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Clinical Utility of Serologic Testing for Celiac Disease in Ontario

An Evidence-Based Analysis

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List of Abbreviations

AGA	Anti-gliadin antibody
AHRQ	Agency for Healthcare Research and Quality
AUC	Area under the curve
CD	Celiac disease
CI	Confidence interval(s)
DGP	Deamidated gliadin peptides
DOR	Diagnostic odds ratio
ELISA	Enzyme-linked immunosorbent assay
EMA	Endomysial antibody
ESPGAN	European Society of Paediatric Gastroenterology and Nutrition
FN	False negative
FP	False positive
FTT	Failure-to-thrive
GFD	Gluten-free diet
GI	gastrointestinal
IBS	Irritable bowel syndrome
IDA	Iron-deficiency anemia
IgA, IgG	Immunoglobulin A or G
IQR	Interquartile range
LR	Likelihood ratio
MAS	Medical Advisory Secretariat
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
N/A	Not available
NR	Not reported
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
sROC	Summary receiver operating characteristic
TN	True negative
TP	True positive
tTG	Tissue transglutaminase
VA	Villous atrophy

Executive Summary

Objective of Analysis

The objective of this evidence-based evaluation is to assess the accuracy of serologic tests in the diagnosis of celiac disease in subjects with symptoms consistent with this disease. Furthermore the impact of these tests in the diagnostic pathway of the disease and decision making was also evaluated.

Celiac Disease

Celiac disease is an autoimmune disease that develops in genetically predisposed individuals. The immunological response is triggered by ingestion of gluten, a protein that is present in wheat, rye, and barley. The treatment consists of strict lifelong adherence to a gluten-free diet (GFD).

Patients with celiac disease may present with a myriad of symptoms such as diarrhea, abdominal pain, weight loss, iron deficiency anemia, dermatitis herpetiformis, among others.

Serologic Testing in the Diagnosis Celiac Disease

There are a number of serologic tests used in the diagnosis of celiac disease.

- Anti-gliadin antibody (AGA)
- Anti-endomysial antibody (EMA)
- Anti-tissue transglutaminase antibody (tTG)
- Anti-deamidated gliadin peptides antibodies (DGP)

Serologic tests are automated with the exception of the EMA test, which is more time-consuming and operator-dependent than the other tests. For each serologic test, both immunoglobulin A (IgA) or G (IgG) can be measured, however, IgA measurement is the standard antibody measured in celiac disease.

Diagnosis of Celiac Disease

According to celiac disease guidelines, the diagnosis of celiac disease is established by small bowel biopsy. Serologic tests are used to initially detect and to support the diagnosis of celiac disease. A small bowel biopsy is indicated in individuals with a positive serologic test. In some cases an endoscopy and small bowel biopsy may be required even with a negative serologic test. The diagnosis of celiac disease must be performed on a gluten-containing diet since the small intestine abnormalities and the serologic antibody levels may resolve or improve on a GFD.

Since IgA measurement is the standard for the serologic celiac disease tests, false negatives may occur in IgA-deficient individuals.

Incidence and Prevalence of Celiac Disease

The incidence and prevalence of celiac disease in the general population and in subjects with symptoms consistent with or at higher risk of celiac disease based on systematic reviews published in 2004 and 2009 are summarized below.

Incidence of Celiac Disease in the General Population

- Adults or mixed population: 1 to 17/100,000/year
- Children: 2 to 51/100,000/year

In one of the studies, a stratified analysis showed that there was a higher incidence of celiac disease in younger children compared to older children, i.e., 51 cases/100,000/year in 0 to 2 year-olds, 33/100,000/year in 2 to 5 year-olds, and 10/100,000/year in children 5 to 15 years old.

Prevalence of Celiac Disease in the General Population

The prevalence of celiac disease reported in population-based studies identified in the 2004 systematic review varied between 0.14% and 1.87% (median: 0.47%, interquartile range: 0.25%, 0.71%). According to the authors of the review, the prevalence did not vary by age group, i.e., adults and children.

Prevalence of Celiac Disease in High Risk Subjects

- Type 1 diabetes (adults and children): 1 to 11%
- Autoimmune thyroid disease: 2.9 to 3.3%
- First degree relatives of patients with celiac disease: 2 to 20%

Prevalence of Celiac Disease in Subjects with Symptoms Consistent with the Disease

The prevalence of celiac disease in subjects with symptoms consistent with the disease varied widely among studies, i.e., 1.5% to 50% in adult studies, and 1.1% to 17% in pediatric studies. Differences in prevalence may be related to the referral pattern as the authors of a systematic review noted that the prevalence tended to be higher in studies whose population originated from tertiary referral centres compared to general practice.

Research Questions

- What is the sensitivity and specificity of serologic tests in the diagnosis celiac disease?
- What is the clinical validity of serologic tests in the diagnosis of celiac disease? The clinical validity was defined as the ability of the test to change diagnosis.
- What is the clinical utility of serologic tests in the diagnosis of celiac disease? The clinical utility was defined as the impact of the test on decision making.
- What is the budget impact of serologic tests in the diagnosis of celiac disease?
- What is the cost-effectiveness of serologic tests in the diagnosis of celiac disease?

Methods

Literature Search

A literature search was performed on November 13th, 2009 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1st 2003 and November 13th 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified

through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist, then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Inclusion Criteria Inclusion Criteria

- Studies that evaluated diagnostic accuracy, i.e., both sensitivity and specificity of serology tests in the diagnosis of celiac disease.
- Study population consisted of untreated patients with symptoms consistent with celiac disease.
- Studies in which both serologic celiac disease tests and small bowel biopsy (gold standard) were used in all subjects.
- Systematic reviews, meta-analyses, randomized controlled trials, prospective observational studies, and retrospective cohort studies.
- At least 20 subjects included in the celiac disease group.
- English language.
- Human studies.
- Studies published from 2000 on.
- Clearly defined cut-off value for the serology test. If more than one test was evaluated, only those tests for which a cut-off was provided were included.
- Description of small bowel biopsy procedure clearly outlined (location, number of biopsies per patient), unless if specified that celiac disease diagnosis guidelines were followed.
- Patients in the treatment group had untreated CD.

Exclusion Criteria

- Studies on screening of the general asymptomatic population.
- Studies that evaluated rapid diagnostic kits for use either at home or in physician's offices.
- Studies that evaluated diagnostic modalities other than serologic tests such as capsule endoscopy, push enteroscopy, or genetic testing.
- Cut-off for serologic tests defined based on controls included in the study.
- Study population defined based on positive serology or subjects pre-screened by serology tests.
- Celiac disease status known before study enrolment.
- Sensitivity or specificity estimates based on repeated testing for the same subject.
- Non-peer-reviewed literature such as editorials and letters to the editor.

Population

The population consisted of adults and children with untreated, undiagnosed celiac disease with symptoms consistent with the disease.

Serologic Celiac Disease Tests Evaluated

- Anti-gliadin antibody (AGA)
- Anti-endomysial antibody (EMA)
- Anti-tissue transglutaminase antibody (tTG)
- Anti-deamidated gliadin peptides antibody (DGP)
- Combinations of some of the serologic tests listed above were evaluated in some studies

Both IgA and IgG antibodies were evaluated for the serologic tests listed above.

Outcomes of Interest

- Sensitivity
- Specificity
- Positive and negative likelihood ratios
- Diagnostic odds ratio (OR)
- Area under the sROC curve (AUC)

Small bowel biopsy was used as the gold standard in order to estimate the sensitivity and specificity of each serologic test.

Statistical Analysis

Pooled estimates of sensitivity, specificity and diagnostic odds ratios (DORs) for the different serologic tests were calculated using a bivariate, binomial generalized linear mixed model. Statistical significance for differences in sensitivity and specificity between serologic tests was defined by P values less than 0.05, where "false discovery rate" adjustments were made for multiple hypothesis testing. The bivariate regression analyses were performed using SAS version 9.2 (SAS Institute Inc.; Cary, NC, USA). Using the bivariate model parameters, summary receiver operating characteristic (sROC) curves were produced using Review Manager 5.0.22 (The Nordiac Cochrane Centre, The Cochrane Collaboration, 2008). The area under the sROC curve (AUC) was estimated by bivariate mixed-efects binary regression modeling framework. Model specification, estimation and prediction are carried out with xtmelogit in Stata release 10 (Statacorp, 2007). Statistical tests for the differences in AUC estimates could not be carried out.

The study results were stratified according to patient or disease characteristics such as age, severity of Marsh grade abnormalities, among others, if reported in the studies. The literature indicates that the diagnostic accuracy of serologic tests for celiac disease may be affected in patients with chronic liver disease, therefore, the studies identified through the systematic literature review that evaluated the diagnostic accuracy of serologic tests for celiac disease in patients with chronic liver disease were summarized. The effect of the GFD in patiens diagnosed with celiac disease was also summarized if reported in the studies eligible for the analysis.

Summary of Findings

Published Systematic Reviews

Five systematic reviews of studies that evaluated the diagnostic accuracy of serologic celiac disease tests were identified through our literature search. Seventeen individual studies identified in adults and children were eligible for this evaluation.

In general, the studies included evaluated the sensitivity and specificity of at least one serologic test in subjects with symptoms consistent with celiac disease. The gold standard used to confirm the celiac disease diagnosis was small bowel biopsy. Serologic tests evaluated included tTG, EMA, AGA, and DGP, using either IgA or IgG antibodies. Indirect immunoflurorescence was used for the EMA serologic tests whereas enzyme-linked immunosorbent assay (ELISA) was used for the other serologic tests.

Common symptoms described in the studies were chronic diarrhea, abdominal pain, bloating, unexplained weight loss, unexplained anemia, and dermatitis herpetiformis.

The main conclusions of the published systematic reviews are summarized below.

- IgA tTG and/or IgA EMA have a high accuracy (pooled sensitivity: 90% to 98%, pooled specificity: 95% to 99% depending on the pooled analysis).

- Most reviews found that AGA (IgA or IgG) are not as accurate as IgA tTG and/or EMA tests.
- A 2009 systematic review concluded that DGP (IgA or IgG) seems to have a similar accuracy compared to tTG, however, since only 2 studies identified evaluated its accuracy, the authors believe that additional data is required to draw firm conclusions.
- Two systematic reviews also concluded that combining two serologic celiac disease tests has little contribution to the accuracy of the diagnosis.

MAS Analysis

Sensitivity

The pooled analysis performed by MAS showed that IgA tTG has a sensitivity of 92.1% [95% confidence interval (CI) 88.0, 96.3], compared to 89.2% (83.3, 95.1, p=0.12) for IgA DGP, 85.1% (79.5, 94.4, p=0.07) for IgA EMA, and 74.9% (63.6, 86.2, p=0.0003) for IgA AGA. Among the IgG-based tests, the results suggest that IgG DGP has a sensitivity of 88.4% (95% CI: 82.1, 94.6), 44.7% (30.3, 59.2) for tTG, and 69.1% (56.0, 82.2) for AGA. The difference was significant when IgG DGP was compared to IgG tTG but not IgG AGA. Combining serologic celiac disease tests yielded a slightly higher sensitivity compared to individual IgA-based serologic tests.

IgA deficiency

The prevalence of total or severe IgA deficiency was low in the studies identified varying between 0 and 1.7% as reported in 3 studies in which IgA deficiency was not used as a referral indication for celiac disease serologic testing. The results of IgG-based serologic tests were positive in all patients with IgA deficiency in which celiac disease was confirmed by small bowel biopsy as reported in four studies.

Specificity

The MAS pooled analysis indicates a high specificity across the different serologic tests including the combination strategy, pooled estimates ranged from 90.1% to 98.7% depending on the test.

Likelihood Ratios

According to the likelihood ratio estimates, both IgA tTG and serologic test combination[a] were considered very useful tests (positive likelihood ratio above ten and the negative likelihood ratio below 0.1).

Moderately useful tests included IgA EMA, IgA DGP, and IgG DGP (positive likelihood ratio between five and ten and the negative likelihood ratio between 0.1 and 0.2).

Somewhat useful tests: IgA AGA, IgG AGA, generating small but sometimes important changes from pre- to post-test probability (positive LR between 2 and 5 and negative LR between 0.2 and 0.5)

Not Useful: IgG tTG, altering pre- to post-test probability to a small and rarely important degree (positive LR between 1 and 2 and negative LR between 0.5 and 1).

Diagnostic Odds Ratios (DOR)

Among the individual serologic tests, IgA tTG had the highest DOR, 136.5 (95% CI: 51.9, 221.2). The statistical significance of the difference in DORs among tests was not calculated, however, considering the wide confidence intervals obtained, the differences may not be statistically significant.

[a] Positive serology interpreted as any positive result among the different tests.

Area Under the sROC Curve (AUC)

The sROC AUCs obtained ranged between 0.93 and 0.99 for most IgA-based tests with the exception of IgA AGA, with an AUC of 0.89.

Sensitivity and Specificity of Serologic Tests According to Age Groups

Serologic test accuracy did not seem to vary according to age (adults or children).

Sensitivity and Specificity of Serologic Tests According to Marsh Criteria

Four studies observed a trend towards a higher sensitivity of serologic celiac disease tests when Marsh 3c grade abnormalities were found in the small bowel biopsy compared to Marsh 3a or 3b (statistical significance not reported). The sensitivity of serologic tests was much lower when Marsh 1 grade abnormalities were found in small bowel biopsy compared to Marsh 3 grade abnormalities. The statistical significance of these findings were not reported in the studies.

Diagnostic Accuracy of Serologic Celiac Disease Tests in Subjects with Chronic Liver Disease

A total of 14 observational studies that evaluated the specificity of serologic celiac disease tests in subjects with chronic liver disease were identified. All studies evaluated the frequency of false positive results (1-specificity) of IgA tTG, however, IgA tTG test kits using different substrates were used, i.e., human recombinant, human, and guinea-pig substrates. The gold standard, small bowel biopsy, was used to confirm the result of the serologic tests in only 5 studies. The studies do not seem to have been designed or powered to compare the diagnostic accuracy among different serologic celiac disease tests.

The results of the studies identified in the systematic literature review suggest that there is a trend towards a lower frequency of false positive results if the IgA tTG test using human recombinant substrate is used compared to the guinea pig substrate in subjects with chronic liver disease. However, the statistical significance of the difference was not reported in the studies. When IgA tTG with human recombinant substrate was used, the number of false positives seems to be similar to what was estimated in the MAS pooled analysis for IgA-based serologic tests in a general population of patients. These results should be interpreted with caution since most studies did not use the gold standard, small bowel biopsy, to confirm or exclude the diagnosis of celiac disease, and since the studies were not designed to compare the diagnostic accuracy among different serologic tests. The sensitivity of the different serologic tests in patients with chronic liver disease was not evaluated in the studies identified.

Effects of a Gluten-Free Diet (GFD) in Patients Diagnosed with Celiac Disease

Six studies identified evaluated the effects of GFD on clinical, histological, or serologic improvement in patients diagnosed with celiac disease. Improvement was observed in 51% to 95% of the patients included in the studies.

Grading of Evidence

Overall, the quality of the evidence ranged from moderate to very low depending on the serologic celiac disease test. Reasons to downgrade the quality of the evidence included the use of a surrogate endpoint (diagnostic accuracy) since none of the studies evaluated clinical outcomes, inconsistencies among study results, imprecise estimates, and sparse data. The quality of the evidence was considered moderate for IgA tTg and IgA EMA, low for IgA DGP, and serologic test combinations, and very low for IgA AGA.

Clinical Validity and Clinical Utility of Serologic Testing in the Diagnosis of Celiac Disease

The clinical validity of serologic tests in the diagnosis of celiac disease was considered high in subjects with symptoms consistent with this disease due to

- High accuracy of some serologic tests.
- Serologic tests detect possible celiac disease cases and avoid unnecessary small bowel biopsy if the test result is negative, unless an endoscopy/ small bowel biopsy is necessary due to the clinical presentation.
- Serologic tests support the results of small bowel biopsy.

The clinical utility of serologic tests for the diagnosis of celiac disease, as defined by its impact in decision making was also considered high in subjects with symptoms consistent with this disease given the considerations listed above and since celiac disease diagnosis leads to treatment with a gluten-free diet.

Economic Analysis

A decision analysis was constructed to compare costs and outcomes between the tests based on the sensitivity, specificity and prevalence summary estimates from the MAS Evidence-Based Analysis (EBA). A budget impact was then calculated by multiplying the expected costs and volumes in Ontario. The outcome of the analysis was expected costs and false negatives (FN). Costs were reported in 2010 CAD$. All analyses were performed using TreeAge Pro Suite 2009.

Four strategies made up the efficiency frontier; IgG tTG, IgA tTG, EMA and small bowel biopsy. All other strategies were dominated. IgG tTG was the least costly and least effective strategy ($178.95, FN avoided=0). Small bowel biopsy was the most costly and most effective strategy ($396.60, FN avoided =0.1553). The cost per FN avoided were $293, $369, $1,401 for EMA, IgATTG and small bowel biopsy respectively. One-way sensitivity analyses did not change the ranking of strategies.

All testing strategies with small bowel biopsy are cheaper than biopsy alone however they also result in more FNs. The most cost-effective strategy will depend on the decision makers' willingness to pay. Findings suggest that IgA tTG was the most cost-effective and feasible strategy based on its Incremental Cost-Effectiveness Ratio (ICER) and convenience to conduct the test.
The potential impact of IgA tTG test in the province of Ontario would be $10.4M, $11.0M and $11.7M respectively in the following three years based on past volumes and trends in the province and basecase expected costs.

The panel of tests is the commonly used strategy in the province of Ontario therefore the impact to the system would be $13.6M, $14.5M and $15.3M respectively in the next three years based on past volumes and trends in the province and basecase expected costs.

Conclusions

- The clinical validity and clinical utility of serologic tests for celiac disease was considered high in subjects with symptoms consistent with this disease as they aid in the diagnosis of celiac disease and some tests present a high accuracy.
- The study findings suggest that IgA tTG is the most accurate and the most cost-effective test.
- AGA test (IgA) has a lower accuracy compared to other IgA-based tests

- Serologic test combinations appear to be more costly with little gain in accuracy. In addition there may be problems with generalizability of the results of the studies included in this review if different test combinations are used in clinical practice.
- IgA deficiency seems to be uncommon in patients diagnosed with celiac disease.
- The generalizability of study results is contingent on performing both the serologic test and small bowel biopsy in subjects on a gluten-containing diet as was the case in the studies identified, since the avoidance of gluten may affect test results.

