	97.7
Hansson *et al.*, 2000[166]	IgA TTG (human erythrocyte)	22	0	17	0	100.0	85.1	100.0	100.0	81.6	100.0	100.0	100.0
Lock *et al.*, 1999[169]	IgA TTG	23	2	63	4	85.2	67.5	94.1	96.9	89.5	99.2	92.0	94.0
Stern, 2000[180]	IgA TTG	101	0	89	2	98.1	93.2	99.5	100.0	95.9	100.0	100.0	97.8
Sulkanen *et al.*, 1998[183]	IgA TTG	129	13	194	7	94.9	89.8	97.5	93.7	89.6	96.3	90.8	96.5
Teesalu *et al.*, 2001[184]	IgA TTG	30	1	17	12	71.4	56.4	82.8	94.4	74.2	99.0	96.8	58.6
Troncone *et al.*, 1999[185]	IgA TTG	4	1	62	4	50.0	21.5	78.5	98.4	91.5	99.7	80.0	93.9
West *et al.*,2002[187]	IgA TTG (cut-off ≥4U/ml)	112	9	91	18	86.2	79.2	91.1	91.0	83.8	95.2	92.6	83.5
West *et al.*, 2002[187]	gA TTG (cut-off ≥9U/ml)	92	2	98	38	70.8	62.4	77.9	98.0	93.0	99.4	97.9	72.1

[a] Two studies reported IgG TTG ELISA tests. No information on test reproducibility was given.

TABLE 40 *Studies including IgG TTG antibody tests*

Author, year	Details of method (test kit, substrate, manufacturer)	Thresholds for positivity
Lock *et al.*, 1999[169]	Method by Dieterich *et al.*, 1997	Not stated
Troncone *et al.*, 1999[185]	In-house	97th percentile of control group

TABLE 41 *IgG TTG sensitivity and specificity*

Author, year	TP	FP	TN	FN	SENS	SENS LCI	SENS UCI	SPEC	SPEC LCI	SPEC UCI	PPV	NPV
Lock *et al.*, 1999[169]	12	7	51	15	44.4	27.6	62.7	87.9	77.1	94.0	63.2	77.3
Troncone *et al.*, 1999[185]	11	1	62	37	22.9	13.3	36.5	98.4	91.5	99.7	91.7	62.6

Appendix 9

Searches to inform parameter estimates: MEDLINE 1966 to present (at September 2002)

A. Search strategy for primary studies on compliance with gluten-free diet:
1. celiac disease/ (8522)
2. celiac disease$.mp. (8776)
3. coeliac disease$.mp. (2914)
4. coeliac sprue.mp. (36)
5. celiac sprue.mp. (256)
6. gluten sensitive enteropath$.mp. (333)
7. gluten enteropath$.mp. (117)
8. or/1-7 (9222)
9. gluten-free diet$.tw. (1246)
10. diet protein restricted/ (641)
11. gluten/ (2571)
12. 10 and 11 (44)
13. 9 or 12 (1258)
14. patient compliance/ (21695)
15. 13 and 14 (52)
16. from 15 keep 1-52 (52)

B. Search strategy for systematic review of lifeexpectancy of childhood onset insulin-dependent diabetes:
1. Diabetes Mellitus, Insulin-Dependent/ (35184)
2. prognos$.mp. (254236)
3. exp mortality/ (133033)
4. predict$.mp. (308935)
5. course.mp. (217117)
6. or/2-5 (818515)
7. 1 and 6 (3612)
8. child/ or infant/ or adolescence/ or child preschool/ (1548316)
9. 7 and 8 (1354)
10. (meta-analysis or review literature).sh. (5006)
11. meta-analy$.tw. (8298)
12. metaanal$.tw. (340)
13. (systematic$ adj4 (review$ or overview$)).tw. (4428)
14. meta-analysis.pt. (6810)
15. review.pt. (888632)
16. case report.sh. (1048348)
17. letter.pt. (467083)
18. historical article.pt. (201057)
19. review of reported cases.pt. (45144)
20. review multicase.pt. (7027)
21. review.ti. (100234)
22. review literature.pt. (28632)
23. 10 or 11 or 12 or 13 or 14 or 15 or 21 or 22 (944295)
24. or/16-20 (1632610)
25. 23 not 24 (852864)
26. animal.sh. (3307217)
27. human.sh. (7695861)
28. 26 not (26 and 27) (2580370)
29. 25 not 28 (770636)
30. 9 and 29 (94)
31. from 30 keep 1-94 (94)

C. Search strategy for systematic review of health outcomes of coeliac disease:
1. celiac disease/ (8522)
2. celiac disease$.mp. (8776)
3. coeliac disease$.mp. (2914)
4. or/1-3 (9090)
5. incidence/ (69091)
6. follow-up studies/ (253534)
7. prognos$.mp. (254236)
8. exp mortality/ (133033)
9. predict$.mp. (308935)
10. course.mp. (217117)
11. or/5-10 (1056422)
12. 4 and 11 (899)
13. limit 12 to human (894)
14. coeliac sprue.mp. (36)
15. celiac sprue.mp. (256)
16. gluten sensitive enteropath$.mp. (333)
17. gluten enteropath$.mp. (117)
18. 4 or 14 or 15 or 16 or 17 (9222)
19. 11 and 18 (914)
20. limit 19 to human (909)
21. (meta-analysis or review literature).sh. (5006)
22. meta-analy$.tw. (8298)
23. metaanal$.tw. (340)
24. (systematic$ adj4 (review$ or overview$)).tw. (4428)
25. meta-analysis.pt. (6810)
26. review.pt. (888632)
27. case report.sh. (1048348)
28. letter.pt. (467083)
29. historical article.pt. (201057)
30. review of reported cases.pt. (45144)
31. review multicase.pt. (7027)
32. review.ti. (100234)
33. review literature.pt. (28632)

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34. 21 or 22 or 23 or 24 or 25 or 26 or 32 or 33 (944295)
35. or/27-31 (1632610)
36. 34 not 35 (852864)
37. animal.sh. (3307217)
38. human.sh. (7695861)
39. 37 not (37 and 38) (2580370)
40. 36 not 39 (770636)
41. 19 and 40 (99)
42. limit 41 to human (99)
43. from 42 keep 1-99 (99)