Background

Objective of Analysis

The objective of this evidence-based evaluation is to assess the accuracy of serologic tests in the diagnosis of celiac disease in subjects with symptoms consistent with this disease. Furthermore the impact of these tests in the diagnostic pathway of the disease and decision making was also evaluated.

Clinical Need and Target Population

Celiac Disease

Celiac disease is an autoimmune disease characterized by a chronic inflammatory state of the proximal small bowel mucosa accompanied by structural and functional changes. (1) This results in impaired digestion and absorption of nutrients. (2) Almost all patients with celiac disease carry the HLA class II heterodimer HLA-DQ2 or HLA-DQ8 whereas 25% to 40% in the general population are carriers. (2) The immunological response is triggered by the ingestion of gluten, a protein that is present in wheat, rye, and barley. (1) Treatment consists of strict lifelong adherence to a gluten-free diet (GFD). (1) Symptoms improve with a GFD but recur when gluten-containing foods are restarted. (2)

Celiac disease can have different presentations:

- Classic: patients present with gastrointestinal symptoms and the classic features of intestinal malabsorption with fully developed gluten-induced villous atrophy and other classic histologic features. (3)
- Atypical: patients present with little or no gastrointestinal symptoms. Presenting symptoms include iron deficiency anemia among others. Fully developed gluten-induced villous atrophy is present. (3)
- Silent: patients do not present clear gastrointestinal or atypical symptoms but present gluten-induced villous atrophy. (3)
- Latent: patients with a previous diagnosis of celiac disease that responded to a GFD and a normal small bowel mucosa. It may also include subjects with normal small bowel mucosa on ingestion of gluten but who may later develop celiac disease. (3)
- Refractory: patients diagnosed with celiac disease who either do not or stopped responding to a GFD. This may be due to either lack of compliance with the diet or inadvertent consumption of gluten, however refractory celiac disease can occur in patients who develop ulcerative-jejunoileitis or enteropathy-associated T-cell lymphoma. (3)

Subjects with some autoimmune disorders may have an increased risk for celiac disease as explained by shared HLA DQ2/DQ8 susceptibility genes, which is the case with type 1 diabetes and autoimmune thyroid disease. (2) On the other hand, in autoimmune disorders in which DQ2/DQ8 do not act as a susceptibility gene or whose prevalence of DQ2/DQ8 is not higher than the general population, it is less clear if there is an increased risk of celiac disease. (2) First degree relatives of subjects with celiac disease may also have an increased risk of celiac disease. (2)

Dermatitis herpetiformis, a skin manifestation of celiac disease, (4) is an inflammatory cutaneous disease (5) characterized by a blistering rash. (6) Patients with dermatitis herpetiformis may have concomitant small bowel mucosa abnormalities characteristic of celiac disease. (4) Both the rash and the small bowel mucosa abnormalities improve on a gluten-free diet. (4;5)

Gluten-Free Diet

Following a gluten-free diet (GFD) consists of avoiding foods that contain wheat, barley, and rye. (7)

The small bowel mucosa abnormalities and symptoms characteristic of celiac disease improve with GFD. (8) Clinical improvement may start to be seen within weeks of starting the GFD, however, histologic recovery may take months to years, especially in adults. (1) Reasons for lack of response to GFD are often due to non-adherence or due to inadvertent consumption of gluten, (1;2;9) however it can also be due to incompletely healed celiac disease, an associated condition, a complication, or another unrelated diagnosis. (9)

Celiac Disease Diagnosis Guidelines

According to celiac disease guidelines, the diagnosis of celiac disease is established by small bowel biopsy. (4;9;10) Serologic tests are used to initially detect and to support the presence of celiac disease. (2;4;9;10) Different serologic tests for celiac disease are available, anti-gliadin antibody (AGA), anti-endomysial antibody (EMA), anti-tissue transglutaminase antibody (tTG), and anti-deamidated gliadin peptides antibodies (DGP). (11) A small bowel biopsy is indicated in individuals with a positive serologic test. (12) In some cases, an endoscopy and small bowel biopsy may be necessary even with a negative serologic test depending to the clinical presentation (1;13) since this could be due to factors such as a false negative result or IgA deficiency. (12)

The diagnosis of celiac disease is confirmed by the presence of characteristic villous morphology abnormalities in the small bowel mucosa through a histological evaluation of small bowel biopsy specimens. (2;10) Small bowel mucosa abnormalities are classified according to the Marsh criteria (14-16) summarized in table 1. Presence of Marsh grade 3 abnormalitiy on small bowel biopsy is considered a positive diagnosis for celiac disease. (2) Nevertheless some subjects may present with less pronounced abnormalities such as changes in crypt lengthening with an increase in intraepithelial lymphocytes, or simply an increase in intraepithelial lymphocytes. (2) Due to the patchy nature of the mucosal lesions, the guidelines recommend that four to six small bowel biopsy specimens be taken from the distal duodenum part of the small bowel. (2;4;10) The biopsy specimens need to be well oriented and of adequate size (2;10). Failure to follow these guidelines may affect the interpretation of the results. (2) Ideally the small bowel biopsy specimens need to be examined by a pathologist who is experienced with the mucosal changes characteristic of celiac disease. (2)

The diagnosis of celiac disease must be performed on a gluten-containing diet since the small bowel abnormalities and the serologic antibody levels may resolve or improve on a GFD. (2) Consequently, serologic celiac disease testing should not be performed in infants if gluten has not been introduced in the diet. (11) In individuals who haven't consumed gluten regularly, a gluten challenge is necessary before serologic testing and small bowel biopsy are done. (2;13) Additionally, the use of medications such as immunosuppressants and corticosteroids may also interfere with the small bowel biopsy results. (2)

IgA measurement is the standard for the serologic celiac disease tests, however in individuals with both celiac disease and IgA deficiency, antibody levels cannot be accurately detected. (2) According to the guidelines of the American Gastroenterological Association, although patients with celiac disease have a 10 to 15-fold higher prevalence of IgA deficiency compared to the general population, it is still relatively low, 1.7% to 3.0%, and does not justify upfront testing for total serum IgA levels concomitant with serologic tests unless there is a strong indication of IgA deficiency. (2) On the other hand the their guidelines stipulate that total serum IgA may be measured if there is a suspicion of celiac disease but the result of the serologic test was negative (IgA tTG or IgA EMA). (2) Table 2 provides information on the recommendations from other celiac disease guidelines on addressing IgA deficiency. A review of IgA

EMA test results performed between March 2003 and July 2004 in laboratories in Calgary showed that 35/4,698 (0.75%) patients tested for both celiac disease and total serum IgA levels had IgA deficiency. (17) Nineteen out of thirty-five (54%) patients diagnosed with IgA deficiency were appropriately diagnosed with either small bowel biopsy or an IgG-based serologic test. (17)

Table 1: Marsh Criteria for the Histological Diagnosis of Celiac Disease on Small Bowel Biopsy

Marsh grade	Characteristics
Marsh grade 0	Normal duodenal mucosa and villous architecture
Marsh grade 1	Infiltrative Normal mucosa and villous architecture Increased numbers of intraepithelial lymphocytes
Marsh grade 2	Hyperplastic Similar to Marsh grade 1, additionaly, with enlarged crypts and increased crypt cell division.
Marsh grade 3	Presence of a raised intraepithelial lymphocyte count and different levels crypt hyperplasia according to subgrade (a, b, or c) - Grade 3a: partial villous atrophy - Grade 3b: subtotal villous atrophy - Grade 3c: total villous atrophy
Marsh grade 4	Hypoplastic Total villous atrophy Normal crypt depth, but hypoplasia Normal intraepithelial lymphocyte count It is believed to represent severe malnutrition

Based on the American Gastroenterological Association Review on the Diagnosis and Management of Celiac Disease. (2)

Table 2: Celiac Disease Guidelines – IgA Deficiency Considerations

Guidelines	NASPGHAN, 2006 (4) Pediatrics	NICE Guidelines, 2009 (11) Adults and children	American Gastroenterological Association Institute Technical Review on the Diagnosis and Management of Celiac Disease, 2006 (2)
IgA deficiency considerations	Total serum IgA measurement should be considered: ▪ In patients with symptoms consistent with celiac disease. If IgA deficient and strong suggestive symptoms are present, small bowel biopsy should be performed. If IgA deficient and low suspicion of celiac disease, an IgG-based serologic test is recommended to identify those who require small bowel biopsy.	Total serum IgA measurement if ▪ Low optical density or very low IgA tTG results or ▪ Low background on IgA EMA test result. IgG tTG or EMA should be measured if known IgA deficiency.	Total serum IgA measurement if: ▪ There is strong indication of IgA deficiency or ▪ Suspicion of celiac disease but negative serologic test results. If suspicion of celiac disease is strong but with negative serologic test results, a disease-associated HLA alleles test may be performed. If positive, a small bowel biopsy should be performed. As an alternative, endoscopy with small bowel biopsy can be performed if the signs and symptoms suggestive of celiac disease justify these procedures.

EMA refers to endomysial antibody; FTT failure to thrive; GFD gluten-free diet;GI gastrointestinal; IgA immuneglobulin A; IgG immuneglobulin G; IBS irritable bowel syndrome; IDA iron-deficiency anemia; GI gastrointestinal; NASPGHAN North American Society of Pediatric Gastroenterology and Nutrition; NICE National Institute for Health and Clinical Excellence; NIH National Institutes of Health; tTG tissue transglutaminase

Incidence and Prevalence of Celiac Disease

Incidence of Celiac Disease

A systematic review published in 2004 by the Agency for Healthcare Research and Quality (AHRQ) evaluated the incidence of celiac disease in the general population. (3) Crude incidence was defined as the number of new cases per 100,000 population at risk. The authors found a higher risk of developing celiac disease in younger children than in older children or adults. (3) Table 3 summarizes the results of these studies.

Table 3: Incidence of Celiac Disease [AHRQ Systematic review (3)].

Age group	Number of studies	Crude Incidence per 100,000/yr, Range
Adults or mixed population	6	1.0-17.2
Children overall	7	2.2 – 51.0
Children excluding specific results for 0-5 yrs	7	2.2-16.0
Children, age stratified	1	0-2 yrs: 51.0 2-5 yrs: 33.0 5-15 yrs: 10.0
	1	0-4 yrs: 42.0 0-14 yrs: 6.9-16.0

Source: Agency for Healthcare Research and Quality (AHRQ) (3)

Prevalence of Celiac Disease

The 2004 AHRQ systematic review (3) and the systematic review published in 2009 by the National Institute for Health and Clinical Excellence (NICE) (11)evaluated the prevalence of celiac disease in the general population, in subjects with symptoms consistent with celiac disease, and in individuals with a higher risk of developing celiac disease such as subjects with type 1 diabetes and family members of celiac disease patients. In addition, the 2009 NICE review evaluated the prevalence of celiac disease in other higher risk groups such as those with autoimmune thyroid disease. (11) The 2004 AHRQ review also evaluated the prevalence of celiac disease in subjects with suspected celiac disease. (3)

The prevalence of celiac disease in the general population, in family members of patients with celiac disease, and in subjects at high risk for celiac disease as explained by shared HLA DQ2/DQ8 susceptibility genes, i.e., type 1 diabetes and autoimmune thyroid disease, as reported in these systematic reviews is summarized below. The prevalence of celiac disease was assessed by serologic tests in all studies, however, only the studies that used small bowel biopsy to confirm the diagnosis were included in this report.

General Population

The prevalence of celiac disease in the studies varied between 0.14% and 1.87%. (3) A pooled estimate was not calculated due to concerns with heterogeneity across studies, however the median prevalence reported across the studies was 0.47% [interquartile range (IQR) 0.25%, 0.71%]. (3) According to the authors of the 2004 AHRQ review the prevalence did not vary by age group, i.e., adults and children. (3)

High Risk Subjects

The prevalence of celiac disease in high risk individuals such as type 1 diabetes, first degree relatives of patients with celiac disease, and patients with autoimmune thyroid disease is summarized in table 4.

Table 4: Prevalence of Celiac Disease in High Risk Subjects.

Subgroup	Number of studies	Median Prevalence Across Studies (IQR: 25th , 75th percentiles)	Range
Type 1 diabetes (adults and children)	31 studies (3;11)	4.3% (2.3, 6.2)	1 to 11%
First degree relatives of subjects with celiac disease¶	9 studies* (3;11)	8.7% (IQR 5.5, 11.5)	2.0% to 20.0%
Autoimmune thyroid disease	2 studies (11)	N/A	2.9% and 3.29%

IQR interquartile range

* Only studies where celiac disease diagnosis was confirmed by small bowel biopsy were included. Studies in which some degree of villous atrophy in the small bowel biopsy was not used as a criterion for diagnosis were excluded.

¶ . Five studies that reported the prevalence of celiac disease in second-degree relatives of celiac patients were identified one review, (3) however since none of the studies used small bowel biopsy to confirm the diagnosis, these studies were not included in this report.

Individuals with Symptoms Consistent with Celiac Disease

The AHRQ systematic review identified 13 studies that evaluated the prevalence of celiac disease in adults and children with symptoms consistent with celiac disease. (3) Symptoms reported include anemia, persistent iron deficiency, chronic intermittent diarrhea, abdominal pain, constipation, severe malabsorption, tiredness and weight loss, mineral metabolism deficiencies, and failure to thrive in children. (3)

The prevalence reported varied widely among studies, i.e., 1.5% to 50% among 5 adult/mixed adult and pediatrics studies, and 1.1% to 17% among 9 pediatric studies. (3) Differences in prevalence may be related to the referral pattern as the authors of the review noted that the prevalence tended to be higher in studies whose population originated from tertiary referral centres compared to general practice, i.e., 11.6% to 50% and 1.5%, respectively in adults. (3)

Technology under Review

Serologic Tests for Celiac Disease

There are a number of serologic tests for celiac disease available (table 5). Serologic tests are automated with the exception of the anti-endomysial antibody test, which is more time-consuming and operator-dependent than the other tests. (2;4)

For each serologic test, both immunoglobulin A (IgA) or G (IgG) can be measured, however, IgA measurement is the standard antibody measured in celiac disease. (2)

Table 5: Types of Serologic Celiac Disease Tests.

Serologic test	Type of assay
Anti-gliadin antibody (AGA) IgA and IgG	ELISA (automated)
Anti-endomysial antibody (EMA) IgA and IgG	Indirect immunofluorescence (not automated)
Anti- tissue transglutaminase antibody (tTG) IgA and IgG	ELISA (automated)
Anti-deamidated gliadin peptides antibodies (DGP)	ELISA (automated)

ELISA refers to enzyme-linked immunosorbent assay.

Regulatory Status

Diagnostic kits for the serologic tests for celiac disease listed in table 5 have been licenced by Health Canada. (19)

Ontario Context

Serologic tests for celiac disease are available in both community and hospital laboratories. The volumes of serologic celiac disease tests performed in Ontario in the past 6 years are provided in table 6.

Table 6. Volumes of Serologic Tests for Celiac Disease in Ontario.

Setting/Year	2004	2005	2006	2007	2008	2009
Community Laboratories						
IgA AGA	-	-	-	-	-	3,310
IgG AGA	-	-	-	-	-	3,052
tTG	-	-	-	-	-	10,002
Hospital Laboratories						
EMA	1,068	344	4,081	4,153	4,288	4,597
IgA AGA	246	25,114	30,266	35,460	35,230	32,058
IgG AGA	246	25,108	30,248	35,474	35,224	32,214
tTG	883	20,510	27,442	38,278	37,255	32,806

AGA anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;
Data Source: Ontario Assocition of Medical Laboratories - accessed March 2010

Evidence-Based Analysis

Research Questions

1. What is the sensitivity and specificity of serologic tests in the diagnosis celiac disease?
2. What is the clinical validity of serologic tests in the diagnosis of celiac disease? The clinical validity was defined as the ability of the test to change diagnosis.
3. What is the clinical utility of serologic tests in the diagnosis of celiac disease? The clinical utility was defined as the impact of the test on decision making.
4. What is the budget impact of serologic tests in the diagnosis of celiac disease?
5. What is the cost-effectiveness of serologic tests in the diagnosis of celiac disease?

Research Methods

Literature Search

A literature search was performed on November 13th 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2003 to November 13th 2010.

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. The reference list of systematic reviews identified through the systematic literature search was also examined for any additional relevant studies; these studies were included if they met the eligibility criteria described below. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

- Studies that evaluated diagnostic accuracy, i.e., both sensitivity and specificity of serologic tests in the diagnosis of celiac disease.
- Study population consisted of untreated patients with symptoms consistent with celiac disease.
- Studies in which both the serologic test evaluated and small bowel biopsy (gold standard) were performed in all subjects.
- Systematic reviews, meta-analyses, randomized controlled trials, prospective observational or retrospective cohort studies.
- At least 20 patients included in the celiac disease group.
- English language.
- Human studies.
- Studies published from 2000 on.
- Clearly defined cut-off value for the serology test. If more than one test was evaluated, only those tests for which a cut-off was provided were included.
- Description of small bowel biopsy procedure clearly outlined (location and number of biopsies per patient), unless it was specified that celiac disease diagnosis guidelines such as ESPGAN, (10) American Gastroenterological Association, (2) or the guidelines by Oberhuber et al. (16) were followed.

Exclusion Criteria

- Studies on screening of the general asymptomatic population.
- Studies that evaluated rapid diagnostic kits for use either at home or in physician's offices.
- Studies that evaluated diagnostic modalities other than serologic tests such as capsule endoscopy, push enteroscopy, or genetic testing.
- Cut-off for serologic tests either not defined or based on controls included in the study.
- Study population defined based on positive celiac disease serology or subjects pre-screened by serologic celiac disease tests.
- Known celiac disease status before enrolment.
- Sensitivity or specificity based on repeated testing for the same subject.
- Non-peer-reviewed literature such as editorials, letters to the editor.

Population

The population consisted of adults and children with untreated, undiagnosed celiac disease with symptoms consistent with the disease.

Serologic tests evaluated

- Anti-gliadin antibody (AGA)
- Anti-endomysial antibody (EMA)
- Anti-tissue transglutaminase antibody (tTG)
- Anti-deamidated gliadin peptides antibody (DGP)
- Combinations of some of the serologic tests listed above were evaluated in some of the studies

Both IgA and IgG antibodies were evaluated.

Outcomes of Interest

- Sensitivity
- Specificity
- Positive and negative likelihood ratios
- Diagnostic odds ratio (OR)
- Area under the sROC curve (AUC)

Small bowel biopsy was used as the gold standard in order to estimate the sensitivity and specificity of each serologic test.

Statistical Analysis

Pooled estimates of sensitivity, specificity and diagnostic odds ratios (DORs) for each different serologic test for celiac disease were calculated using a bivariate, binomial generalized linear mixed model. Statistical significance for the differences in sensitivity and specificity between serologic celiac disease tests was defined by P values less than 0.05, where "false discovery rate" adjustments were made for multiple hypothesis testing. The bivariate regression analyses were performed using SAS version 9.2 (SAS Institute Inc.; Cary, NC, USA). Using the bivariate model parameters, summary receiver operating characteristic (sROC) curves were produced using Review Manager 5.0.22 (The Nordiac Cochrane Centre, The Cochrane Collaboration, 2008). The area under the sROC curve (AUC) was estimated by

bivariate mixed-efects binary regression modeling framework. Model specification, estimation and prediction are carried out with xtmelogit in Stata release 10 (Statacorp, 2007). Statistical tests for the differences in AUC results obtained could not be carried out. The sROC curves were produced using Review Manager 5.0.22 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) using parameters obtained from the bivariate model.

In cases where more than one cut-off was used for the serologic celiac disease test, the cut-off suggested by the manufacturer was used to calculate the pooled estimate.

The study results were stratified according to patient or disease characteristics such as age, severity of Marsh grade abnormalities, among others, if reported in the studies. The literature indicates that the diagnostic accuracy of serologic tests for celiac disease may be affected in patients with chronic liver disease, therefore, the studies identified through the systematic literature review that evaluated the diagnostic accuracy of serologic tests for celiac disease in patients with chronic liver disease were summarized. The effect of the GFD in patiens diagnosed with celiac disease was also summarized if reported in the studies eligible for the analysis.

The sensitivity and specificity of the serologic tests were calculated according to the formulas described below where TP refers to true positives, TN true negatives, FP false positives, and FN false negatives.

$$\text{Sensitivity} = \frac{\text{TP}}{(\text{TP} + \text{FN})} \qquad \text{Specificity} = \frac{\text{TN}}{(\text{TN} + \text{FP})}$$

The positive and negative likelihood ratios were calculated according to the formulas below:

$$\text{Positive Likelihood Ratio} = \frac{Sensivity}{(1 - specificity)} \qquad \text{Negative Likelihood Ratio} = \frac{(1 - sensitivity)}{specificity}$$

The likelihood ratios of each serologic test were evaluated using the following guidelines:

- Positive LRs greater than ten and negative LRs less than 0.1 generate large, and often conclusive changes from pre- to post-test probability (very useful test). (20;21)
- Positive LRs between five and ten and negative LRs between 0.1 and 0.2 generate moderate shifts from pre- to post-test probability (moderately useful test). (20;21)
- Positive LRs between two and five and negative LRs between 0.2 and 0.5 generate small but sometimes important changes from pre- to post-test probability (somewhat useful test). (20;21)
- Positive LRs between one and two and negative likelihood ratios between 0.5 and one alter pre- to post-test probability to a small and rarely important degree (not useful test). (20;21)

The diagnostic odds ratio was calculated according to the formula below. It combines the measures of sensitivity, specificity, positive and negative likelihood ratios. It provides the ratio of the odds of a positive test in a subject with the disease compared to a subject without disease.

$$\text{Diagnostic Odds Ratio} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{FN} + \text{FP} + \text{TN}}$$

Quality of Evidence

The quality of evidence assigned to individual studies was determined using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. (22) The quality of systematic reviews was evaluated according to the AMSTAR tool. (23) The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (24;25) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

Five systematic reviews of studies that evaluated the diagnostic accuracy of serologic celiac disease tests were identified through our literature search. (3;11;26-28) Seventeen individual studies identified either through our systematic literature search or by examining the reference list of systematic reviews met the eligibility criteria for this evaluation. (29-45) Table 7 provides a list of the studies according to study design and the level of evidence.

Table 7: Quality of Evidence of Included Studies

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	17
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modelling	4d	0
Case series presented at international conference	4(g)	0
	Total	17

Source: Goodman. (46)
RCT refers to randomized controlled trial;

Results of Published Systematic Reviews

Five systematic reviews evaluated the use of one or more serologic tests in the diagnosis of celiac disease were identified through the literature search. (3;11;26-28) One of the reviews was published in 2009, (11) the others were published between 2004 and 2006. (3;26-28)

In general, the studies included in the systematic reviews evaluated the sensitivity and specificity of at least one serologic celiac disease test or combination of serologic tests in subjects with symptoms consistent with celiac disease. The gold standard used to confirm the celiac disease diagnosis was small bowel biopsy. The systematic reviews evaluated different serologic tests such as tTG, EMA, and AGA using either IgA or IgG antibodies. Only the most recent systematic review included IgA and IgG DGP. Details in Appendix 2.

Three systematic reviews provided a pooled estimate of sensitivity and specificity of individual serologic tests, (3;26;28) the remaining two provided a qualitative summary of the results of the studies included. (11;27) Two systematic reviews had a relatively high quality, i.e., satisfied most of the AMSTAR quality criteria, (3;28) the three remaining systematic reviews satisfied some of the AMSTAR criteria, (11;26;27) however, this may be due to the difficulties in including a detailed description of the methods used in the publication.

The results of the systematic reviews are provided in Appendix 3.

The main conclusions of the systematic reviews are summarized below, additional details in table 8.

- IgA tTG and/or IgA EMA have a high accuracy (pooled sensitivity: 90% to 98%, pooled specificity: 95% to 99% depending on the pooled analysis, Appendix 3).
- Most reviews found that AGA (IgA or IgG) are not as accurate as IgA tTG and/or EMA tests.
- The authors of one review concluded that if the pretest probability (prevalence) is low (< 25%), the human recombinant IgA tTG is the preferred test. (26) If, however, the pretest probability is >25% a small bowel biopsy is preferred as it would still be required even with a negative serologic celiac disease test. (26)
- The systematic review published in 2009 concluded that DGP (IgA or IgG) seems to have a similar accuracy compared to IgA tTG, however, since only 2 studies that evaluated its accuracy were identified, the authors believe that additional data is required in order to draw conclusions. (11)
- Two systematic reviews also concluded that combining two serologic tests has little contribution to the accuracy of the diagnosis. (11;27)
- With regards to IgA deficiency, one review concluded that there are very few cases of concomitant celiac disease and IgA deficiency and that in symptomatic subjects known to have IgA deficiency small bowel biopsy should be performed directly to diagnose celiac disease. (27) The authors of another review concluded that IgA deficiency should be checked if there is a low optical density detected on the IgA tTG, very low IgA tTG results or low background on IgA EMA test. (11)
- One systematic review found limited evidence that IgA tTG may result in a higher number of false positives in individuals with liver disease than in the general population. (11) This is based on one study.

Table 8: Conclusions of Systematic Reviews on Serologic Testing in Suspected Celiac Disease

Systematic Review	Serologic test accuracy (single test)	Serologic test accuracy (combination of tests)	IgA deficiency
Lewis et al. 2006 (26)	▪ If pretest probability is low (< 25%), human recombinant IgA tTG was the preferred test. ▪ If pretest probability > 25% small bowel biopsy is preferred as it would still be required even with a negative test.	▪ Not assessed	▪ Not assessed
Zintzaras et al. 2006 (28)	▪ Human antigen tTG test is sensitive and specific.	▪ Not assessed	▪ Not assessed
Hill et al. 2005 (27)	▪ Findings show that IgA EMA and rh IgA tTG are the most sensitive and specific serologic tests. ▪ Small bowel biopsy should be considered in symptomatic subjects even if serologic test is negative. ▪ No difference in results of adults and children. ▪ The results were based in research setting studies. Results may differ in the clinical setting.	▪ No advantage to using a panel of tests compared to a single test.	▪ Very few cases of concomitant celiac disease and IgA deficiency based on IgG AGA results . ▪ In symptomatic subjects known to have IgA deficiency, small bowel biopsy should be performed directly to diagnose celiac disease.
Rostom et al. 2004 (3)	▪ EMA and TTG tests have high sensitivity and specificity. ▪ AGA seems to have a limited role if EMA and/or tTG are available.	▪ Not assessed	▪ Not assessed
NICE 2009 (11)	▪ IgA tTG should be the first choice test. Use IgA EMA if tTG results are equivocal. ▪ Results suggest lower accuracy for IgA AGA compared to the other serologic tests. ▪ 2 studies on DGP (IgA or IgG) tests showed that sensitivity and specificity are similar to IgA tTG, however further evaluation is needed. ▪ IgA AGA seemingly more accurate than IgG AGA. ▪ Sparse data for IgG tTG and IgG EMA did not permit conclusions to be drawn. ▪ Serologic tests showed comparable results in adults and children. ▪ The authors found limited evidence that IgA tTG may yield more false positive results in individuals with liver disease than in the general population. The conclusion was based on one study.	▪ Combination of IgA tTG and IgA EMA did not seem to improve the diagnostic accuracy.	▪ IgA deficiency should be checked if there is a low optical density detected on the IgA tTG test, very low IgA tTG results or low background on the IgA EMA test.

Gp refers to guinea-pig; AGA anti-gliadin antibody; EMA endomysial antibody; DGP deamidated gliadin peptides; IgA immunoglobulin A; IgG immunoglobulin G; NICE National Institute for Health and Clinical Excellence; Ph purifed human; Rh human recombinant; tTG tissue transglutaminase;

Study Results (MAS Analysis)

Since the most recent systematic review (2009) did not calculate a pooled estimate of the diagnostic accuracy of different serologic tests, it was decided to perform a pooled analysis of the individual studies. Eligible studies identified either through the systematic literature search or by examining the reference lists of the published systematic reviews were included.

Seventeen observational studies were eligible for this evaluation. (29-45) There were two studies in adults, (30;34) 11 studies in children, (31;32;35-42;44) and 4 in a mixed population of adults and children. (29;33;43;45) The studies evaluated the sensitivity and specificity of at least serologic celiac disease test or a combination of serologic tests in subjects with symptoms consistent with celiac disease. No eligible studies on IgG EMA were identified. Subjects included in the studies were on a gluten-containing diet.

Subjects included in the studies were those with suspected celiac disease based on the presence of symptoms consistent with the disease. Common symptoms described in the studies were gastrointestinal symptoms such as chronic diarrhea and abdominal pain, unexplained weight loss, unexplained anemia, and failure to thrive in children. Some studies also included a small number of subjects at high risk for celiac disease such as first degree relatives of celiac patients, and patients with type 1 diabetes mellitus. Different serologic celiac disease tests were evaluated in the studies (Table 9). An indirect immunofluorescence assay was used for EMA studies whereas enzyme-linked immunosorbent assay (ELISA) was used for the other serologic tests.

Table 9: Number of Eligible Studies Identified

Serologic Test	Number of studies
IgA anti-tissue transglutaminase antibody (tTG)	**15** (29-38;40-43;45)
IgA anti-gliadin antibody (AGA)	**6** (30;33;39;42;44;45)
IgA anti-deamidated gliadin peptides antibody (DGP)	**5** (34;38;40;41;45)
IgA anti-endomysial antibodies (EMA)	**4** (33;36;37;42)
IgG anti-tissue transglutaminase antibody (tTG)	**5** (35-37;40;45)
IgG anti-gliadin antibody (AGA)	**4** (30;33;42;45)
IgG anti-deamidated gliadin peptides antibody (DGP)	**5** (34;38;40;41;45)
Combination of serologic tests (more than one of the serologic tests listed above performed) ▪ Different combinations were used, the most common was IgA and IgG DGP ± IgA tTG. ▪ The results of test combinations can be interpreted differently, either by assuming a positive serology if at least 1 serologic test is positive or if all tests are positive	**7** (30;34;36;38;40;41;45)

Most studies used the manufacturer's suggested cut-off for each serologic test. The cut-off used for each serologic test varied across studies, possibly due to the use of different manufacturer's kits (Appendix 4). Some studies used more than one cut-off for the serologic test, in these cases, the cut-off suggested by the manufacturer was used to calculate the pooled estimate. Most studies that evaluated the accuracy of IgA tTG used human instead of guinea-pig substrate, and most EMA studies used primate esophagus antibodies (Appendix 4).

Serologic celiac disease tests were performed in all patients included in each study. Small bowel biopsy was performed in all patients as the gold standard to assess the sensitivity and specificity of the serologic tests.

The celiac disease diagnosis was based on the presence of Marsh 3 grade abnormalities or villous atrophy on small bowel biopsy in 8 studies, (29-31;34;42-45) 4 studies used a broader definition of celiac disease that also included Marsh 1 or 2 grade abnormailities. (32;35;36;38) In five studies, a response to GFD was also part of the celiac disease diagnosis. (29;31;34;43;44) The definition of response to GFD varied among these studies as some based it on clinical/symptom resolution while others used histological criteria. Five studies reported following ESPGAN or Marsh criteria for the diagnosis of celiac disease however further details were not provided. (33;37;39-41) One study included Marsh 4 grade abnormalities in the definition of celiac disease. (47) Since, according to Oberhuber et al. Marsh 4 grade abnormalities are not consistent with celiac disease, (16) it was decided to exclude this study from the analysis. In studies using Marsh grade abnormalities greater than 1 as a definition of celiac disease, if possible only patients with Marsh 3 grade abnormalities were included in the analysis. The non-diseased group consisted of subjects included in the studies who underwent both serologic test and small bowel biopsy but did not meet the criteria for diagnosis of celiac disease. In most studies, subjects with a normal small bowel biopsy or Marsh 0 on biopsy were defined as the non-diseased group, (31;33-45) however, some studies also included subjects with Marsh 1-2 grade. (29;30;32)

In eight studies the blood sample and the small bowel biopsy were collected on the same day. (30;32-34;36;38;41;43) A time lag between the serologic test and biopsy of < 1 month to up to 6 months was reported in 3 studies, (29;39;45) it was unclear in 6 studies. (31;35;37;40;42;44)

There was a low proportion of subjects with total or severe IgA deficiency in the studies identified, ranging between 0 and 1.7% as reported in 3 studies in which IgA deficiency was not used as a referral indication for celiac disease testing, (30;38;47) or 4.2% to 9.8% in studies where IgA deficiency was one of the indications for patient inclusion in the study. (33;35-37;40)

The quality of the studies was considered relatively high, as most studies satisfied most quality items of the QUADAS tool. (22) This may be partly due to the strict inclusion criteria used in our review. Additional details about study characteristics are provided in Appendix 4.

The pooled estimate of the sensitivity and specificity of each serologic test calculated according to a bivariate, binomial generalized linear mixed model is shown in table 10. Table 11 summarizes the likelihood ratio, diagnostic OR and AUC estimates for each test.

Sensitivity

The pooled analysis performed by MAS showed that IgA tTG has a trend to a higher sensitivity, 92.1% [95% confidence interval (CI) 88.0, 96.3], compared to the other serologic tests, i.e., 89.2% (83.3, 95.1, p=0.11) for IgA DGP, 85.1% (79.5, 94.4, p=0.07) for IgA EMA, 74.9% (63.6, 86.2, p=0.0003) for IgA AGA. However, a statistically significant difference was only observed when IgA tTG was compared to IgA AGA (table 10). The IgA AGA test had a lower sensitivity than all other IgA-based tests (table 10). Among the IgG-based tests, the results suggest that IgG DGP has a sensitivity of 88.4% (95% CI: 82.1, 94.6), 44.7% (30.3, 59.2) for tTG, and 69.1% (56.0, 82.2) for AGA. The difference was significant when DGP was compared to IgG tTG but not IgG AGA (table 10).

It was observed that the sensitivity of combinations of serologic tests was higher than the sensitivity of individual serologic tests if any positive result among the different tests included in the combination was interpreted as a positive serology (vs. IgA tTG: 3.0%, p .0381). Interpreting a positive serology if all tests used in the combination were positive resulted in a lower sensitivity (81.1%, 95% CI: 71.3, 90.8)

compared to other IgA-based tests, with the exception of IgA AGA (table 10). These results need to be interpreted with caution since different combinations of tests were used in the studies, i.e., IgA tTG + IgA EMA, IgA tTG + DGP IgA and IgG, DGP IgA + IgG, and because the results may not be generalizable if other serologic tests' combinations are used. A combination of IgA and IgG DGP tests ± IgA tTG was the most common combination (8 out of 10 studies).

IgA deficiency

The prevalence of total or severe IgA deficiency was low in the studies identified ranging between 0 and 1.7% as reported in 3 studies in which IgA deficiency was not used as a referral indication for celiac disease testing. (30;38;39) The prevalence of IgA deficiency ranged from 4.2% to 9.8% in studies where IgA deficiency was one of the indications for testing. (33;35-37;40) The results of IgG-based serologic tests were positive in all patients with IgA deficiency in which celiac disease was confirmed by small bowel biopsy as reported in four studies. (33;36;37;40)

Specificity

A high specificity was observed across the different serologic tests including the two combination strategies, pooled estimates ranging between 90.1% and 98.7% depending on the test. The pooled specificity estimate was similar among the different serologic tests including the combination strategy[b]. It was slightly higher when concordant[c] results of combinations of tests were used compared to individual tests or combination strategy (any positive test[d]), 98.7% (95% CI: 98.1, 99.3) (table 10).

Likelihood Ratios (LR)

According to the likelihood ratio estimates, both IgA tTG and serologic test combinations[e] were considered very useful tests, generating large and often conclusive changes from pre- to post test probability (positive LR > 10 and negative LR < 0.1).

Moderately useful tests included IgA EMA, IgA DGP, IgG DGP, and combination (concordant results), generating moderate shifts from pre- to post-test probability (positive LR between 5 and 10 and negative LR between 0.1 and 0.2).

Somewhat useful tests: IgA AGA, IgG AGA, generating small but sometimes important changes from pre- to post-test probability (positive LR between 2 and 5 and negative LR between 0.2 and 0.5)

Not Useful: IgG tTG, altering pre- to post-test probability to a small and rarely important degree (positive LR between 1 and 2 and negative LR between 0.5 and 1).

Additional information in table 11.

Diagnostic Odds Ratios (DOR)

The DOR combines the measures of sensitivity, specificity, positive and negative likelihood ratios. It provides the ratio of the odds of a positive test in a subject with the disease compared to a subject without disease.

[b] Interpreting a positive serology if any of the tests in the combination had a positive result.

[c] Interpreting a positive serology if all tests used in the combination were positive.

[d] Interpreting a positive serology if any of the tests in the combination had a positive result.

[e] Interpreting a positive serology if any of the tests in the combination had a positive result.