D. Search strategy for prevalence of coeliac disease in people with diabetes:
1. (meta-analysis or review literature).sh. (5006)
2. meta-analy$.tw. (8298)
3. metaanal$.tw. (340)
4. (systematic$ adj4 (review$ or overview$)).tw. (4428)
5. meta-analysis.pt. (6810)
6. review.pt. (888632)
7. case report.sh. (1048348)
8. letter.pt. (467083)
9. historical article.pt. (201057)
10. review of reported cases.pt. (45144)
11. review multicase.pt. (7027)
12. review.ti. (100234)
13. review literature.pt. (28632)
14. 1 or 2 or 3 or 4 or 5 or 6 or 12 or 13 (944295)
15. or/7-11 (1632610)
16. 14 not 15 (852864)
17. animal.sh. (3307217)
18. human.sh. (7695861)
19. 17 not (17 and 18) (2580370)
20. 16 not 19 (770636)
21. celiac disease/ (8522)
22. coeliac disease$.mp. (8776)
23. celiac disease$.mp. (2914)
24. coeliac sprue.mp. (36)
25. celiac sprue.mp. (256)
26. gluten sensitive enteropath$.mp. (333)
27. gluten enteropath$.mp. (117)
28. or/21-27 (9222)
29. 20 and 28 (938)
30. exp PREVALENCE/ or prevalence.mp. (142291)
31. 29 and 30 (62)
32. limit 31 to human (62)
33. from 32 keep 1-62 (62)

When these searches are combined and duplicates removed, 296 studies were identified. Of these, 41 were selected by one reviewer on the basis of title or abstract as relevant or potentially relevant for informing one or more parameter estimate.

Appendix 10

Cost calculations for gluten-free diet

TABLE 42 *Abbreviated list of prescribable gluten-free foods, BNF 43, March 2002*

				Range of unit costs		Range of costs per kg	
	Weight (g)	**Unit cost (£)**	**£ per 1000 g**	**Min.**	**Max.**	**Min.**	**Max.**
Plain biscuits				**1.53**	**3.98**	**9.15**	**14.44**
Bi-Aglut	180	2.60	14.44				
Ener-G	435	3.98	9.15				
Glutafin	125	1.53	12.24				
Glutano	125	1.58	12.64				
Juvela	160	2.16	13.50				
Schar	175	1.72	9.83				
Bread				**1.41**	**3.75**	**4.48**	**9.38**
Barkat	450	2.79	6.20				
Glutafin	400	2.46–2.76	6.15–6.90				
Glutano	200–500	1.49–2.24	4.48–7.45				
Juvela	375–400	2.47–3.42	6.18–9.12				
Lifestyle	400	2.38	5.95				
Rite-Diet	400	2.46–2.76	6.15–6.90				
Schar	200–400	1.41–2.39	5.98–7.05				
Ultra	400	2.39	5.98				
Valpiform	400	3.75	9.38				
Crackers				**1.72**	**3.60**	**12.45**	**17.20**
Bi-Aglut	240	3.60	15.00				
Glutafin	200	2.49	12.45				
Ultra	100	1.72	17.20				
Crispbread				**1.46**	**3.28**	**7.30**	**15.62**
Juvela	210	3.28	15.62				
Orgran	200	1.46	7.30				
Flour mixes				**1.84**	**5.87**	**3.73**	**10.18**
Aproten	300	1.84	6.13				
Barkat	500	4.12	8.24				
Clara's Kitchen	500	3.53	7.06				
Dietary Specialties	500	4.75	9.50				
Glutafin	500	4.83	9.66				
Juvela	500	5.09	10.18				
Rite-Diet	500	4.83	9.66				
Schar	1000	3.50	3.50				
Tritamyl	1000	5.60	5.60				
Trufree	1000	5.24	5.24				
Trufree	1000	5.87	5.87				
Valpiform	1000	3.73	3.73				

continued

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TABLE 42 *Abbreviated list of prescribable gluten-free foods, BNF 43, March 2002 (cont'd)*

				Range of unit costs		Range of costs per kg	
	Weight (g)	**Unit cost (£)**	**£ per 1000 g**	**Min.**	**Max.**	**Min.**	**Max.**
Pasta				**1.31**	**4.88**	**5.24**	**10.24**
Bi-Aglut	500	4.86	9.72				
Ener-G	454	3.98	8.77				
Glutafin	250–500	2.56–4.88	9.76–10.24				
Juvela	250–500	2.54–4.84	9.68–10.16				
Orgran	200–250	1.31–1.39	5.24–6.95				
Pizza bases				**2.21**	**6.09**	**6.43**	**16.92**
Barkat	150	2.21	14.73				
Glutafin	220	3.46	15.73				
Juvela	360	6.09	16.92				
Schar	300	3.78	12.60				
Ultra	400	2.57	6.43				

TABLE 43 *Calculation of estimated range of annual costs*

			Range of unit costs		Range of total costs per month		Range of annual costs	
Age/physical activity	**kcal/day**	**Approx. monthly requirement**	**Min.**	**Max.**	**Min.**	**Max.**	**Min.**	**Max.**
Child up to 2 years	1000–1200	4–8 loaves	1.41	3.75	6	30	68	360
		2 pkts biscuits	1.53	3.98	3	8	37	96
		1 pkt pizza bases	2.21	6.09	2	6	27	73
		1 pkt pasta	1.31	4.88	1	5	16	59
		1 pkt flour	1.84	5.87	2	6	22	70
Total							**169**	**658**
3–5 year old child	1300–1700	8–16 loaves bread	1.41	3.75	11	60	135	720
		2 pkts biscuits	1.53	3.98	3	8	37	96
		1 pkt pizza bases	2.21	6.09	2	6	27	73
		1 pkt pasta	1.31	4.88	1	5	16	59
		1 pkt flour	1.84	5.87	2	6	22	70
Total							**236**	**1018**
6–10 year old child	1500–1900	8–24 loaves	1.41	3.75	11	90	135	1080
Younger inactive female		2 pkts biscuits	1.53	3.98	3	8	37	96
Older inactive male		1 pkt pizza bases	2.21	6.09	2	6	27	73
		1 pkt pasta	1.31	4.88	1	5	16	59
		1 pkt flour	1.84	5.87	2	6	22	70
Total							**236**	**1378**
10–15 year old child	2000–2500	16–32 loaves	1.41	3.75	23	120	271	1440
Younger active		3 pkts biscuits	1.53	3.98	5	12	55	143
female/ inactive male		1 pkt pizza bases	2.21	6.09	2	6	27	73
Older active male		1 pkt pasta	1.31	4.88	1	5	16	59
		1 pkt flour	1.84	5.87	2	6	22	70
Total							**390**	**1785**
15–18 years-old	2800+	20–40 loaves	1.41	3.75	28	150	338	1800
		3 pkts biscuits	1.53	3.98	5	12	55	143
		1 pkt pizza bases	2.21	6.09	2	6	27	73
		1 pkt pasta	1.31	4.88	1	5	16	59
		1 pkt flour	1.84	5.87	2	6	22	70
Total							**458**	**2145**

Appendix 11

Results of decision analytic model and sensitivity analyses

The following tables give the results of the decision analytic model developed for this report, with base case and sensitivity analyses on all parameters. The first set of tables give the results in terms of cost/QALY gained and the second set in terms of cost per case detected.