Among the individual serologic tests, IgA tTG had the highest DOR, 136.5 (95% CI: 51.9, 221.2). The serologic tests' combination (any positive result[f]) strategy had the highest DOR, i.e., 184.4 (95% CI: 58.5, 310.3), and combination (concordant results[g]), DOR 322.5 (95% CI 86.6, 558.3). The statistical significance of the difference in DORs among tests was not calculated, however, considering the wide confidence intervals obtained (table 11), the differences may not be statistically significant.

Table 10: Pooled Sensitivity and Specificity - Study Results

Serologic test	Pooled Sensitivity (95% CI)	Difference between tests – Sensitivity (p value)	Pooled Specificity (95% CI)	Difference between tests - Specificity (p value)
IgA-based Serologic Tests				
IgA tTG	92.1% (88.0, 96.3)	vs. IgA DGP: +3.0% (p .1160) vs. IgA EMA: +7.0% (p .0688) **vs. IgA AGA: +17.2% (p .0003)** **vs. Comb (any*): -3.0% (p .0381)** **vs. Comb (all¦): +11.1% (p.0038)**	92.1% (89.1, 95.1)	vs. IgA DGP: -0.4% (p .7989) vs. gA EMA: -1.8% (p .3379) vs. IgA AGA: +2.0% (p .0986) vs. Comb (any*): +1.6% (p .1563) **vs. Comb (all¦): -6.6% (p.0018)**
IgA DGP	89.2% (83.3, 95.1)	vs. IgA EMA: +4.1% (p .2948) **vs. IgA AGA: +14.3% (p .0006)** **vs. Comb (any*): -5.9% (p .0079)** **vs. Comb (all¦): +8.2% (p.020)**	92.5% (88.5, 96.5)	vs. IgA EMA: -1.4% (p .6696) vs. IgA AGA: 2.4% (p .3379) vs. Comb (any*): +2.0% (p .3750) **vs. Comb (all¦): -6.2% (p .020)**
IgA EMA	85.1% (75.9, 94.4)	**vs. IgA AGA: +14.3% (p .0006)** **vs. Comb (any*): -10.0% (p .0192)** vs. Comb (all¦): +4.1% (p.355)	93.9% (90.6, 97.2)	vs. IgA AGA: +2.4% (p .3379) vs. Comb (any*): +3.4% (p .0987) **vs. Comb (all¦): -4.8% (p.0108)**
IgA AGA	74.9% (63.6, 86.2)	**vs. Comb (any*): -20.2% (p .0003)** vs. Comb (all¦): -6.2% (p.1063)	90.1% (86.3, 93.9)	vs. Comb (any*): -0.3% (p .7204) **vs. Comb (all¦): -8.6% (p .0007)**
Combination of serologic tests(any test positive*)	95.1% (92.2, 98%)	**vs. Comb (all¦): +14.02% (p.0011)**	90.5% (86.8, 94.2)	**vs. Comb (all¦): -8.2% (p.016)**
Combination of serologic tests (concordant results¦)	81.1% (71.3, 90.8)	As above	98.7% (98.1, 99.3)	As above
IgG-based Serologic Tests				
IgG DGP	88.4% (82.1, 94.6)	vs. IgG AGA: +19.2% (p .3379) **vs. IgG tTG: +43.6% (p .0003)**	95.2% (92.3, 98.1)	vs. IgG AGA: +0.7% (p .7333) vs. IgG tTG: +1.2% (p .6696)
IgG AGA	69.1% (56.0, 82.2)	As above	94.6% (92.4, 96.9)	As above
IgG tTG	44.7% (30.3, 59.2)	**vs. IgG AGA: -24.4% (p .0003)**	94.0% (90.6, 97.5)	vs. IgG AGA: -0.6% (p .7492)

CI refers to confidence interval; AGA anti-gliadin antibody; Comb combination; EMA endomysial antibody; DGP deamidated gliadin peptides; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;
* Interpreting a positive serology if any of the tests in the combination had a positive result.
¦ Interpreting a positive serology if all tests used in the combination were positive.

[f] Interpreting a positive serology if any of the tests in the combination had a positive result.

[g] Interpreting a positive serology if all tests used in the combination were positive.

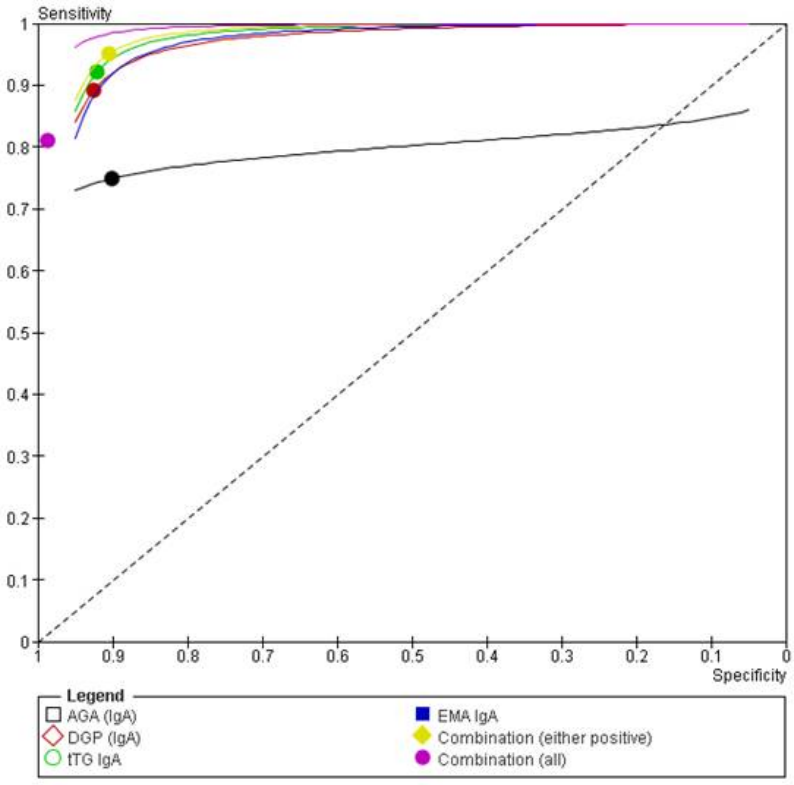
Table 11: Diagnostic Accuracy of Serologic Tests - Study Results

Serologic test	Positive Likelihood Ratio	Negative Likelihood Ratio	Diagnostic OR (95% CI)	AUC (95% CI)
IgA tTG	11.75	0.07	136.5 (51.9, 221.2)	0.98 (0.97, 0.99)
IgA AGA	7.57	0.28	27.1 (9.4, 44.9)	0.89 (0.86, 0.91)
IgA EMA	13.95	0.16	88.2 (11.2, 164.5)	0.93 (0.90, 0.95)
IgA DGP	11.90	0.12	101.8 (23.7, 180.0)	0.94 (0.92, 0.96)
IgG DGP	18.42	0.12	151.4 (28.3, 274.6)	0.98 (0.96, 0.99)
IgG AGA	12.80	0.33	39.4 (12.7, 66.0)	0.85 (0.81, 0.88)
IgG tTG	7.51	0.59	12.8 (2.8, 22.8)	0.90 (0.87, 0.92)
Combination of tests, any test positive	10.01	0.05	184.4 (58.5, 310.3)	0.97 (0.95, 0.98)
Combination (concordant results)	62.4	0.19	322.5 (86.6, 558.3)	0.99 (0.97, 0.99)

AUC refers to area under the curve; CI confidence interval; AGA anti-gliadin antibody; EMA endomysial antibody; DGP deamidated gliadin peptides; IgA immunoglobulin A; IgG immunoglobulin G; OR odds ratio; tTG tissue transglutaminase;

Area Under the sROC Curve (AUC)

Figure 1 provides the summary receiver operating characteristics (sROC) curves for the IgA-based tests. The sROC AUCs estimated ranged between 0.93 and 0.99 for most IgA-based tests and the two combinations (table 10). The AUC for IgA AGA was 0.89 (95% CI: 0.86, 0.91). Statistical tests for the differences in results obtained could not be carried out.



AUC refers to area under the curve; CI confidence interval; AGA anti-gliadin antibody; EMA endomysial antibody; DGP deamidated gliadin peptides; IgA immunoglobulin A; IgG immunoglobulin G; OR odds ratio; tTG tissue transglutaminase;

Figure 1: sROC Curve for IgA-based Tests and Serologic Test Combinations

Sensitivity and Specificity of Serologic Tests According to Age Groups

The accuracy of serologic celiac disease tests was similar among adults and pediatric studies (Appendix 5).

Four studies reported the sensitivity and specificity of IgA tTG and IgA DGP serologic tests in children of different ages. (31;32;38;41) The sensitivity and specificity of these serologic tests appeared to be similar in younger and older children (Table 12). In one study there was a trend towards a lower sensitivity of both IgA DGP and IgA tTG in children ≤ 5 years old compared to older children, however the statistical significance of the difference was not reported in the study. (41)

Table 12: Sensitivity and Specificity of Serologic Tests In Children of Different Age Groups

Study	Serologic test	Sensitivity (%)	Specificity (%)
Poddar et al. (2008) (31) Children	IgA tTG Overall (N=306) ≤ 2 years (N=12)	 94% 100%	 97% NR
Barker et al. (2005) (32) Children	IgA tTG (≥ 20 U/ml) Overall (N=103) < 2years (n=6)	 94.8% 100%*	 77.8% 100%
Basso et al. (2009) (38)	IgA tTG Overall (N=290) ≤ 2 years (N=N/A) 2-4 yrs (N=N/A) 4-10 yrs (N=N/A) > 10 years (N=N/A)	 92.5% 96.4%¶ 97.0% 97.0% 81.3% Differences among age groups was not statistically significant	 97.6% 100% 100% 97.9% 96.3% Differences among age groups was not statistically significant
Basso et al. (2009) (38) Children	IgA DGP Overall (N=290) ≤ 2 years (N=N/A) 2-4 yrs (N=N/A) 4-10 yrs (N=N/A) > 10 years (N=N/A)	 80.7% 85.7%¶ 87.9% 84.8% 65.6% Differences among age groups not statistically significant	 92.9% 93.8% 100% 93.6% 90.7% Differences among age groups not statistically significant
Leach et al. (2008) (41) Children	IgA tTG Overall (N=76) 0-5 years (n=7)	 93.3% 85.7%	 90.9% 92.3%
Leach et al. (2008) (41) Children	IgA DGP Overall (N=76) 0-5 years (n=7)	 83.3% 57.1%	 91.5% 100%

DGP refers to deamidated gliadin peptides; IgA immunoglobulin A; tTG tissue transglutaminase.
* Excludes 1 false negative in an IgA deficient subject.
¶ 2 out of 3 children with celiac disease and IgA deficiency were 2 years old or younger. Therefore results on non-IgA deficient children are reported in the table.

Sensitivity of Serologic Tests According to Marsh Grade Classification

Six studies stratified the results of serologic test sensitivity according to Marsh grade classification. (29-31;38;43;48) Four studies observed a trend towards a higher sensitivity when Marsh 3c lesions were found in the small bowel biopsy compared to Marsh 3a or 3b (statistical significance not reported). (29;30;43;45) Two studies reported a similar trend, however, sensitivity estimates were not provided. (31;38) The sensitivity was much lower when Marsh 1 was used as a criterion for celiac disease diagnosis. (30;43) The statistical significance of these findings were not reported in the studies. In these 2 studies the sensitivity of IgA tTG in patients with Marsh 2 grade abnormalities was 100%, however, since only 2 patients were included in one study and one in the other these results should be interpreted with caution. Results are shown in Table 13.

Table 13: Sensitivity of Diagnostic Serologic Tests According to Marsh Criteria

Study N	Serologic test Cut-off	Marsh Criteria (n)	Sensitivity
Emami et al. (29) N= 21	IgA tTG	Marsh 3c (n=5) Marsh 3a-b (n=16)	80% 36.8% [Overall: 38%]
Hopper et al. (30) N=77	IgA tTG > 15 U/ml	Marsh 3c (n=27) Marsh 3b (n=44) Marsh 3a (n=43) Marsh 2 (n=2) Marsh 1 (n=39)	100% Approx. 92%§ 86% 100% Approx. 18%§ [Overall: 90.9%]
	IgA EMA	Marsh 3c (n=27) Marsh 3b (n=44) Marsh 3a (n=43) Marsh 2 (n=2) Marsh 1 (n=39)	100% Approx. 86%§ 79% Approx. 50%§ Approx. 18%§
Rashtak et al. (45) N= 92	IgA tTG > 10 U/L	Marsh 3c Marsh 3a	90% 67% [Overall: 78%]
Santaolalla et al. (43) N= 42	IgA tTG	Marsh 3c (n=13) Marsh 3b (n=18) Marsh 3a (n=11) Marsh 2 (n=1) Marsh 1 (n=27)	100% (11/11) 94% (17/18) 85% (11/13) 100% 19% [Overall: 92.9%]
Poddar et al. (31) N= 180		10/10 (100%) CD with negative serology had Marsh 3a or 3b	
Basso et al. (38)		Higher sensitivity in Marsh 3c (results not provided)	

AGA anti-gliadin antibody; approx approximately; EMA endomysial antibody; DGP deamidated gliadin peptides; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

§ Values derived from a graph.

Diagnostic Accuracy of Serologic Tests in Subjects with Chronic Liver Disease

Since one systematic review identified in the systematic literature review concluded that there may be a higher rate of false positive results with IgA tTG in individuals with chronic liver disease compared to the general population, (11) the studies identified through MAS' systematic literature search that evaluated the diagnostic accuracy of serologic tests in patients with chronic liver disease were reviewed.

A total of 14 observational studies that evaluated the specificity of serologic celiac disease tests in subjects with chronic liver disease were identified. (49-62) All studies evaluated the frequency of false positive results (1-specificity) of IgA tTG, however, IgA tTG test kits using different substrates were used, i.e., human recombinant, human, and guinea-pig substrates. IgA EMA was used in all studies, however, in half of the studies it was only used in subjects with a positive IgA tTG as a confirmatory test. IgA AGA was evaluated in 4 studies. The gold standard, small bowel biopsy, was used to confirm the result of the serologic tests in only 5 studies, other studies used IgA EMA to confirm the celiac disease diagnosis. The studies do not seem to have been designed or powered to compare the diagnostic accuracy among different serologic celiac disease tests. The patients included in the studies were those recruited from gastrointestinal clinics with a previous diagnosis of chronic liver diseases such as primary biliary cirrhosis, chronic active hepatitis, liver cirrhosis, chronic liver disease, autoimmune hepatitis, unexplained elevated liver enzymes, end-stage autoimmune liver disease, and autoimmune cholangitis. Some studies also evaluated the frequency of false positive results of serologic celiac disease tests in a control group of healthy subjects. (49;50;53;55;58-60;63) The statistical significance of the difference in the frequency of false positive results between subjects with chronic liver disease and healthy subjects and between different serologic celiac disease tests among patients with chronic liver disease was not reported in the studies.

The study results suggest that there is a trend towards a higher frequency of false positive results with IgA tTG in patients with chronic liver disease compared to healthy controls, although the statistical significance of the difference was not reported in the studies. However, the rate of false positives in studies using IgA tTG with human recombinant substrate was closer to the rate in healthy controls compared to guinea pig substrate (Appendix 6).

The study results suggest that among individuals with chronic liver disease there is a trend towards a lower frequency of false positives if the IgA tTG test using human recombinant substrate is used compared to the guinea pig substrate. However, the statistical significance of the difference was not reported in the studies (Appendix 6). Some authors believe that this may be caused by impurities of the guinea-pig transglutaminase used as a substrate. (52;58;64) When IgA tTG with human recombinant substrate was used, the number of false positives seems to be similar to what was estimated in the MAS pooled analysis for IgA-based serologic tests in a general population of patients (table 10, 1-specificity). Some authors observed that when false positives occurred, the anti-IgA tTG antibody titer was close to the cut-off level. (53) No false positives were observed with IgA EMA in six studies. False positives with IgA AGA in individuals with chronic liver disease were also reported in 4 studies (Appendix 6).

These results should be interpreted with caution since most studies did not use the gold standard, small bowel biopsy, to confirm or exclude the diagnosis of celiac disease, and since the studies were not designed to compare the diagnostic accuracy among different serologic tests. In most cases, IgA EMA was used to confirm the occurrence of false positive results, however, the current evidence indicates that IgA EMA does not seem to have 100% specificity. Moreover, little to no information is currently available on the performance of other celiac serologic tests, AGA (4 studies identified) and DGP (no studies identified) in a chronic liver disease population, therefore we cannot infer if the accuracy of these tests would be affected in subjects with chronic liver disease. The sensitivity of the different serologic tests in patients with chronic liver disease was not evaluated in the studies identified.

Effects of a Gluten-Free Diet (GFD) in Patients Diagnosed with Celiac Disease

Ten studies identified through the systematic literature search evaluated the effects of GFD on clinical, histological, or serologic improvement in patients diagnosed with celiac disease. (29-31;37;38;40;42-44;48) The most common symptoms presented by these patients prior to the diagnosis were gastrointestinal symptoms such as chronic diarrhea and abdominal pain, anemia, weight loss, and failure to thrive in pediatric patients. In 4 studies, (29;31;42;43) the response to GFD was incorporated as a criterion for the diagnosis of celiac disease and therefore all patients diagnosed with celiac disease were GFD responders. Four studies evaluated the response to GFD through serologic testing, IgA tTG in most cases. (37;38;40;48) Improvement, defined as antibody titres below the cut-off level used in each study, was observed in 51% to 95% of the patients included in the studies (table 14) In one study where the response to GFD in patients with celiac disease was evaluated through clinical response, an 88% improvement in symptoms was observed after a mean of 19.6 months of follow-up. (31) The symptoms subsided after a mean of 16 days. (31) A second study that evaluated the effects of a GFD for longer than 1 year in patients diagnosed with celiac disease found that histological improvement, i.e., Marsh 0 to 2 lesions on small bowel biopsy after GFD, occurred in 32 (66.7%) patients. (30) In these 2 studies, most patients diagnosed with celiac disease presented with diarrhea, anemia, and failure to thrive (in children). Additional information in table 14.