Five single autoantibody tests were considered: AGA IgA, AGA IgG, EMA IgA, ARA IgA and TTG IgA. In addition, the combinations of EMA IgA + AGA IgG and TTG IgA + AGA IgG were considered.

These seven approaches to testing were considered in two scenarios: in one scenario, all positive results are confirmed with biopsy before diagnosis is confirmed, whereas in the other no biopsy confirmation is sought.

A further screening scenario of biopsying all patients was considered in the model.

Comparisons made

All screening strategies were compared against 'no screening'.

Those antibody testing strategies not using confirmatory biopsy were compared against the equivalent strategies with confirmatory biopsy.

All strategies based on antibody testing were further compared against the strategy of 'biopsy all patients'.

Finally, the strategies employing two antibody tests were compared against the equivalent strategy using the single best test from the combination.

Interpretation of results

Results are expressed both as cost/QALY (the additional cost incurred per quality-adjusted life-year gained) and as cost/case detected (the additional cost for each screen-detected case).

For all comparisons, the order of the comparison was chosen such that the difference in costs would be a positive number in the base case (and this is usually true in the sensitivity analyses also). Thus, where a figure for cost/QALY or cost/case detected is negative, the more expensive strategy (listed first in the comparison) led to a drop in utility and thus is 'dominated' by the alternative strategy (being both more expensive and less effective). There are a very few obvious exceptions to this rule in the sensitivity analyses (where a change in a parameter made the comparator relatively more expensive), in which case the strategy listed first 'dominates' the comparator (being both cheaper and more effective). These exceptions are clear from the context of the other results in the analysis.

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Cost per QALY for different screening strategies (£)	Base case	Prevalence		Sensitivity of test		Specificity of test		Sens & spec		Cost of test		Cost of endoscopy and biopsy		Cost of GFD	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Strategy vs no screening															
Biopsy all	45174	178572	23434	45174	45174	45174	45174	45174	45174	45174	45174	30544	65123	36727	53124
AGA IgA + biopsy	14770	23997	12493	15461	14535	19625	12742	21247	12634	14636	15036	13286	16792	7214	21881
AGA IgG + biopsy	20160	44357	14553	21533	19295	24305	16932	26337	16379	20003	20472	16455	25212	12453	27413
EMA IgA + biopsy	12246	15146	11510	12341	12233	14437	11936	14703	11927	12123	12307	11778	12884	4759	19293
ARA IgA + biopsy	13503	19471	12006	13584	13451	14475	12858	14589	12820	13376	13629	12620	14706	5987	20576
TTG IgA + biopsy	12970	17638	11794	13055	12929	14250	12334	14392	12307	12844	13220	12228	13980	5464	20034
EMA IgA + AGA IgG + biopsy	19099	40105	14158	19301	19075	23880	16330	24209	16315	18852	19407	15922	23431	11428	26318
TTG IgA + AGA IgG + biopsy	19160	40323	14183	19364	19136	23943	16391	24273	16375	18913	19654	15983	23493	11490	26380
AGA IgA	54088	–40599	18632	84586	47514	–59532	17579	–45228	16996	53740	54785	54690	53268	16164	89782
AGA IgG	–54321	–21508	59934	–44182	–65645	–33286	–711860	–29864	438825	–54098	–54767	–54656	–53865	–16174	–90224
EMA IgA	14447	33121	11607	14845	14395	46459	12390	53914	12364	14307	14516	14706	14092	4290	24006
ARA IgA	23948	–249087	14218	24641	23522	40685	17415	42901	17225	23761	24136	24287	23486	7371	39551
TTG IgA	19987	231325	13230	20586	19712	39618	14625	42471	14516	19818	20324	20294	19568	5991	33159
EMA IgA + AGA IgG	–77025	–22983	43496	–72461	–77618	–34976	202156	–34201	197662	–76468	–77721	–77551	–76307	–23294	–127595
TTG IgA + AGA IgG	–77164	–23034	43552	–72593	–77759	–35020	202648	–34244	198143	–76607	–78278	–77691	–76446	–23434	–127734
Confirmatory biopsy vs strategy															
AGA IgA	–9551	–10641	–7120	–9790	–9449	–10494	–6401	–10587	–6085	–9551	–9551	–12324	–5771	1678	–20120
AGA IgG	–10524	–10927	–9632	–10596	–10465	–10709	–10170	–10758	–10076	–10524	–10524	–12840	–7365	660	–21049
EMA IgA	–3419	–8874	9489	–3984	–3338	–9432	4768	–9551	4940	–3419	–3419	–9068	4283	8096	–14257
ARA IgA	–8177	–10239	–3514	–8270	–8114	–9280	–6190	–9338	–6085	–8177	–8177	–11594	–3517	3116	–18805
TTG IgA	–7397	–10013	–1438	–7553	–7318	–9260	–3581	–9338	–3419	–7397	–7397	–11180	–2238	3933	–18059
EMA IgA + AGA IgG	–10425	–10898	–9378	–10441	–10423	–10689	–10001	–10699	–9998	–10425	–10425	–12788	–7203	763	–20955
TTG IgA + AGA IgG	–10425	–10898	–9378	–10441	–10423	–10689	–10001	–10699	–9998	–10425	–10425	–12788	–7203	763	–20955

continued

Cost per QALY for different screening strategies (£)	Base case	Prevalence		Sensitivity of test		Specificity of test		Sens & spec		Cost of test		Cost of endoscopy and biopsy		Cost of GFD	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Biopsy all vs strategy															
AGA IgA + biopsy	–1741737	–330215	227066	226171	–345241	25275785	–1276224	171418	–337201	–1749556	–1726101	–983734	–2775378	–1697818	–1783073
AGA IgG + biopsy	206697	–782477	63239	117173	612463	166091	245371	98712	884761	207706	204679	121525	322840	193469	219147
EMA IgA + biopsy	–299482	–258938	–452945	–1228045	–269455	–304181	–298876	–1745646	–269240	–300763	–298841	–165885	–481660	–297883	–300987
ARA IgA + biopsy	–453771	–282003	1603217	–919563	–337481	–466300	–446195	–1007399	–335019	–455768	–451775	–251833	–729142	–447540	–459636
TTG IgA + biopsy	–387602	–274659	–3076040	–900416	–300082	–397185	–383263	–1014182	–298841	–389285	–384235	–215594	–622158	–383399	–391557
EMA IgA + AGA IgG + biopsy	–250926	–242427	–271856	–351556	–242322	–251155	–250828	–389967	–243109	–253729	–247422	–135505	–408318	–250559	–251272
TTG IgA + AGA IgG + biopsy	–250225	–241765	–271059	–350586	–241645	–250281	–250201	–388631	–242501	–253028	–244619	–134805	–407617	–249858	–250571
AGA IgA	39504	41772	35956	33412	43206	5358	169500	5774	265218	39725	39061	15186	72664	49807	29807
AGA IgG	7607	6780	8939	7764	7464	495	20388	938	21390	7691	7438	–1625	20196	16753	–1001
EMA IgA	1019611	1705739	564788	290458	1616121	44042	–786687	39614	–614011	1024038	1017397	532806	1683435	1065389	976525
ARA IgA	99911	110280	84562	90141	107865	49768	221186	47203	263430	100395	99427	46681	172498	112432	88127
TTG IgA	148185	167175	121244	122239	166243	51124	588032	47588	1017397	148873	146807	72467	251435	162430	134777
EMA IgA + AGA IgG	5203	4670	6374	5288	5192	–3341	20145	–3201	20184	5385	4975	–4813	18862	17094	–5989
TTG IgA + AGA IgG	5158	4626	6326	5243	5147	–3368	20067	–3227	20105	5340	4793	–4859	18816	17049	–6034
Strategy vs single test															
EMA IgA + AGA IgG + biopsy	–816767	–335157	415803	184325	–427943	–519688	4760615	314520	–684286	–801837	–846627	–489527	–1263002	–802043	–830624
TTG IgA + AGA IgG + biopsy	432792	–541158	97825	208113	–2142101	4637040	192498	516092	817684	424423	449530	266869	659051	414091	450393
EMA IgA + AGA IgG	–16102	–15870	–16626	–17079	–15958	–15927	–16492	–16626	–16258	–16009	–16288	–16105	–16098	–4922	–26624
TTG IgA + AGA IgG	–16632	–16046	–18017	–17020	–16237	–16198	–17326	–16437	–16686	–16527	–16842	–16639	–16622	–5100	–27486

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Cost per QALY for different screening strategies (£)	Base case	Utility treated CD		Utility untreated CD		Disutility of endoscopy		Disutility of GFD		Compliance GFD		Discounting	
		Low	High	Low	High	Low	High	Low	High	Low	High	Both 0%	Both 6%
Strategy vs no screening													
Biopsy all	45174	102582	32899	29490	96495	42368	48377	28964	177972	90095	32757	31860	323934
AGA IgA + biopsy	14770	29574	11074	10008	28173	14674	14866	9842	44415	19048	13400	16444	64152
AGA IgG + biopsy	20160	41190	15040	13573	39162	19831	20500	13346	63150	30347	16944	19301	93815
EMA IgA + biopsy	12246	24299	9203	8322	23167	12223	12269	8185	36165	13915	11724	15089	51619
ARA IgA + biopsy	13503	26892	10138	9166	25631	13452	13554	9014	40171	16455	12560	15764	57611
TTG IgA + biopsy	12970	25798	9740	8807	24591	12929	13010	8662	38488	15377	12206	15479	55107
EMA IgA + AGA IgG + biopsy	19099	38835	14265	12879	36940	18832	19373	12663	59240	28072	16252	18743	87395
TTG IgA + AGA IgG + biopsy	19160	38960	14312	12920	37059	18892	19436	12704	59432	28198	16293	18775	87677
AGA IgA	54088	–174530	28874	24094	–220875	54273	53905	15223	–22500	53878	54419	50670	–220528
AGA IgG	–54321	–31421	–105656	–176724	–32093	–54219	–54424	34214	–12206	–55137	–53956	–228272	–55958
EMA IgA	14447	33267	10490	9395	31246	14468	14426	8617	147444	14444	14491	18716	72741
ARA IgA	23948	91339	16053	14078	80144	23994	23903	11348	–49836	24278	23915	28318	249548
TTG IgA	19987	60312	13825	12221	54821	20022	19952	10324	–80629	20048	20029	24588	145632
EMA IgA + AGA IgG	–77025	–35885	–326783	860340	–36862	–76797	–77255	29167	–13157	–79012	–76146	–1097439	–63143
TTG IgA + AGA IgG	–77164	–35950	–327373	861895	–36929	–76936	–77394	29220	–13181	–79293	–76238	–1098218	–63257
Confirmatory biopsy vs strategy													
AGA IgA	–9551	–9551	–9551	–9551	–9551	–9432	–9673	–41330	–4716	–3334	–11555	–25457	–18216
AGA IgG	–10524	–10524	–10524	–10524	–10524	–10414	–10636	–44933	–5207	–5372	–12193	–26121	–19997
EMA IgA	–3419	–3419	–3419	–3419	–3419	–3334	–3509	–16167	–1667	9928	–7569	–21302	–6675
ARA IgA	–8177	–8177	–8177	–8177	–8177	–8052	–8306	–36068	–4026	–423	–10655	–24520	–15675
TTG IgA	–7397	–7397	–7397	–7397	–7397	–7271	–7526	–32990	–3636	1244	–10146	–23990	–14222
EMA IgA + AGA IgG	–10425	–10425	–10425	–10425	–10425	–10314	–10538	–44571	–5157	–5165	–12128	–26053	–19816
TTG IgA + AGA IgG	–10425	–10425	–10425	–10425	–10425	–10314	–10538	–44571	–5157	–5165	–12128	–26053	–19816
Biopsy all vs strategy													
AGA IgA + biopsy	–1741737	–445484	1853219	986640	–462573	712659	–391930	912016	–356936	–434462	921410	445301	–318163
AGA IgG + biopsy	206697	1672200	130469	112771	1236869	149056	337025	110157	–1226521	1711760	114902	92417	–594589