Table 14. Effects of a Gluten-Free Diet in Patients Diagnosed with Celiac Disease

Study (Year)	N. Diagnosed with Celiac Disease	Symptoms	Length of Gluten-Free Diet (GFD)	% Patients with Improvement on GFD
Studies that evaluated the effects of GFD clinically or histologically				
Poddar et al. (2002) (44) Children	N= 50	Symptoms in GFD respondents: Chronic diarrhea, failure-to-thrive, anemia	Mean:19.6 mos (4-86)	50/57 (88%) Symptoms subsided at mean 16 days (4-30). Authors reported weight and height gain.
Hopper et al, 2008 (30) Adults	N= 48 (group 2)	Most common symptoms in those diagnosed with celiac disease: Diarrhea, abdominal pain, weight loss, anemia	> 1 yr	Clinical: NR Histological: 32 (66.7%) had Marsh 0-2 after GFD
Studies that used response to GFD as a criterion for celiac disease diagnosis				
Emami et al, 2008 (29) Adults and children	N= 21	Classic, inflammatory bowel syndrome, failure-to-thrive	NR	21 (100%)
Poddar et al, 2008 (31) Children < 14 yrs	N= 180	Chronic diarrhea, failure-to-thrive, anemia	Mean: 12.4 mos (3-36)	180 (100%) Authors report improvement in height and weight gain
Santaolalla, 2008 (43) Adults and children	N= 70	GI or extraintestinal symptoms	NR	70 (100%)
Wolters et al. (2002) (42) Children	N= 52	Abdominal pain/distention, growth failure, diarrhea, anemia	NR	52 (100%)
Studies that evaluated response to GFD through serologic testing				
Dahlbom et al. (2008) (37) Children	N= 20	NR	> 6 mos	19 (95%) – according to IgA tTG
Basso et al. (2009) (38) Children	N= 161	NR	1 yr	51% - IgA tTG negative (< 20 AU) after GFD in patients who complied with the diet
Agardh et al. (2007) (40) Children	N= 20	NR	6 mos	75% to 93% depending on serologic test.

Study (Year)	N. Diagnosed with Celiac Disease	Symptoms	Length of Gluten-Free Diet (GFD)	% Patients with Improvement on GFD
Rashtak et al. (2008) (45) Adults and children	N= 42 (> 6 mos f-up)	Gastrointestinal symptoms, weight loss, and anemia	Median: 11 mos (3-43)	36 (84%) – based on IgA tTG

AU refers to arbitrary units; CD celiac disease; f-up follow-up; GFD gluten-free diet; IgA immunoglobulin A; mos months; NR not reported; tTG tissue transglutaminase; yr year.

Grading of Evidence

The quality of the evidence for each serologic tests evaluated based on the GRADE Working Group criteria. (24;25)

Overall, the quality of the evidence ranged from moderate to very low depending on the serologic test. Reasons to downgrade the quality of the evidence included the use of a surrogate endpoint (diagnostic accuracy) since none of the studies evaluated clinical outcomes, inconsistencies among study results, imprecision of estimate, and sparse data (table 15).

Table 15: GRADE Quality of Evidence: Diagnostic Accuracy of Serologic Celiac Disease Tests

Serologic Test Outcome	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings Pooled estimate (95% CI)	Overall Quality
tTG IgA Diagnostic accuracy (sensitivity / and specificity)	15 Observational	No important limitations*.	Fairly consistent results.	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability No limitation‖	▪ Preciseness No limitation ▪ Publication bias No evidence of publication bias	Sensitivity 92.1% (88.0, 96.3) Specificity 92.1% (89.1, 95.1)	
	High	High	High	Moderate →			Moderate
DGP IgA Diagnostic accuracy (sensitivity / and specificity)	5 Observational	No important limitations*.	Important inconsistency (-1).	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability No limitation‖	▪ Preciseness No limitation ▪ Publication bias No evidence of publication bias	Sensitivity 89.2% (83.3, 95.1) Specificity 92.5% (88.5, 96.5)	
	High	High	Moderate	Low →			Low
EMA IgA Diagnostic accuracy (sensitivity / and specificity)	4 Observational	No important limitations*.	No inconsistency in 3 out of 4 studies.	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability No limitation‖	▪ Preciseness No limitation ▪ Publication bias No evidence of publication bias	Sensitivity 85.1% (75.9, 94.4) Specificity 93.9% (90.6, 97.2)	
	High	High	High	Moderate →			Moderate
Combination of tests (any test positive) Diagnostic accuracy (sensitivity / and specificity)	6 Observational	No important limitations*.	Fairly consistent results.	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability: combination of tests used in clinical practice may be different, which may jeopardize the generalizability of study results (-1)	▪ Preciseness No limitation ▪ Publication bias No evidence of publication bias	Sensitivity 95.1% (92.2, 98.0) Specificity 90.5% (89.1, 95.1)	
	High	High	High	Low →			Low

Serologic Test Outcome	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings Pooled estimate (95% CI)	Overall Quality
Combination of tests (all tests positive) Diagnostic accuracy (sensitivity / and specificity)	2 Observational	No important limitations*.	Important inconsistency (-1).	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability: combination of tests used in clinical practice may be different, which may jeopardize the generalizability of study results (-1)	▪ Preciseness No limitation ▪ Publication bias No evidence of publication bias ▪ Sparse Data (-1)	Sensitivity 81.1% (71.3, 90.8) Specificity 98.7% (98.1, 99.3)	
	High	High	Moderate	Very Low	Very Low (-1)		Very Low (-1)
AGA IgA Diagnostic accuracy (sensitivity / and specificity)	6 Observational	No important limitations*.	Important inconsistency (-1).	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability No limitation‖	▪ Preciseness Imprecise estimate¦ (-1) ▪ Publication bias No evidence of publication bias	Sensitivity 74.9% (63.6, 86.2) Specificity 90.1% (86.3, 93.9)	
	High	High	Moderate	Low	Very Low		Very Low
tTG IgG Diagnostic accuracy (sensitivity / and specificity)	5 Observational	No important limitations*.	Important inconsistency (-1).	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability No limitation‖	▪ Preciseness Imprecise estimate¦ (-1) ▪ Publication bias No evidence of publication bias	Sensitivity 44.7% (30.3, 59.2) Specificity 94.0% (90.6, 97.5)	
	High	High	Moderate	Low	Very Low		Very Low
DGP IgG Diagnostic accuracy (sensitivity / and specificity)	5 Observational	No important limitations*.	Important inconsistency (-1).	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability No limitation‖	▪ Preciseness No limitation ▪ Publication bias No evidence of publication bias	Sensitivity 88.4% (82.1, 94.6) Specificity 95.2% (92.3, 98.1)	
	High	High	Moderate	Low →			Low

Serologic Test Outcome	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings Pooled estimate (95% CI)	Overall Quality
AGA IgG Diagnostic accuracy (sensitivity / and specificity)	4 Observational	No important limitations*.	Important inconsistency (-1).	▪ Patient population No limitations.¶ ▪ Outcome Surrogate outcome used§ (-1) Generalizability: no limitation‖	▪ Preciseness Imprecise estimate¦ (-1) ▪ Publication bias No evidence of publication bias	Sensitivity 69.1% (56.0, 82.2) Specificity 94.6% (92.4, 96.9)	
	High	High	Moderate	Low	Very Low		Very Low

CI refers to confidence interval; AGA anti-gliadin antibody; EMA endomysial antibody; DGP deamidated gliadin peptides; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

* Recruitment seemed to have been done appropriately since consecutive subjects with suspected celiac disease were used in most studies. Disease status and serologic test results not known before enrolment. Gold standard used in all subjects. Blinding assessment in most studies

¶ Referral patterns similar to clinical practice.

§ Surrogate outcomes evaluated (sensitivity and specificity), i.e., impact on clinical outcomes not evaluated. Therefore the quality of evidence was downgraded by 1 point. Diagnostic accuracy results assumed to be generalizable to clinical practice.

¦ Estimate considered imprecise when the upper and lower limits of the 95% confidence interval were greater than 10 percentage points above or below the point estimate for either sensitivity or specificity.

‖ Study results considered generalizable to clinical practice as it was assumed that both serologic tests and small bowel biopsy would follow similar procedures in clinical practice. Likewise, it was assumed that the diagnostic criteria used to define celiac disease in small bowel biopsies in clinical practice would be similar to the ones used in the studies.

Clinical Validity and Clinical Utility of Serologic Tests in the Diagnosis of Celiac Disease

According to the current guidelines, the diagnosis of celiac disease is confirmed by small bowel biopsy, however, serologic tests are used to detect and support the presence of disease. (4;9) According to the guidelines, individuals with a positive serologic test result should undergo small bowel biopsy to confirm the diagnosis of celiac disease. (12) Exceptions are subjects in whom an endoscopy/small bowel biopsy is required based on clinical presentation. (12)

The clinical validity of serologic tests in the diagnosis of celiac disease was considered high in subjects with symptoms consistent with this disease due to:

- High accuracy of some serologic tests.
- Serologic tests detect possible celiac disease cases and avoid unnecessary small bowel biopsies if the test result is negative, unless an endoscopy/small bowel biopsy is necessary due to clinical presentation.
- Serologic tests support the results of small bowel biopsy.

The clinical utility of serologic tests in the diagnosis of celiac disease, as defined by its impact in decision making was also considered high in subjects with symptoms consistent with this disease given the considerations listed above and since the celiac disease diagnosis leads to treatment with a gluten-free diet.

Discussion

The results MAS' pooled analysis suggest that IgA anti-tissue transglutaminase (tTG) test is the most accurate individual test. The difference in sensitivity was not statistically significant when compared to the IgA DGP and EMA tests. However, the quality of the evidence (GRADE) for the IgA DGP was considered low due to inconsistency in results, compared to moderate with IgA tTG. The IgA EMA test had moderate quality evidence, but not being automated, is more time-consuming and operator-dependent than the other tests, (2;4) demanding more experience of the operator. The AUC for IgA tTG was higher than IgA DGP and IgA EMA, 0.98 (95% CI: 0.97, 0.99), 0.94 (0.92, 0.96), and 0.93 (0.90, 0.95), respectively, however, the statistical significance of the difference in AUCs between the tests was not calculated. Additionally, while IgA tTG was considered a very useful test according to the likelihood ratios, IgA DGP and EMA were considered moderately useful. The sensitivity of the IgA AGA test is statistically significantly lower than other IgA-based tests. Combinations[h] of serologic tests have a slightly higher sensitivity compared to IgA tTG. The results of combinations of serologic celiac disease tests must be interpreted with caution since the results may not be generalizable to different combinations of serologic tests.

The estimated prevalence of IgA deficiency in celiac disease is low, i.e., 1.7% to 3.0%, (2) raising questions regarding the need to measure total serum IgA levels or perform IgG-based serologic celiac disease tests as an initial step in all patients in addition to the IgA-based serologic test for celiac disease. Some celiac disease guidelines reached similar conclusions. (2;11)

The pooled estimate of sensitivity and specificity of each serologic test was calculated using a bivariate binomial generalized linear mixed model which takes into account the negative correlation between sensitivity and specificity in producing the summary estimate. (65) The authors of some systematic reviews identified decided not to pool the sensitivity and specificity estimates of different studies due to

[h] Refers to the assumption that a positive serology was defined by a positive result in any of the tests included in the combination.

heterogeneity concerns. Another advantage of using the bivariate, binomial generalized linear mixed model is that by incorporating a random effects model it accounts both for a possible heterogeneity between study results and the variation within studies. (65) Moreover, the fact that stricter criteria were used for study inclusion in this analysis improves the homogeneity of the studies. For instance, only studies published in or after the year 2000 were included, consequently most tTG studies used human recombinant or human substrate as opposed to guinea-pig substrate for the tTG test, and the fact that the latter seems to show a lower sensitivity than the former was raised in other systematic reviews. (26-28) The exclusion of studies with unclear description of the small bowel biopsy procedure, or those in which celiac disease status was known at enrolment may have further contributed to the homogeneity among study results.

The results of this review are corroborated by the results of previous systematic reviews. (3;11;26-28) In addition, this review included more recently published studies including studies with the newer DGP serologic tests.

Although the diagnosis of celiac disease is confirmed by small bowel biopsy, serologic testing assists in the diagnosis of celiac disease either by detecting the individuals who require a small bowel biopsy or by supporting its results. Depending on the clinical presentation, an endoscopy/small bowel biopsy may be necessary regardless of serologic celiac disease test result. According to Lewis et al. if the pre-test probability of celiac disease is higher than 25%, small bowel biopsy might be a preferred first step instead of serologic tests. (26)

Given that serologic tests evaluated aid in the diagnosis of celiac disease, the high accuracy of some of the tests evaluated, and the fact that once celiac disease is diagnosed patients can be treated with a gluten-free diet, the clinical validity and clinical utility of these tests was considered high in subjects with symptoms consistent with this disease.

The existing celiac disease guidelines stress the importance of the subjects being on a gluten-containing diet when both the serologic tests and the small bowel biopsy are performed since gluten avoidance affects the results of these investigations. (2) It is important to take this into account when generalizing the results of the studies to clinical practice since the studies included in this review were based on patients on a gluten-containing diet. Other factors that may affect the generalizability of study results include following different procedures for either the serologic test or the small bowel biopsy than the ones used in the studies included in this review. Similarly, the use in clinical practice of different criteria to diagnose celiac disease in small bowel biopsies than what was used in the studies (at least partial villous atrophy in most studies) may also affect the generalizability of study results, especially since some studies observed a lower sensitivity with celiac disease serologic tests when lower Marsh grade abnormalities are present in the small bowel biopsy.

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of this study was to assess the cost-effectiveness of serologic tests for testing celiac disease (CD) and to calculate the budget impact of these tests in the province of Ontario. Different serologic tests for celiac disease exist and the following tests were assessed:

- Endomysial antibody (EMA)
- Antigliadin antibody (IgA & IgG AG)
- Deaminated gliadin peptides (IgA & IgG DGP)
- Tissue transglutaminase (IgA & IgG tTG)
- CD Panel (Combination of tests)

Analysis Method

A decision analysis was constructed to compare costs and outcomes between the tests based on the sensitivity, specificity and prevalence summary estimates from the MAS Evidence-Based Analysis (EBA). A budget impact was then calculated by multiplying the costs and volumes in Ontario.

Economic Literature Review

A literature search was conducted on November 19th, 2009 and the following databases were searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and EconLit. The search strategy is presented in Appendix 8. We reviewed published articles that fit the following inclusion criteria:

- full economic evaluations [cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA)]
- economic evaluations reporting Incremental Cost-Effectiveness Ratios (ICER) i.e. cost per quality adjusted life year (QALY)/life years gained (LYG) or cost per event avoided
- studies in patients with symptoms consistent with CD
- studies reporting on serologic testing for CD
- studies in English

Three articles were identified that conducted CEAs in a patient population suspected of CD.

Yagil et al 2005 (66) conducted a cost-effectiveness analysis of serologic testing for CD in symptomatic adults. They evaluated a serologic screening policy for CD among military personnel. The study population was divided into subgroups according to the clinical presentation prior to screening: isolated (low-risk) and combined complaints (high-risk). Cost-effect ratio was expressed as cost per newly diagnosed patient and cost minimization was expressed as cost per screened individual. Five hundred thirty-eight military personnel were serologically tested for CD. EMA measured the highest sensitivity, specificity and predictive values. Average screening expenditure was $287 USD per patient. It was recommended that from a cost-effect perspective, implemented screening procedures need to be dependent on subgroup: low-risk should be clinically followed-up; and high-risk, should be biopsied only following a positive EMA test.

Shamir et al 2006 (67) examined the cost-effectiveness of screening for CD in the adult population. A Markov model was designed to evaluate screening of an entire population starting at the age of 18. Screening strategies included EMA, tTG, and tTG & IgA combined verified by EMA. All strategies were examined with and without evaluation for IgA deficiency and they all included small bowel biopsy. Basecase analysis revealed $49,491 USD and $572,616 USD per LYG for screening compared to no screening using EMA or tTG respectively. Screening was cost-effective in populations with a relatively high prevalence of CD or when the standardized mortality ratio for untreated CD patients was higher than 1.5. The model was insensitive to changes in the cost of serologic markers and diagnostic endoscopy. EMA was the preferred serologic marker for mass screening.

Dorn et al 2008 (68) compared strategies for diagnosing CD. A decision analytical model was used to compare five strategies on diagnostic performance and costs: tTG screening alone; tTG followed by small bowel biopsy; tTG & IgA plus biopsy; tTG & HLA plus biopsy; and biopsy alone. The authors concluded that when the pre-test probability of CD is low, patients with positive tTG serology should undergo small bowel biopsy to confirm disease. As the pre-test probability of disease increases the added cost of small bowel biopsy should be weighed against the consequences of a false-positive diagnosis.

Target Population

The target population of this economic analysis was patients experiencing symptoms consistent with CD including adults and children.

Perspective

The primary analytic perspective was that of the Ministry of Health and Long-Term Care (MOHLTC).

Comparators & Effect Estimates

Prevalence, sensitivity and specificity summary estimates were obtained from the clinical literature review. Prevalence was estimated to be 28.1% (26.8, 29.4) from a weighted average of the number of people with positive and negative test results from the trials included in the review. Sensitivity and specificity summary estimates were obtained from a meta-analysis of the data extracted from the included trials. The method of analysis is described in the clinical section.

The following table describes the parameters discussed above that were included in the economic model.

Table 16. Economic model parameters.

Serologic test	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Reference
EMA	85.1% (75.9, 94.4)	93.9% (90.6, 97.2)	MAS EBA
IgA AGA	74.9% (63.6, 86.2)	90.1% (86.3, 93.9)	MAS EBA
IgA DGP	89.2% (83.3, 95.1)	92.5% (88.5, 96.5)	MAS EBA
IgA tTG	92.1% (88.0, 96.3)	92.1% (89.1, 95.1)	MAS EBA
IgG AGA	69.1% (56.0, 82.2)	94.6% (92.4, 96.9)	MAS EBA
IgG DGP	88.4% (82.1, 94.6)	95.2% (92.3, 98.1)	MAS EBA
IgG tTG	44.7% (30.3, 59.2)	94.0% (90.6, 97.5)	MAS EBA
Panel (combination of serologic tests, any positive result)	95.1% (92.2, 98%)	90.5% (86.8, 94.2)	MAS EBA
Panel (combination of serologic tests)	81.1% (71.3, 90.8)	98.7% (98.1, 99.3)	MAS EBA

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; MAS EBA Medical Advisory Secretariat Evidence Based Analysis; tTG tissue transglutaminase;

Discounting & Time Horizon

There was no time horizon to the decision tree therefore discounting was not necessary. The tree was built to illustrate decisions/events happening with acute diagnosis of disease.