continued

Cost per QALY for different screening strategies (£)	Base case	Utility treated CD		Utility untreated CD		Disutility of endoscopy		Disutility of GFD		Compliance GFD		Discounting	
		Low	High	Low	High	Low	High	Low	High	Low	High	Both 0%	Both 6%
EMA IgA + biopsy	–299482	–270789	–322245	–333017	–272083	–762441	–186337	–334976	–262409	–269520	–336445	–372362	–257523
ARA IgA + biopsy	–453771	–321178	–626085	–746755	–325905	–5513163	–236624	–772819	–292671	–317176	–783092	–1709519	–277567
TTG IgA + biopsy	–387602	–303184	–475950	–527073	–306498	–1775647	–217544	–537169	–282663	–300236	–542347	–777885	–271401
EMA IgA + AGA IgG + biopsy	–250926	–244963	–255065	–256868	–245253	–527850	–164582	–257186	–243038	–244654	–257485	–262980	–241873
TTG IgA + AGA IgG + biopsy	–250225	–244279	–254353	–256150	–244568	–526376	–164122	–256468	–242360	–243970	–256767	–262248	–241198
AGA IgA	39504	43051	37446	36635	42860	35573	44411	135414	20317	120027	20024	10594	102830
AGA IgG	7607	8207	7253	7112	8175	7301	7940	20489	4138	30684	750	–8954	16780
EMA IgA	1019611	1608571	819562	756408	1563732	317382	–840872	–474892	196228	–614531	266120	275000	–587228
ARA IgA	99911	111030	93658	91229	110420	80450	131792	717423	46521	420972	52308	43687	397102
TTG IgA	148185	167239	137723	133707	166179	110247	225930	7163442	64267	1013391	74939	67179	997884
EMA IgA + AGA IgG	5203	5211	5198	5195	5211	4976	5451	28020	2495	29917	–2064	–15484	10557
TTG IgA + AGA IgG	5158	5166	5152	5150	5165	4933	5404	27775	2473	29817	–2094	–15517	10465
Strategy vs single test													
EMA IgA + AGA IgG + biopsy	–816767	–413452	–2335764	–11197478	–423841	1677284	–328420	–33313151	–355017	–406271	–42023340	1182666	–326707
TTG IgA + AGA IgG + biopsy	432792	–1810885	237017	198757	–2438409	246806	1756250	193297	–663799	–1673106	198691	148627	–478115
EMA IgA + AGA IgG	–16102	–16005	–16167	–16195	–16009	–16102	–16102	–68611	–7969	–16421	–15995	–30494	–29837
TTG IgA + AGA IgG	–16632	–16378	–16806	–16881	–16390	–16631	–16633	–78890	–8104	–16985	–16514	–31690	–30501

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Cost per QALY for different screening strategies (£)	Base case	Life expectancy		Life lost treated CD		Life lost untreated CD		FN never diagnosed		Delay to diagnosis		FP never corrected		Time to correction	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Strategy vs no screening															
Biopsy all	45174	43166	47109	38051	55722	105612	24855	89533	31777	49120	39892	45174	45174	45174	45174
AGA IgA + biopsy	14770	14128	15377	12659	17769	30279	8524	22125	12182	14014	15003	14770	14770	14770	14770
AGA IgG + biopsy	20160	19296	20981	17225	24359	42201	11541	32962	15767	20153	19487	20160	20160	20160	20160
EMA IgA + biopsy	12246	11705	12756	10511	14703	24873	7093	17189	10487	11150	12894	12246	12246	12246	12246
ARA IgA + biopsy	13503	12912	14060	11583	16226	27529	7810	19627	11334	12576	13945	13503	13503	13503	13503
TTG IgA + biopsy	12970	12400	13507	11128	15581	26408	7505	18594	10974	11971	13499	12970	12970	12970	12970
EMA IgA + AGA IgG + biopsy	19099	18280	19877	16330	23053	39780	10955	30779	15067	18942	18607	19099	19099	19099	19099
TTG IgA + AGA IgG + biopsy	19160	18339	19941	16383	23128	39909	10991	30899	15109	19012	18658	19160	19160	19160	19160
AGA IgA	54088	45815	64495	37610	97168	–159592	18561	–178867	27765	69993	41098	28127	176340	42047	96960
AGA IgG	–54321	–64130	–47635	–71904	–43550	–31140	855222	–29199	–195645	–43074	–83118	–1503916	–33384	–64818	–44054
EMA IgA	14447	13644	15227	12156	17853	34300	7902	23509	11754	13525	14764	13008	16062	13822	15714
ARA IgA	23948	22034	25936	19216	31901	97542	11519	65313	16842	24769	22184	18116	32602	21441	29687
TTG IgA	19987	18581	21409	16342	25816	63213	10104	43503	14833	19944	19186	16086	25154	18308	23645
EMA IgA + AGA IgG	–77025	–98919	–64069	–125140	–55458	–35477	114401	–33158	860282	–55781	–155215	202868	–40133	–105765	–55294
TTG IgA + AGA IgG	–77164	–99099	–64185	–125366	–55558	–35541	114608	–33225	861700	–55889	–155471	203326	–40194	–105982	–55375
Confirmatory biopsy vs strategy															
AGA IgA	–9551	–9845	–9278	–9551	–9551	–9551	–9551	–9551	–9551	–9551	–9551	–8018	–10206	–7578	–12245
AGA IgG	–10524	–10859	–10214	–10524	–10524	–10524	–10524	–10524	–10524	–10524	–10524	–9649	–10898	–8679	–13034
EMA IgA	–3419	–3445	–3378	–3419	–3419	–3419	–3419	–3419	–3419	–3419	–3419	2480	–5875	–607	–7290
ARA IgA	–8177	–8412	–7954	–8177	–8177	–8177	–8177	–8177	–8177	–8177	–8177	–5696	–9229	–6019	–11130
TTG IgA	–7397	–7598	–7203	–7397	–7397	–7397	–7397	–7397	–7397	–7397	–7397	–4370	–8677	–5133	–10498
EMA IgA + AGA IgG	–10425	–10756	–10119	–10425	–10425	–10425	–10425	–10425	–10425	–10425	–10425	–9483	–10828	–8567	–12954
TTG IgA + AGA IgG	–10425	–10756	–10119	–10425	–10425	–10425	–10425	–10425	–10425	–10425	–10425	–9483	–10828	–8567	–12954
Biopsy all vs strategy															
AGA IgA + biopsy	–1741737	–2264572	–1444729	##########	–877124	–438225	536545	–454891	985077	–1010409	1149168	–1741737	–1741737	–1741737	–1741737
AGA IgG + biopsy	206697	193116	220475	159784	293932	1986763	90688	1252444	115462	257389	157433	206697	206697	206697	206697