Modelling

A decision tree described in the following figure was constructed to evaluate the outcomes and costs associated with each diagnostic strategy. The decision node (square node) represents the choice between competing strategies. Events are represented by branches that are connected by chance nodes (circular nodes). The likelihood of a given event is represented by branch probabilities specified by sensitivity and specificity estimates which in turn depend on the underlying prevalence of CD. Resources can be incurred during events therefore costs can be assigned to these events. Strategies were compared on the basis of test characteristics and costs of each strategy. All analyses were performed using decision analysis software TreeAge Pro Suite 2009.

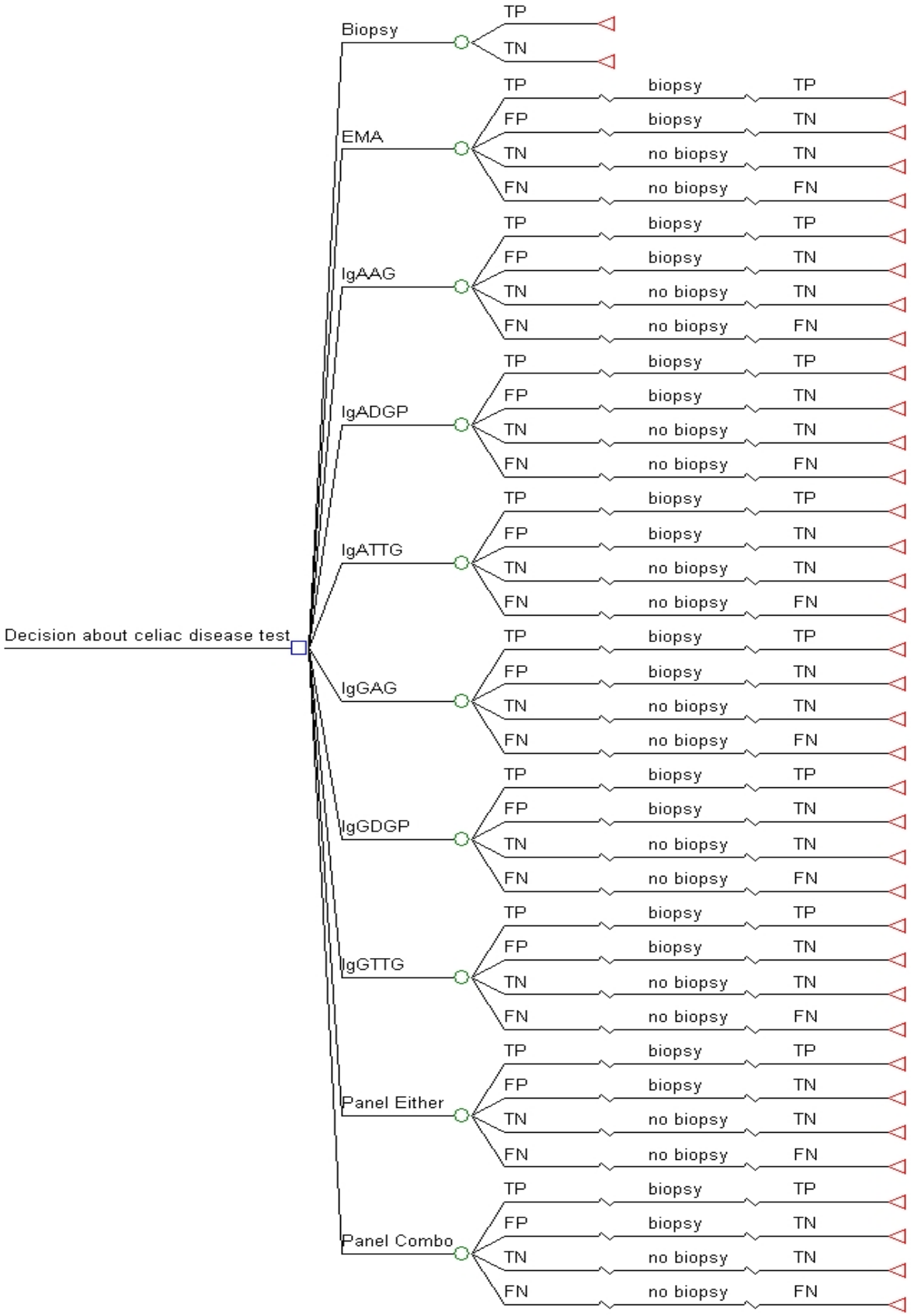


Figure 2. Decision tree structure for diagnosing celiac disease with serologic tests

Small bowel biopsy was assumed to have sensitivity and specificity estimates of 1 since it is considered the gold standard and all tests are compared to it when estimating these values. Therefore in the biopsy strategy there are only two chances: a true positive (TP) and a true negative (TN). In all other strategies there is a possibility for a false positive (FP) and a false negative (FN). The positive cases are then confirmed with a biopsy and the FP then becomes a TN. In all strategies a family physician consult is incurred but only those receiving a biopsy incurred a specialist i.e. gastroenterologist consult.

Valuing Outcomes

Costs and numbers of TPs, FPs, TNs and FN were outcomes predicted by the economic model. The positive numbers predicted who received a small bowel biopsy. From these estimates cost per FN avoided was calculated and reported. FN was chosen as the primary outcome because a diagnostic test should avoid FNs and identify cases of CD accurately. Therefore a comparison of the various serologic tests was conducted to identify the most accurate and cost-effective strategy.

Resource Use and Costs

The following table outlines the resources and their associated costs used the economic model. It was assumed that all patients being tested for CD with a serology test would incur a family physician consult. If the test result was positive then a referral to the gastroenterologist was made and all these patients would incur a specialist visit and a biopsy. Costs were reported in 2010 CAD$.

Table 17. Resources associated with celiac disease serology testing.

Resource	Unit	Value/Unit	Assumption	Reference
GP	Consult	$62.65	Everyone sees GP and gets serology done	OSB: A005 (69)
Specialist	Consult	$143.40	All positive cases are seen by specialist	OSB: A415 (69)
Biopsy*	Procedure	$190.55	All positive cases get a biopsy	OSB: Z399 + E702 (69)
EMA	Test	$55		OAML - Communication in March 2010
AGA & DGP (IgA, IgG)	Test	$90	Assumed DGP test has the same cost as AG test	OAML - Communication in March 2010
tTG (IgA, IgG)	Test	$60		OAML - Communication in March 2010
Panel	Test	$125		OAML - Communication in March 2010

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; OAML Ontario Association of Medical Laboratories; OSB Ontario Schedule of Benefits; tTG tissue transglutaminase;
*Small bowel biopsy cost was assumed to include 4 base units plus one unit within the first hour of procedure of anaesthesia as per Ontario schedule of benefits. Anaesthesia units may vary based on individual practice, time required to perform procedure and patient preference.

Variability and Uncertainty

One-way sensitivity analyses were conducted to address variability and uncertainty. Sensitivity, specificity and prevalence estimates were varied in one-way sensitivity analyses and did not change the direction of the results (see Appendix 9). Prevalence rates were varied based on the variation around the weighted mean (results shown in Appendix 9) and the lowest and highest prevalence rates identified in the trials included in the EBA. The lowest reported prevalence in the included trials was 3.9% (30) in the

adult population and the highest reported prevalence was 73.3% (36) in children.

Case scenarios were also investigated. In the basecase scenario only those patients that incurred a positive test received a biopsy. However it is feasible that a proportion of patients that incur a negative test also receive a biopsy (personal communication, clinical expert opinion, March 2010). In case scenario 1 it was assumed that 10% of patients who had a negative result also incurred the cost of a biopsy. It's also feasible that patients in the biopsy only strategy also receive a serologic test to confirm disease if their biopsy result was negative (personal communication, clinical expert opinion, March 2010). Therefore it was assumed in case scenario 2 that 10% of patients that receive a biopsy only are also tested with serologic tests and incur a panel cost.

Generalizability

The sensitivity, specificity and prevalence summary estimates were obtained from the clinical review literature which includes international trials. These estimates may vary within the Ontario context due to differences in health system infrastructure and resource utilization between geographic regions. For example the combination of tests strategies i.e. panel combo and panel either, reported in the clinical trials included in the review consisted of IgA and IgG DGP tests which don't appear to be used currently in Ontario as reflected by volumes data. In Ontario the panel strategy consists of IgA and IgG AG and tTG tests.

Results

Basecase Analysis

The following table describes the basecase results from the economic model. Four strategies made up the efficiency frontier; IgG tTG, IgA tTG, EMA and biopsy. All other strategies were dominated. IgG tTG was the least costly and least effective strategy ($178.95, FN avoided=0). Biopsy was the most costly and most effective strategy ($396.60, FN avoided =0.1553). The cost per FN avoided were $293, $369, $1,401 for EMA, IgA tTG and biopsy respectively. The results can be further illustrated by the following efficiency diagram.

Table 18. Economic model basecase results.

Strategy	Cost/Test	Cost	Incremental Cost	TP	FP	TN	FN	FN Avoided	Cost/FN Avoided
IgG tTG	$60.00	$178.95	$0.00	0.12574	0.04285	0.67611	0.1553	0	reference
EMA	$55.00	$212.15	$33.20	0.23919	0.04378	0.67517	0.04185	0.11345	$292.64
IgA tTG	$60.00	$228.12	$49.17	0.25895	0.05687	0.66209	0.02209	0.13321	$369.12
IgG AGA	$90.00	$230.42	$51.47	0.1942	0.03868	0.68028	0.08684	0.06846	$751.83
IgA AGA	$90.00	$246.74	$67.79	0.2105	0.07125	0.64771	0.07054	0.08476	$799.79
IgG DGP	$90.00	$247.02	$68.07	0.25061	0.05378	0.66518	0.03274	0.12256	$555.40
IgA DGP	$90.00	$254.30	$75.35	0.2483	0.03429	0.68466	0.03044	0.12486	$603.48
Panel Combo	$125.00	$266.86	$87.91	0.22778	0.00942	0.70954	0.05326	0.10204	$861.52
Panel Either	$125.00	$299.74	$120.79	0.26727	0.06837	0.65059	0.01377	0.14153	$853.46
Biopsy	$190.55	$396.60	$217.65	0.28104	0	0.71896	0	0.1553	$1,401.48

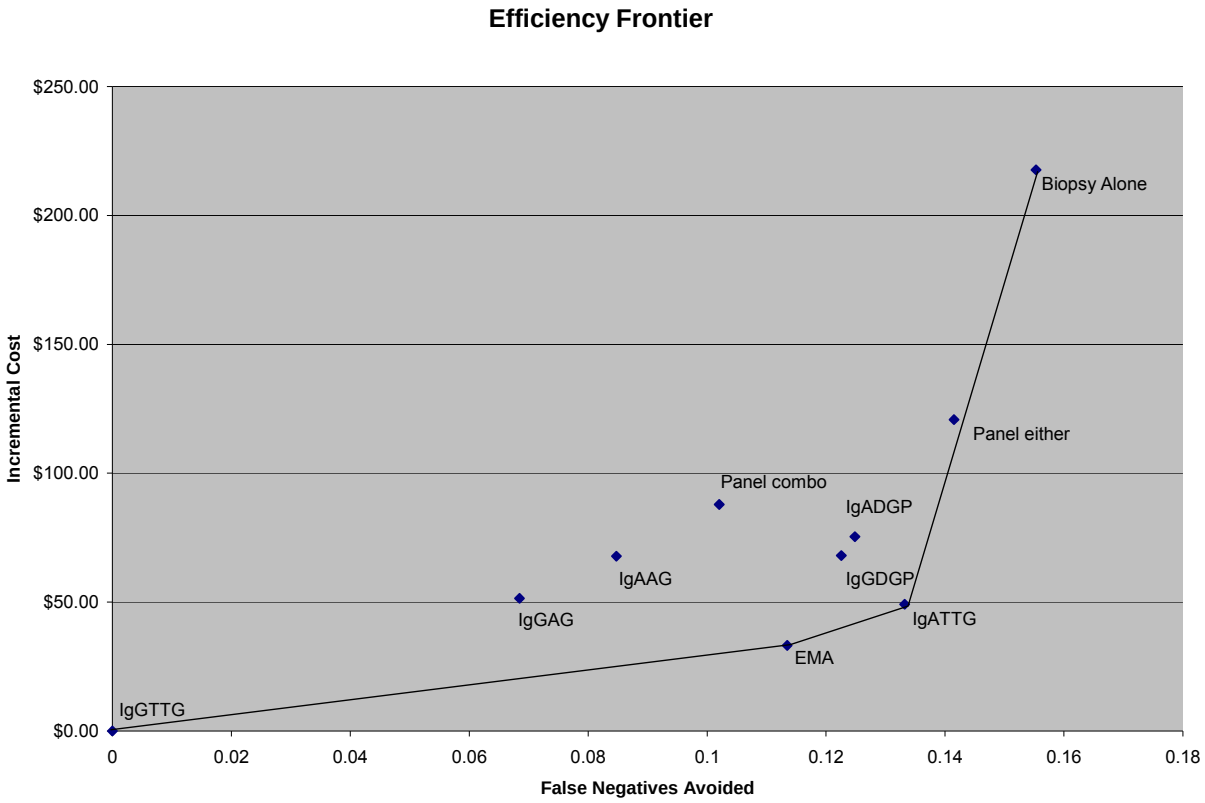


Figure 3. Efficiency frontier of strategies analyzed in the celiac disease economic model.

Prevalence Rate Variations

The lowest prevalence rate reported in the trials included in the clinical review was 3.9% in adults. This value was used to vary prevalence in the economic model. The ranking of strategies did not change with this low prevalence rate. EMA and IgA tTG strategies still avoided the most FNs at a lower expected cost while biopsy and panel either strategies avoided the most FNs but at a greater expected cost. This was consistent with the basecase results.

Figure 4 illustrates the efficiency frontier with a low prevalence rate of disease. All strategies left to the curve are considered to be dominated by strategies that made up the efficency frontier.

Table 19. Economic model results using lowest prevalence rate.

Strategy	Cost	Incremental Cost	TP	FP	TN	FN	FNs Avoided	Cost/FN Avoided
IgG tTG	$147.54	$0.00	0.01722	0.05731	0.90419	0.02128	0	reference
EMA	$148.15	$0.61	0.03277	0.05856	0.90294	0.00573	0.01555	$39.23
IgA tTG	$159.89	$12.35	0.03547	0.07605	0.88545	0.00303	0.01825	$676.71
IgG AGA	$178.81	$31.27	0.0266	0.05173	0.90977	0.0119	0.00938	$3,333.69
IgG DGP	$179.33	$31.79	0.03404	0.04586	0.91564	0.00449	0.01679	$1,893.39
IgA DGP	$188.13	$40.59	0.03433	0.07192	0.88958	0.00417	0.01711	$2,372.30
IgA AGA	$194.10	$46.56	0.02884	0.09528	0.86622	0.00966	0.01162	$4,006.88
Panel Combo	$202.28	$54.74	0.0312	0.0126	0.9489	0.0073	0.01398	$3,915.59
Panel Either	$230.41	$82.87	0.03661	0.09144	0.87006	0.00189	0.01939	$4,273.85
Biopsy	$396.60	$249.06	0.0385	0	0.9615	0	0.02128	$11,703.95

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

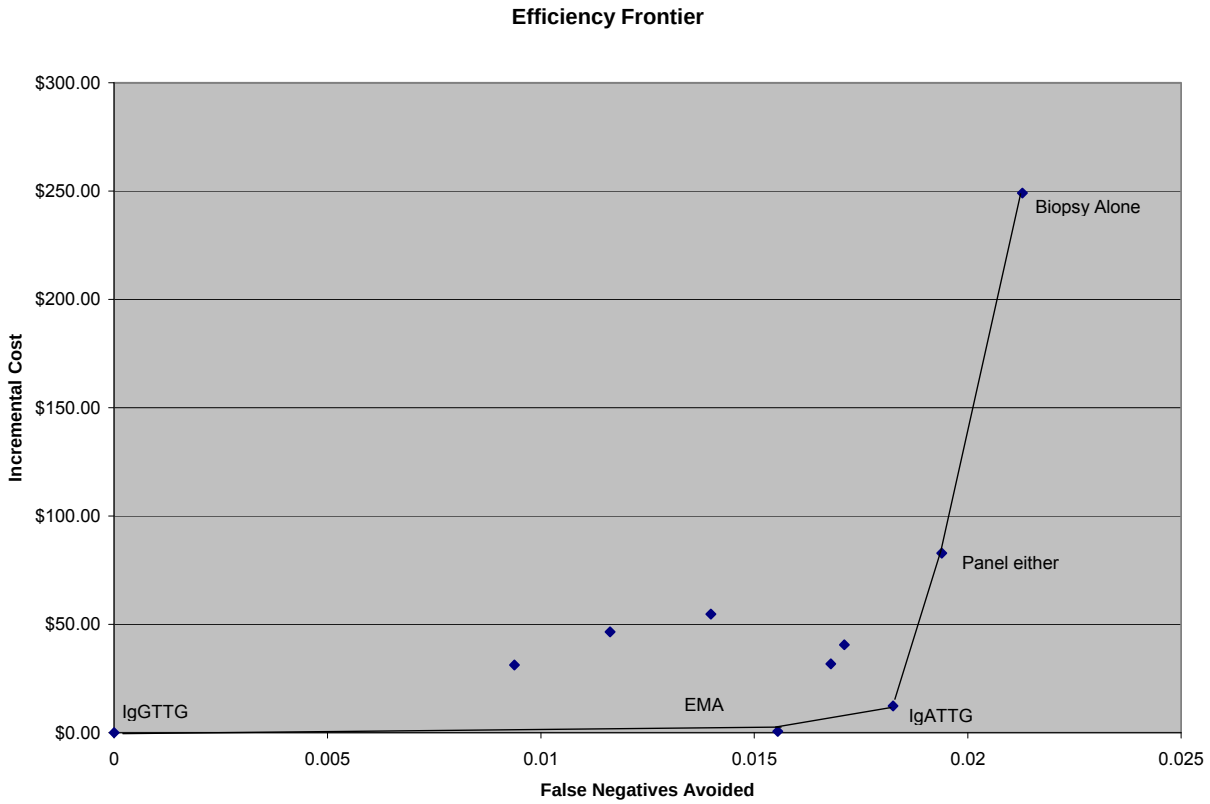


Figure 4. Efficiency frontier – low prevalence rate

With a low prevalence rate, expected costs and FNs avoided were lower in general for all strategies but the direction of the results did not change.

The highest prevalence rate reported in the trials included in the clinical review was 73.3% in children. This value was also used to vary prevalence in the economic model (see Table 20). Similarly with a high prevalence rate, the expected outcomes were higher but overall direction of the results did not change as illustrated in Figure 5 below.

Table 20. Economic model results using highest prevalence rate.

Strategy	Cost	Incremental Cost	TP	FP	TN	FN	FNs Avoided	Cost/FN Avoided
IgG tTG	$237.45	$0.00	0.32784	0.01593	0.25131	0.40492	0	reference
IgG AGA	$326.54	$89.09	0.50634	0.01438	0.25286	0.22642	0.1785	$0.00200
EMA	$331.35	$93.90	0.62365	0.01627	0.25097	0.10911	0.29581	$0.00315
IgA AGA	$344.78	$107.33	0.54884	0.02648	0.24076	0.18392	0.221	$0.00206
IgA tTG	$355.18	$117.73	0.67516	0.02114	0.2461	0.05759	0.34733	$0.00295
IgG DGP	$373.10	$135.65	0.64739	0.01275	0.25449	0.08537	0.31955	$0.00236
IgA DGP	$377.53	$140.08	0.6534	0.01999	0.24725	0.07936	0.32556	$0.00232
Panel Combo	$387.15	$149.70	0.5939	0.0035	0.26374	0.13886	0.26606	$0.00178
Biopsy	$396.60	$159.15	0.73276	0	0.26724	0	0.40492	$0.00254
Panel Either	$428.85	$191.40	0.69685	0.02541	0.24183	0.03591	0.36901	$0.00193

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

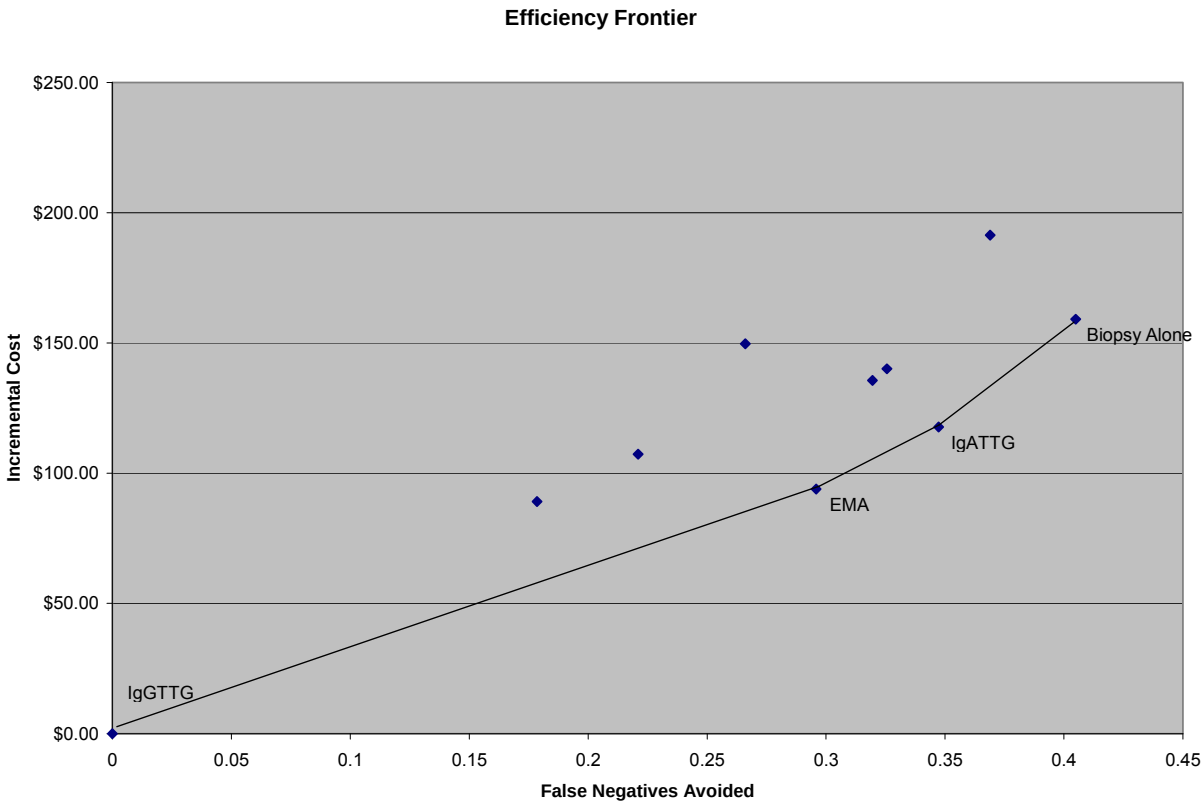


Figure 5. Efficiency frontier – high prevalence rate

Case Scenario 1

In case scenario 1 it was assumed that 10% of patients who had a negative result also incurred the cost of a biopsy. The following efficiency frontier describes the outcomes of this scenario.

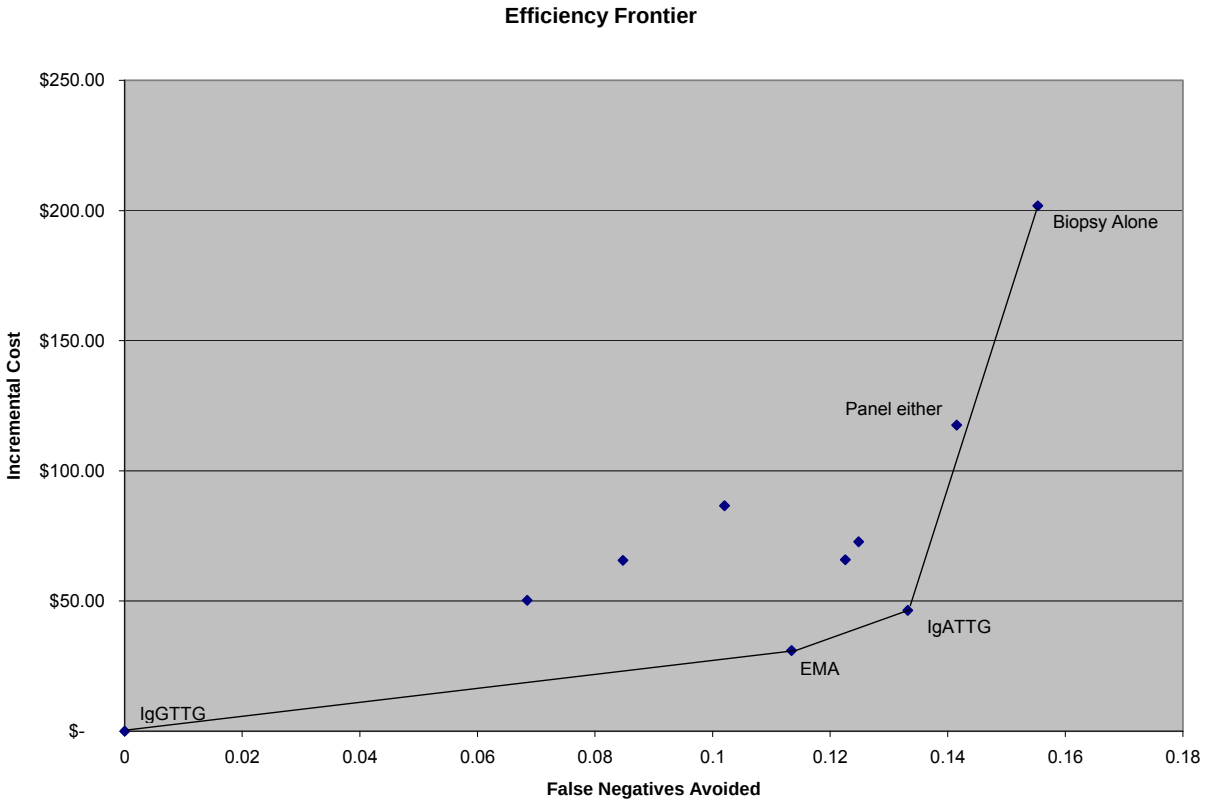


Figure 6. Efficiency frontier – Case scenario 1

The effects were assumed to be the same as there were no data to illustrate a difference in effect estimates but there was a difference in cost since now 10% of patients with a negative result after a serologic test were also incurring the cost of the biopsy. The direction of results did not change from basecase in this case scenario.

Case Scenario 2

In case scenario 2 it was assumed that 10% of patients that received a biopsy only and received a negative result were also tested with a disease panel test to confirm biopsy results. The following efficiency frontier describes the outcomes of scenario 2.

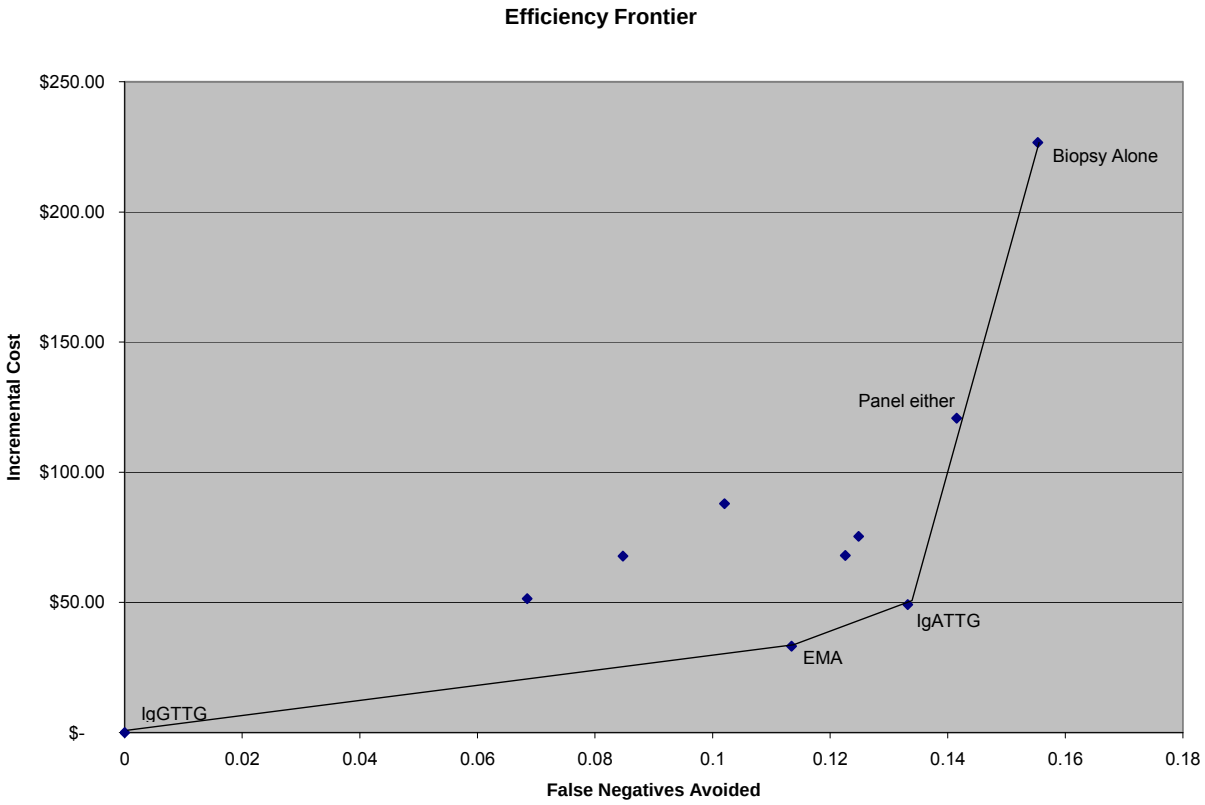


Figure 7. Efficiency frontier – case scenario 2

The effects in this scenario were also assumed to be the same as there were no data to illustrate a difference in effect estimates but there was a difference in cost in the biopsy arm only since now 10% of patients in this strategy also received a panel test after the biopsy result was negative. As expected this did not change the direction of results from basecase results.

Ontario Perspective

Table 21 describes the volumes of tests in Ontario for the last 6 years. Data were only available for EMA, IgA AGA, IgG AGA and tTG tests within the hospital setting. tTG was not broken down by the type of antibody assessed, but in Ontario most cases are tested for IgA antibodies while the IgG test is rarely used. Data were not available for the combination of tests, therefore, it was assumed that the number of cases receiving the panel of tests would be the same as tTG volumes. Experts have confirmed that tTG is often ordered with IgA and IgG AGA tests and the numbers seem to reflect similar volumes for the three tests. It is thus reasonable to interpret that only the panel is being ordered in the province of Ontario and single tests are not. Data for IgA AGA, IgG AGA and tTG tests were only available for the year 2009 for the community setting.

Table 21. Volumes of Serologic Tests for Celiac Disease in Ontario.

Setting/Year	2004	2005	2006	2007	2008	2009
Community						
IgA AGA	-	-	-	-	-	3,310
IgG AGA	-	-	-	-	-	3,052
tTG	-	-	-	-	-	10,002
Panel	-	-	-	-	-	10,002
Hospital						
EMA	1,068	344	4,081	4,153	4,288	4,597
IgA AGA	246	25,114	30,266	35,460	35,230	32,058
IgG AGA	246	25,108	30,248	35,474	35,224	32,214
tTG	883	20,510	27,442	38,278	37,255	32,806
Panel	883	20,510	27,442	38,278	37,255	32,806
Total						
EMA	1,068	344	4,081	4,153	4,288	4,597
IgA AGA	246	25,114	30,266	35,460	35,230	35,368
IgG AGA	246	25,108	30,248	35,474	35,224	35,266
tTG	883	20,510	27,442	38,278	37,255	42,808
Panel (combination of serologic tests)	883	20,510	27,442	38,278	37,255	42,808

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; OAML Ontario Association of Medical Laboratories; tTG tissue transglutaminase;
Data Source: Ontario Assocition of Medical Laboratories - accessed March 2010

EMA and tTG volumes have increased while AGA tests have slightly decreased over the last couple of years. Once these tests become insured there is a likelihood that volumes will increase in the province since patients won't have to pay out of pocket but this is difficult to predict. To calculate future projections an average of the trend between the years of 2007-2009 was calculated from the total volumes data for the province. This time period was chosen because of the consistency in volumes between the years. Projections for the next three years are presented in Table 22.

It's possible that EMA volumes will start to decrease as the test lacks automation and is time-consuming. Likewise it's possible that the panel of tests will be the only strategy being ordered since this is current practice in the province and constitutes tTG, IgA AGA and IgG AGA. The budget impact is shown in Table 23. The existing and projected volumes were multiplied by the basecase expected costs of each test

in order to calculate past and future impact in the province. For the panel strategy the expected cost of the panel either strategy was used to calculate an impact since it was deemed an effective strategy.

Table 22. Projections of serology tests for celiac disease in Ontario in the next three years.

Setting/Year	Year 1	Year 2	Year 3
Community			
IgA AGA	3,306	3,302	3,297
IgG AGA	3,043	3,034	3,025
tTG	10,614	11,263	11,952
Panel	10,614	11,263	11,952
Hospital			
EMA	4,837	5,090	5,356
IgA AGA	32,017	31,976	31,935
IgG AGA	32,120	32,026	31,932
tTG	34,813	36,942	39,201
Panel	34,813	36,942	39,201
Total			
EMA	4,837	5,090	5,356
IgA AGA	35,323	35,277	35,232
IgG AGA	35,163	35,060	34,957
tTG	45,426	48,205	51,153
Panel (combination of serologic tests)	45,426	48,205	51,153

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

Table 23. Budget impact of serology tests for celiac disease in Ontario in the next three years.

Setting/Year	2004	2005	2006	2007	2008	2009	Year 1	Year 2	Year 3
Community									
IgA AGA	-	-	-	-	-	0.82M	0.82M	0.81M	0.81M
IgG AGA	-	-	-	-	-	0.70M	0.70M	0.70M	0.70M
tTG	-	-	-	-	-	2.28M	2.42M	2.57M	2.73M
Panel						3.00M	3.18M	3.38M	3.58M
Hospital									
EMA	0.23M	0.07M	0.87M	0.88M	0.91M	0.98M	1.03M	1.08M	1.14M
IgA AGA	0.06M	6.20M	7.47M	8.75M	8.69M	7.91M	7.90M	7.89M	7.88M
IgG AGA	0.06M	5.79M	6.97M	8.17M	8.12M	7.42M	7.40M	7.38M	7.36M
tTG	0.20M	4.68M	6.26M	8.73M	8.50M	7.48M	7.94M	8.43M	8.94M
Panel	0.26M	6.15M	8.23M	11.47M	11.17M	9.83M	10.43M	11.07M	11.75M
Total									
EMA	0.23M	0.07M	0.87M	0.88M	0.91M	0.98M	1.03M	1.08M	1.14M
IgA AGA	0.06M	6.20M	7.47M	8.75M	8.69M	8.73M	8.72M	8.70M	8.69M
IgG AGA	0.06M	5.79M	6.97M	8.17M	8.12M	8.13M	8.10M	8.08M	8.05M
tTG	0.20M	4.68M	6.26M	8.73M	8.50M	9.77M	10.36M	11.00M	11.67M
Panel (combination of serologic tests)	0.26M	6.15M	8.23M	11.47M	11.17M	12.83M	13.62M	14.45M	15.33M

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

Prevalence of disease affected expected costs in the economic model therefore having the potential to impact the provincial budget. At a lower prevalence of disease the expected costs were lower. Similarly at a higher prevalence of disease the expected costs were higher. Table 24 describes the expected costs at various prevalence rates predicted by the economic model. Based on the different prevalence rates the budget impact varied as illustrated in Table 25. A higher prevalence of disease will have a greater impact on health resources as expected.

Table 24. Expected outcomes from the economic model based on varying prevalence rates.

Prevalence Rate	Low = 3.9%		Basecase = 28.1%		High = 73.3%	
Strategy	Cost	FN	Cost	FN	Cost	FN
IgG tTG	$147.54	0.02128	$178.95	0.1553	$237.45	0.40492
EMA	$148.15	0.00573	$212.15	0.04185	$331.35	0.10911
IgA tTG	$159.89	0.00303	$228.12	0.02209	$355.18	0.05759
IgG AGA	$178.81	0.0119	$230.42	0.08684	$326.54	0.22642
IgA AGA	$194.10	0.00966	$246.74	0.07054	$344.78	0.18392
IgG DGP	$179.33	0.00449	$247.02	0.03274	$373.10	0.08537
IgA DGP	$188.13	0.00417	$254.30	0.03044	$377.53	0.07936
Panel Combo	$202.28	0.0073	$266.86	0.05326	$387.15	0.13886
Panel Either	$230.41	0.00189	$299.74	0.01377	$428.85	0.03591
Biopsy	$396.60	0	$396.60	0	$396.60	0

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

Table 25. Budget impact of serology tests for celiac disease in Ontario in the next three years varying the prevalence rate.