continued

Cost per QALY for different screening strategies (£)	Base case	Life expectancy		Life lost treated CD		Life lost untreated CD		FN never diagnosed		Delay to diagnosis		FP never corrected		Time to correction	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
EMA IgA + biopsy	–299482	–302006	–297267	–310513	–289103	–270214	–354252	–271260	–334080	–291429	–313378	–299482	–299482	–299482	–299482
ARA IgA + biopsy	–453771	–469085	–440946	–526656	–398090	–319105	–1141299	–323253	–755051	–410417	–546152	–453771	–453771	–453771	–453771
TTG IgA + biopsy	–387602	–396321	–380149	–427505	–354188	–301723	–652843	–304559	–531055	–361671	–437915	–387602	–387602	–387602	–387602
EMA IgA + AGA IgG + biopsy	–250926	–251408	–250498	–252991	–248873	–244834	–260166	–245054	–257078	–249326	–253538	–250926	–250926	–250926	–250926
TTG IgA + AGA IgG + biopsy	–250225	–250706	–249798	–252284	–248178	–244151	–259439	–244369	–256361	–248629	–252831	–250225	–250225	–250225	–250225
AGA IgA	39504	41117	38094	38444	40636	43140	35261	42308	37110	39899	38763	75659	24492	47818	27759
AGA IgG	7607	7962	7306	7427	7798	8224	6871	7669	7553	7378	7849	18870	2389	11310	2260
EMA IgA	1019611	1218061	882863	908170	1163961	1629594	664544	1566734	756620	1117597	892003	–1245455	351849	2081944	498339
ARA IgA	99911	104698	95762	96669	103416	111309	87169	109792	91760	101906	96702	212639	62554	119961	73239
TTG IgA	148185	156237	141276	142737	154130	167724	127056	165508	134271	151842	142459	361493	90000	180492	107279
EMA IgA + AGA IgG	5203	5576	4900	5200	5206	5212	5191	5201	5205	5197	5210	17869	110	9269	–397
TTG IgA + AGA IgG	5158	5529	4856	5155	5160	5166	5146	5155	5160	5152	5164	17789	78	9218	–434
Strategy vs single test															
EMA IgA + AGA IgG + biopsy	–816767	–885185	–764159	–1213574	–613891	–408959	1928757	–418947	##########	–655922	–1345240	–816767	–816767	–816767	–816767
TTG IgA + AGA IgG + biopsy	432792	393842	474538	305823	745742	–1623224	154113	–2273046	201589	611433	295214	432792	432792	432792	432792
EMA IgA + AGA IgG	–16102	–16682	–15580	–16135	–16069	–16003	–16246	–15969	–16236	–16048	–16180	–18909	–14889	–14957	–17606
TTG IgA + AGA IgG	–16632	–17260	–16071	–16720	–16545	–16373	–17017	–16289	–16986	–16493	–16836	–19889	–15251	–15529	–18064

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Cost per QALY for different screening strategies (£)	Base case	Prevalence		Sensitivity of test		Specificity of test		Sens & spec		Cost of test		Cost of endoscopy and biopsy		Cost of GFD	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Strategy vs no screening															
Biopsy all	20230	55079	11329	20230	20230	20230	20230	20230	20230	20230	20230	13679	29164	16448	23791
AGA IgA + biopsy	7394	11683	6299	7724	7282	9648	6428	10388	6376	7328	7527	6652	8407	3611	10955
AGA IgG + biopsy	9896	20130	7281	10521	9499	11750	8412	12645	8151	9819	10049	8077	12375	6113	13456
EMA IgA + biopsy	6187	7610	5824	6234	6181	7234	6038	7361	6033	6125	6218	5951	6510	2404	9747
ARA IgA + biopsy	6797	9658	6066	6836	6772	7259	6488	7314	6469	6733	6860	6352	7402	3014	10357
TTG IgA + biopsy	6537	8787	5962	6578	6517	7147	6231	7215	6218	6473	6663	6163	7046	2754	10097
EMA IgA + AGA IgG + biopsy	9419	18510	7096	9512	9407	11571	8137	11717	8130	9297	9571	7852	11555	5636	12979
TTG IgA + AGA IgG + biopsy	9449	18611	7109	9543	9438	11602	8167	11748	8160	9327	9692	7882	11585	5666	13009
AGA IgA	10349	22854	7154	11307	10023	17976	7080	20321	6956	10282	10482	10464	10192	3093	17178
AGA IgG	18680	50997	10425	20651	17429	24956	13659	27837	12870	18603	18834	18795	18523	5562	31027
EMA IgA	6400	9518	5604	6502	6387	9941	5894	10315	5886	6338	6431	6515	6243	1900	10635
ARA IgA	8135	15369	6287	8235	8072	9701	7091	9851	7050	8071	8199	8250	7978	2504	13435
TTG IgA	7492	13204	6033	7597	7443	9558	6459	9752	6431	7429	7618	7607	7335	2246	12429
EMA IgA + AGA IgG	16838	44768	9704	17125	16804	24122	12502	24587	12480	16717	16991	16953	16681	5092	27893
TTG IgA + AGA IgG	16869	44868	9717	17156	16835	24153	12532	24618	12511	16747	17112	16984	16712	5123	27924
Biopsy all vs strategy															
AGA IgA + biopsy	150018	493857	62190	62099	438897	127227	159786	53180	468200	150692	148672	84730	239047	146235	153579
AGA IgG + biopsy	59109	186555	26555	41841	92051	52132	64691	37115	101067	59398	58532	34753	92323	55326	62670
EMA IgA + biopsy	708352	2381079	281079	161751	1411124	657071	715677	150355	1425776	711382	706837	392360	1139249	704569	711912
ARA IgA + biopsy	275473	918079	111329	174263	455402	266682	281333	168768	465170	276685	274261	152881	442643	271690	279033
TTG IgA + biopsy	348882	1166079	140141	177230	692185	334230	356208	169905	706837	350397	345852	194057	560007	345099	352442
EMA IgA + AGA IgG + biopsy	2583686	8725317	1014900	393681	8334849	2073325	2887531	316853	9316501	2612546	2547611	1395246	4204287	2579904	2587247
TTG IgA + AGA IgG + biopsy	2576471	8701507	1011924	392595	8311539	2066110	2880316	315766	9293191	2605331	2518751	1388031	4197072	2572689	2580032
AGA IgA	120146	380910	53538	50105	350282	43024	153199	19927	449439	120820	118800	46187	221000	151482	90654
AGA IgG	26063	70434	14729	19294	38976	2454	44950	3301	69486	26351	25486	–5568	69196	57398	–3430

continued

Cost per QALY for different screening strategies (£)	Base case	Prevalence		Sensitivity of test		Specificity of test		Sens & spec		Cost of test		Cost of endoscopy and biopsy		Cost of GFD	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
EMA IgA	697924	2287577	291872	159045	1390770	524398	722714	120483	1440348	700955	696409	364706	1152313	729260	668432
ARA IgA	250045	809577	107122	158183	413356	220298	269877	139591	446409	251258	248833	116827	431707	281381	220553
TTG IgA	325955	1060077	138434	165517	646830	276376	350744	140727	696409	327470	322924	159403	553070	357290	296462
EMA IgA + AGA IgG	824469	2499855	396518	128428	2652341	–902530	1852642	–131550	5974129	853329	788394	–762717	2988815	2708719	–948942
TTG IgA + AGA IgG	817254	2476046	393541	127342	2629031	–909745	1845427	–132637	5950819	846114	759534	–769932	2981600	2701504	–956157
Strategy vs single test															
EMA IgA + AGA IgG + biopsy	209845	694636	86012	57550	376545	280599	138349	75552	246702	206009	217517	125770	324492	206062	213405
TTG IgA + AGA IgG + biopsy	87545	282034	37865	61901	162497	131049	60083	91794	109924	85852	90930	53982	133312	83762	91105
EMA IgA + AGA IgG	664286	2231149	264054	172800	1202259	903708	422353	233716	762887	660450	671957	664401	664129	203074	1098367
TTG IgA + AGA IgG	268316	893958	108505	185960	509030	415529	175390	287116	331129	266623	271702	268431	268159	82271	443418

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Cost per QALY for different screening strategies (£)	Base case	Utility treated CD		Utility untreated CD		Disutility of endoscopy		Disutility of GFD		Compliance GFD		Discounting	
		Low	High	Low	High	Low	High	Low	High	Low	High	Both 0%	Both 6%
Strategy vs no screening													
Biopsy all	20230	20230	20230	20230	20230	20230	20230	20230	20230	17553	22920	28324	20230
AGA IgA + biopsy	7394	7394	7394	7394	7394	7394	7394	7394	7394	4717	10084	15488	7394
AGA IgG + biopsy	9896	9896	9896	9896	9896	9896	9896	9896	9896	7218	12585	17989	9896
EMA IgA + biopsy	6187	6187	6187	6187	6187	6187	6187	6187	6187	3510	8876	14281	6187
ARA IgA + biopsy	6797	6797	6797	6797	6797	6797	6797	6797	6797	4119	9486	14890	6797
TTG IgA + biopsy	6537	6537	6537	6537	6537	6537	6537	6537	6537	3859	9226	14630	6537
EMA IgA + AGA IgG + biopsy	9419	9419	9419	9419	9419	9419	9419	9419	9419	6741	12108	17512	9419
TTG IgA + AGA IgG + biopsy	9449	9449	9449	9449	9449	9449	9449	9449	9449	6772	12138	17543	9449
AGA IgA	10349	10349	10349	10349	10349	10349	10349	10349	10349	5220	15490	26267	10349
AGA IgG	18680	18680	18680	18680	18680	18680	18680	18680	18680	9413	27959	47806	18680
EMA IgA	6400	6400	6400	6400	6400	6400	6400	6400	6400	3217	9595	16108	6400
ARA IgA	8135	8135	8135	8135	8135	8135	8135	8135	8135	4153	12129	20393	8135
TTG IgA	7492	7492	7492	7492	7492	7492	7492	7492	7492	3782	11214	18882	7492
EMA IgA + AGA IgG	16838	16838	16838	16838	16838	16838	16838	16838	16838	8540	25149	42873	16838
TTG IgA + AGA IgG	16869	16869	16869	16869	16869	16869	16869	16869	16869	8571	25179	42903	16869
Biopsy all vs strategy													
AGA IgA + biopsy	150018	150018	150018	150018	150018	150018	150018	150018	150018	147341	152708	158112	150018
AGA IgG + biopsy	59109	59109	59109	59109	59109	59109	59109	59109	59109	56432	61799	67203	59109
EMA IgA + biopsy	708352	708352	708352	708352	708352	708352	708352	708352	708352	705674	711041	716445	708352
ARA IgA + biopsy	275473	275473	275473	275473	275473	275473	275473	275473	275473	272796	278162	283567	275473
TTG IgA + biopsy	348882	348882	348882	348882	348882	348882	348882	348882	348882	346205	351571	356976	348882
EMA IgA + AGA IgG + biopsy	2583686	2583686	2583686	2583686	2583686	2583686	2583686	2583686	2583686	2581009	2586376	2591780	258368
TTG IgA + AGA IgG + biopsy	2576471	2576471	2576471	2576471	2576471	2576471	2576471	2576471	2576471	2573794	2579161	2584565	2576471
AGA IgA	120146	120146	120146	120146	120146	120146	120146	120146	120146	142259	98046	49120	120146
AGA IgG	26063	26063	26063	26063	26063	26063	26063	26063	26063	48175	3963	–44963	26063

continued

Cost per QALY for different screening strategies (£)	Base case	Utility treated CD		Utility untreated CD		Disutility of endoscopy		Disutility of GFD		Compliance GFD		Discounting	
		Low	High	Low	High	Low	High	Low	High	Low	High	Both 0%	Both 6%
EMA IgA	697924	697924	697924	697924	697924	697924	697924	697924	697924	720037	675824	626898	697924
ARA IgA	250045	250045	250045	250045	250045	250045	250045	250045	250045	272158	227945	179019	250045
TTG IgA	325955	325955	325955	325955	325955	325955	325955	325955	325955	348067	303854	254928	325955
EMA IgA + AGA IgG	824469	824469	824469	824469	824469	824469	824469	824469	824469	2154521	–505570	–3421077	824469
TTG IgA + AGA IgG	817254	817254	817254	817254	817254	817254	817254	817254	817254	2147306	–512785	–3428292	817254
Strategy vs single test													
EMA IgA + AGA IgG + biopsy	209845	209845	209845	209845	209845	209845	209845	209845	209845	207168	212534	217939	209845
TTG IgA + AGA IgG + biopsy	87545	87545	87545	87545	87545	87545	87545	87545	87545	84867	90234	95638	87545
EMA IgA + AGA IgG	664286	664286	664286	664286	664286	664286	664286	664286	664286	338718	989866	1702942	664286
TTG IgA + AGA IgG	268316	268316	268316	268316	268316	268316	268316	268316	268316	136983	399661	687038	268316

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Cost per QALY for different screening strategies (£)	Base case	Life expectancy		Life lost treated CD		Life lost untreated CD		FN never diagnosed		Delay to diagnosis		FP never corrected		Time to correction	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Strategy vs no screening		CCD	CCD	CCD	CCD	CCD	CCD	CCD	CCD	CCD	CCD	CCD	CCD	CCD	CCD
Biopsy all	20230	20190	20262	20237	20224	20237	20221	18601	21860	18995	21844	20230	20230	20230	20230
AGA IgA + biopsy	7394	7354	7426	7401	7387	7401	7385	5765	9023	6159	9007	7394	7394	7394	7394
AGA IgG + biopsy	9896	9855	9927	9902	9889	9902	9886	8266	11525	8661	11509	9896	9896	9896	9896
EMA IgA + biopsy	6187	6147	6219	6194	6180	6194	6178	4558	7816	4952	7800	6187	6187	6187	6187
ARA IgA + biopsy	6797	6757	6828	6803	6790	6803	6787	5167	8426	5562	8410	6797	6797	6797	6797
TTG IgA + biopsy	6537	6497	6568	6543	6530	6543	6527	4907	8166	5302	8150	6537	6537	6537	6537
EMA IgA + AGA IgG + biopsy	9419	9378	9450	9425	9412	9425	9409	7789	11048	8184	11032	9419	9419	9419	9419
TTG IgA + AGA IgG + biopsy	9449	9409	9480	9455	9442	9456	9440	7820	11078	8214	11062	9449	9449	9449	9449
AGA IgA	10349	10272	10409	10355	10342	10355	10339	8719	11978	9114	11962	8878	11820	9480	12008
AGA IgG	18680	18541	18789	18687	18673	18687	18671	17051	20309	17445	20293	14726	22634	16344	23140
EMA IgA	6400	6352	6437	6406	6393	6407	6391	4771	8029	5165	8013	6096	6703	6221	6742
ARA IgA	8135	8075	8182	8141	8128	8142	8125	6506	9764	6900	9748	7352	8918	7672	9018
TTG IgA	7492	7436	7535	7498	7485	7499	7483	5863	9121	6257	9105	6872	8112	7126	8191
EMA IgA + AGA IgG	16838	16714	16936	16845	16832	16845	16829	15209	18468	15603	18452	13466	20211	14846	20643
TTG IgA + AGA IgG	16869	16744	16966	16875	16862	16876	16859	15240	18498	15634	18482	13496	20241	14876	20673
Biopsy all vs strategy															
AGA IgA + biopsy	150018	149978	150050	150025	150012	150025	150009	148389	151648	148783	151632	150018	150018	150018	150018
AGA IgG + biopsy	59109	59069	59141	59116	59102	59116	59100	57480	60738	57874	60722	59109	59109	59109	59109
EMA IgA + biopsy	708352	708312	708383	708358	708345	708359	708342	706722	709981	707117	709965	708352	708352	708352	708352
ARA IgA + biopsy	275473	275433	275504	275479	275466	275480	275463	273844	277102	274238	277086	275473	275473	275473	275473
TTG IgA + biopsy	348882	348842	348913	348888	348875	348889	348873	347253	350511	347647	350495	348882	348882	348882	348882
EMA IgA + AGA IgG + biopsy	2583686	2583646	2583718	2583693	2583680	2583693	2583677	2582057	2585316	2582451	2585300	2583686	2583686	2583686	2583686
TTG IgA + AGA IgG + biopsy	2576471	2576431	2576503	2576478	2576465	2576478	2576462	2574842	2578101	2575236	2578085	2576471	2576471	2576471	2576471
AGA IgA	120146	120478	119888	120153	120140	120153	120137	118517	121776	118911	121760	135020	105273	128933	103368
AGA IgG	26063	26394	25804	26069	26056	26070	26053	24434	27692	24828	27676	40936	11189	34849	9285

continued

Cost per QALY for different screening strategies (£)	Base case	Life expectancy		Life lost treated CD		Life lost untreated CD		FN never diagnosed		Delay to diagnosis		FP never corrected		Time to correction	
		Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
EMA IgA	697924	698256	697665	697931	697917	697931	697915	696295	699553	696689	699537	712798	683051	706711	681146
ARA IgA	250045	250377	249787	250052	250039	250052	250036	248416	251675	248810	251659	264919	235172	258832	233267
TTG IgA	325955	326286	325696	325961	325948	325961	325945	324325	327584	324720	327568	340828	311081	334741	309176
EMA IgA + AGA IgG	824469	844418	808895	824476	824463	824476	824460	822840	826099	823234	826083	1624088	24851	1296848	–77554
TTG IgA + AGA IgG	817254	837203	801680	817261	817248	817261	817245	815625	818884	816019	818868	1616873	17636	1289633	–84769
Strategy vs single test															
EMA IgA + AGA IgG + biopsy	209845	209805	209876	209851	209838	209852	209836	208216	211474	208610	211458	209845	209845	209845	209845
TTG IgA + AGA IgG + biopsy	87545	87505	87576	87551	87538	87551	87535	85915	89174	86310	89158	87545	87545	87545	87545
EMA IgA + AGA IgG	664286	659403	668098	664292	664279	664292	664276	662656	665915	663051	665899	470556	858015	549839	882826
TTG IgA + AGA IgG	268316	266346	269854	268322	268309	268323	268307	266687	269945	267081	269929	191124	345508	222715	355393

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We look forward to hearing from you.

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