Prevalence Rate	3.9%			73.3%		
Setting/Year	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Community						
IgA AGA	0.64M	0.64M	0.64M	1.14M	1.14M	1.14M
IgG AGA	0.54M	0.54M	0.54M	0.99M	0.99M	0.99M
tTG	1.70M	1.80M	1.91M	3.77M	4.00M	4.25M
Panel	2.45M	2.60M	2.75M	4.55M	4.83M	5.13M
Hospital						
EMA	0.72M	0.75M	0.79M	1.60M	1.69M	1.77M
IgA AGA	4.74M	4.74M	4.73M	10.61M	10.60M	10.58M
IgG AGA	4.76M	4.74M	4.73M	10.64M	10.61M	10.58M
tTG	5.16M	5.47M	5.81M	11.54M	12.24M	12.99M
Panel	8.02M	8.51M	9.03M	14.93M	15.84M	16.81M
Total						
EMA	0.72M	0.75M	0.79M	1.60M	1.69M	1.77M
IgA AGA	5.38M	5.38M	5.37M	11.75M	11.73M	11.72M
IgG AGA	5.30M	5.29M	5.27M	11.64M	11.60M	11.57M
tTG	6.85M	7.27M	7.72M	15.30M	16.24M	17.23M
Panel (combination of serologic tests)	10.47M	11.11M	11.79M	19.48M	20.67M	21.94M

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; tTG tissue transglutaminase;

Summary

Currently the province does not pay for these tests since the biopsy is the gold standard in defining CD diagnosis. With an accurate blood test, unnecessary biopsies and anxiety associated with this procedure along with false negatives and false positives would be avoided.

All testing strategies with biopsy are cheaper than biopsy alone however they also result in more FNs. The most cost-effective strategy will depend on the decision makers' willingness to pay.
Findings suggest that IgA tTG was the most cost-effective and feasible strategy based on its Incremental Cost-Effectiveness Ratio (ICER) and convenience to conduct the test.

The potential impact of IgA tTG test in the province of Ontario would be 10.4M, 11.0M and 11.7M respectively in the following three years based on past volumes and trends in the province and basecase expected costs.

A combination of serologic tests is the commonly used strategy in the province of Ontario therefore the impact to the system would be 13.6M, 14.5M and 15.3M respectively in the next three years based on past volumes and trends in the province and basecase expected costs.

The case scenarios did not change the ranking of strategies but the expected costs differed between scenarios therefore the impact to the province also differed as reflected by the variation in disease prevalence.

Conclusions

- The clinical validity and clinical utility of serologic tests for celiac disease was considered high in individuals with symptoms consistent with this disease as they aid in the diagnosis of celiac disease, some tests present a high accuracy, and a celiac disease diagnosis leads to treatment with a gluten-free diet.
- The study findings suggest that IgA tTG is the most accurate and most cost-effective serologic test.
- IgA AGA has a lower accuracy compared to other IgA-based serologic celiac disease tests.
- Combination of serologic tests[i] increase the diagnostic accuracy slightly and present a higher cost compared to individual serologic tests (e.g. IgA tTG). In addition there may be problems with generalizability of the results of the studies included in this review if different serologic test combinations are used in clinical practice.
- IgA deficiency seems to be uncommon in patients diagnosed with celiac disease.
- The generalizability of study results is contingent on performing both the serologic test and small bowel biopsy in subjects on a gluten-containing diet as was the case in the studies identified, since the avoidance of gluten may affect test results.

[i] Defining a positive result if at least one of the serologic tests included in the combination was positive.

Appendices

Appendix 1: Literature Search Strategies

Search date: November 13, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1950 to November Week 1 2009>

Search Strategy:

1 exp Celiac Disease/ (12821)
2 (C?eliac or nontropical sprue or non-tropical sprue or (gluten adj2 enteropath*)).ti,ab. (15922)
3 1 or 2 (19545)
4 exp Serologic Tests/ (163641)
5 exp Transglutaminases/ (4215)
6 exp Immunoglobulin G/ (109328)
7 exp Immunoglobulin A/ (31586)
8 exp Enzyme-Linked Immunosorbent Assay/ or exp Antibodies/ or exp Gliadin/ (655823)
9 ((serum or serologic* or blood or antibod*) adj2 (assay* or test* or analysis* or marker*)).ti,ab. (93903)
10 (serodiagnos* or immunoassay* or MIA).ti,ab. (46444)
11 (IgA or IGG or TTG or EMA or IgG-tTG or anti-gliadin or antigliadin or AGA or human leukocyte antigens or HLA).ti,ab. (181753)
12 or/4-11 (909310)
13 3 and 12 (4736)
14 limit 13 to (english language and humans and yr="2003 -Current") (1525)

Database: EMBASE <1980 to 2009 Week 45>

Search Strategy:

1 exp celiac disease/ (9447)
2 (C?eliac or nontropical sprue or non-tropical sprue).mp. or (gluten adj2 enteropath*).ti,ab. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (15319)
3 1 or 2 (15319)
4 exp blood examination/ (90827)
5 exp protein glutamine gamma glutamyltransferase/ (3538)
6 ((serum or serologic* or blood or antibod*) adj2 (assay* or test* or analysis* or marker*)).ti,ab. (73630)
7 exp immunoglobulin G/ (56664)
8 "immunoglobulin A"/ (21477)
9 exp enzyme linked immunosorbent assay/ (102414)
10 exp gliadin antibody/ (1090)
11 exp gliadin/ (1173)
12 exp immunoglobulin A antibody/ (3589)
13 exp immunoglobulin G antibody/ (14701)
14 exp antibody blood level/ (9454)
15 (IgA or IGG or TTG or EMA or IgG-tTG or anti-gliadin or antigliadin or AGA or human leukocyte antigens or HLA).ti,ab. (151786)
16 (serodiagnos* or immunoassay* or MIA).ti,ab. (38656)
17 or/4-16 (439437)
18 17 and 3 (4283)
19 limit 18 to (human and english language and yr="2003 -Current") (1632)

CINAHL

#	Query	Results
S13	S3 AND S12	280
S12	(S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11)	125638
S11	IgA or IGG or TTG or EMA or IgG-tTG or anti-gliadin or antigliadin or AGA or human leukocyte antigens or HLA	3165
S10	serodiagnos* or immunoassay* or MIA	4318
S9	serum or serologic* or blood or antibod*	120669
S8	"gliadin"	44
S7	(MH "Enzyme-Linked Immunosorbent Assay")	3645
S6	Transglutaminase*	82
S5	(MH "Antibodies")	2060
S4	(MH "Serologic Tests+")	3099
S3	S1 or S2	1167
S2	Celiac or coeliac or nontropical sprue or non-tropical sprue or gluten NEAR enteropath*	1167
S1	(MH "Celiac Disease")	990

Appendix 2: Characteristics of Systematic Reviews Included

Table A1: Characteristics of Systematic Reviews

Systematic Review	Interventions	Inclusion Criteria for Studies	Number of Studies Included	Analysis
Lewis et al. (2006) (26)	▪ IgA tTG ▪ EMA	▪ Adults and children. ▪ Untreated celiac disease. ▪ Both tests (EMA, tTG) done in all patients. ▪ All celiac cases underwent biopsy. ▪ Number of controls who underwent biopsy was clearly stated. ▪ Literature search ended: September 2005	▪ 34 studies (EMA) ▪ 42 studies (IgA tTG)	Pooled analysis performed, details about methodology not provided.
Zintzaras et al. (2006) (28)	▪ IgA tTG	▪ Adults and children. ▪ Consecutive untreated celiac disease diagnosed at least by biopsy ▪ > 10 subjects included. ▪ Controls free of celiac disease ▪ Literature search ended: March 2005	▪ 21 studies (IgA tTG)	Pooled analysis with both fixed and random effects models. Results of random effects models included in this report.
Hill et al. (2005) (27)	▪ IgA tTG ▪ IgA AGA ▪ IgG AGA ▪ IgA EMA ▪ IGA ARA	▪ Adults and children. ▪ Studies that evaluated the sensitivity and specificity of serologic tests for the diagnosis of celiac disease. ▪ Biopsy performed in both celiac disease cases and controls. ▪ Controls had to have normal histologic findings on biopsy or undergone small bowel biopsy evaluation. ▪ Literature search ended: 2003	▪ 22 studies (IgA tTG) ▪ 32 studies (IgA EMA) ▪ 26 studies (IgA AGA) ▪ 17 studies (IgG AGA) ▪ IgA ARA – not evaluated due to sparcity of studies identified	Study results not pooled. Range of sensitivity and specificity results for the different studies included in this report.
Rostom et al. (2004) (3)	▪ IgA tTG ▪ IgA AGA ▪ IgG AGA ▪ IgA EMA ▪ IgG EMA	▪ Adults and children. ▪ Both celiac disease patients and controls had biopsy. ▪ Description of biopsy criteria provided. ▪ Serology test results known for cases and controls. ▪ Control group could not include those with Marsh 1 or 2 lesions. ▪ Excludes AGA test without commercial ELISA kit or before 1990. ▪ English language. ▪ Diagnosis of celiac disease based on a Marsh 3a or greater lesion (not used as inclusion criterion) ▪ Literature search ended: 2003	▪ 19 studies (IgA tTG) ▪ 35 studies (IgA EMA) ▪ 35 studies (IgA AGA) ▪ 30 studies (IgG AGA) ▪ 3 studies (IgG EMA) ▪ 5 studies (IgG tTG)	Results divided by age group, study design, and type of antigen. Study results pooled if clinically and statistically appropriate. Heterogeneity among study results identified graphically through ROC curves. Statistical heterogeneity assessed through Pearson's Chi Square test.
NICE (2009) (11)	▪ IgA tTG ▪ IgG tTG ▪ IgA AGA ▪ IgG AGA ▪ IgA EMA ▪ IgG EMA ▪ IgA DGP ▪ IgG DGP	▪ Adults and children. ▪ Suspected celiac disease. ▪ At least one celiac disease serologic test done with results confirmed by biopsy.	▪ 19 studies (IgA tTG) ▪ 2 studies (IgG tTG) ▪ 31 studies (IgA AGA) ▪ 25 studies (IgG AGA) ▪ 24 studies (IgA EMA) ▪ 1 study (IgG EMA) ▪ 2 studies (IgA DGP) ▪ 2 studies (IgG DGP)	Results not pooled due to heterogeneity among studies. Results summarized through forest plots and ROC curves.

AGA refers to anti-gliadin antibody; ARA antireticulin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; IgA immunoglobulin A; IgG immunoglobulin G; ROC receiver operating characteristics; tTG tissue transglutaminase

Appendix 3: Sensitivity and Specificity of Diagnostic Tests, Results of Systematic Reviews

Table A2: Results of Systematic Reviews

Systematic Review	Sensitivity Pooled, % (95% CI) or Range	Specificity Pooled, % (95% CI) or Range
Lewis et al. (2006) (26) No details about pooled analysis	▪ IgA tTG (all): 92.8% (91.9, 93.6) ▪ IgA tTG (rh): 93.8% (92.8, 94.7) ▪ EMA (all): 93.0% (92.1, 93.8)	▪ IgA tTG (all): 98.1% (97.8, 98.4) ▪ IgA tTG (rh): 98.7% (98.5, 98.9) ▪ EMA (all): 99.7% (99.5, 99.8)
Zintzaras et al. (2006) (28) Random effects model used	▪ IgA tTG (rh): 94.0% (90.0, 96.0) ▪ IgA tTG (ph): 94.0% (87.0, 97.0) ▪ IgA tTG (gp): 91.0% (87.0, 94.0)	▪ IgA tTG (rh): 95.0% (93.0, 97.0) ▪ IgA tTG (ph): 94.0% (88.0, 97.0) ▪ IgA tTG (gp): 89.0% (81.0, 94.0)
Hill et al. (2005) (27)	▪ IgA tTG: 54-100% ▪ IgA AGA: 52-100% ▪ IgA EMA: 86-100% ▪ IgG AGA: 57-100%	▪ IgA tTG: 79-100% ▪ IgA AGA: 71-100% ▪ IgA EMA: 90-100% ▪ IgG AGA: 47-94%
Rostom et al. (2004) (3) Results of pooled analyses in table A3	▪ IgA tTG: 23.0 – 100% ▪ IgA AGA: 22.2-100% ▪ IgA EMA: 74.0-100% ▪ IgG AGA: 17.0-100% ▪ IgG tTG: 23.0-100% ▪ IgG EMA: 39-100% ▪ Combinations: 83.0-100%	▪ IgA tTG: 80.0-100% ▪ IgA AGA: 45.0-100% ▪ IgA EMA: 88.7-100% ▪ IgG AGA: 36.0-100% ▪ IgG tTG: 80.0-100% ▪ IgG EMA: 98.3-100% ▪ Combinations: 36.0-100%
NICE (2009) (11)	▪ IgA tTG: 38-100% ▪ IgG tTG: 23-85% ▪ IgA AGA: 23-100% ▪ IgG AGA: 46-100% ▪ IgA EMA: 68-100% ▪ IgG EMA: 39% ▪ IgA DGP: 90.8-98.3% ▪ IgG DGP: 95-96.7% ▪ IgA / IgG DGP: 97.5-98.3%	▪ IgA tTG: 25-100% ▪ IgG tTG: 89-98% ▪ IgA AGA: 45-100% ▪ IgG AGA: 77-99% ▪ IgA EMA: 89-100% ▪ IgG EMA: 98% ▪ IgA DGP: 94.7-98.3% ▪ IgG DGP: 98.2-100% ▪ IgA / IgG DGP: 98.2-98.8%

AGA refers to anti-gliadin antibody; DGP deamidated gliadin peptides; EMA endomysial antibody; Gp guinea-pig; Rh human recombinant; IgA immunoglobulin A; IgG immunoglobulin G; NICE National Institute for Health and Clinical Excellence; Ph purifed human; ROC receiver operating characteristics; tTG tissue transglutaminase

Table A3: Results from AHRQ Systematic Review

Test	# Studies	Sensitivity (95% CI)	Specificity (95% CI)
		Adults	
tTG IgA (GP)	5	2 Cohort: 100% 3 case-control: 81% - 88%	Pooled: 95.3% (92.5, 98.1)
tTG IgA (hu)	3	Pooled: 98.1% (90.1, 99.7)	Pooled: 98% (95.8, 99.1)
EMA IgA (Me)	11	Pooled: 97% (95.7, 98.5)	Pooled: 99.6% (98.8, 99.9)
EMA IgA (hu)	6	Pooled: 90.2% (85.9, 93.4)	Pooled: 100% (99.1, 100%)
EMA IgG (Me)	1	39%	98%
AGA IgA	10	> 80% in 5 studies (> 90% in 3) < 65% in 4 studies	> 80%
AGA IgG	7	17% - 100%	> 70%
AGA IgA + IgG	3	77-100%	90-97%
		Children	
tTG IgA (Gp)	5	Pooled: 93.1% (88.8, 95.9)	Pooled: 96.3% (93.1, 98)
tTG IgA (hu)	3	Pooled: 95.7% (90.3, 98.1)	Pooled: 99% (94.6, 99.8)
EMA IgA (Me)	18	Pooled: 96.1% (94.4, 97.3)	Pooled: 97.4% (96.3, 98.2)
EMA IgG (Me)	1	100%	100%
EMA IgA (hu)	5	Pooled: 96.9% (93.5, 98.6)	100% in 4 out 5 studies
EMA IgA HU + AGA IgA	1	100% (either positive) 100% (both positive)	73% (either positive) 93% (both positive)
AGA IgA	19	> 80% (10 studies)	> 80% (15 studies)
AGA IgG	17	> 80% (in 15 out of 17 studies)	>79% (11 studies) < 70% in 6 studies
AGA IgA + IgG	6	83% - 100% (either test positive) 50% (both positive)	71-99% (either test positive) 67% (both positive, 36% otherwise)
		Adults and Children	
tTG IgA (Gp)	4	> 94% in 3 studies 84% in 1 study (considered outlier)	Pooled: 95.4% (92.7, 97.2)
tTG IgG (Gp)	2	> 98%	23% and 62%
tTG IgA (hu)	2	Pooled: 90.2% (86.4, 93)	Pooled: 95.4% (91.5, 97.6)
EMA IgA (Me)	4	> 86% (3 studies, 98% in 1) 75% in 1 study	> 98%
EMA IgA (hu)	2	Pooled: 93% (88.1, 95.4)	Pooled: 100% (97.5, 100)
AGA IgA	4	< 70% to 91%	> 90%
AGA IgG	4	> 80% (2 studies)	< 80% (in 3 out of studies)
tTG IgA + IgG	1	98.5% (either positive)	100%

Source: Agency for Healthcare Research and Quality (AHRQ) (3)

AGA refers to anti-gliadin antibody; CI confidence interval; DGP deamidated gliadin peptides; EMA endomysial antibody; Gp guinea-pig; hu human; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; ROC receiver operating characteristics; tTG tissue transglutaminase

Appendix 4: Characteristics of Diagnostic Studies Included in the Review

Table A4. Characteristics of studies assessing serology tests for the detection of celiac disease.

Study, N Cases/ control	Type of study	N. diseased / N. non-diseased	Recruitment, Period	Symptoms	Interventions	Blood test Cut-off levels,	Biopsy blinded to serology Procedure	Time lag btw blood test and biopsy	Biopsy criteria # biopsies	Withdrawals
Emami et al, 2008 (29) N= 350 Adults and children	Retrospective and prospective (biopsy) 1 centre	CD: 21 Non-CD: 329 (Marsh 0-2)	Suspected CD Consecutive subjects 2004-2006	Classic, non-specific, atypical	IgA tTG (Hr) Total serum IgA	> 10 U/ml	Blinded D2 biopsy ≥ 4 biopsies 2 pathologists	< 2 mos (personal communication with the author) Blood test performed before biopsy.	VA (Marsh 3a, b, c) + GFD clinical response Seronegative CD included	No withdrawals
Hopper et al, 2008 (30) N= 2,000 Adults	Prospective 1 centre	CD: 77 Non-CD: 1,923 (Marsh 0-2)	Referred for gastroscopy Consecutive subjects 2004-2006	Classic and atypical symptoms	IgA tTG (Hu) IgA EMA (Me) IgA AGA IgG AGA Test combinations Total serum IgA	> 15 U/ml unclear > 15 U/ml > 15 U/ml	Blinding unclear D2 biopsy 4 biopsies 1 pathologist (2nd pathologist for CD and equivocal cases)	Performed at the same time.	CD: VA (Marsh 3a, b, c) + serology + symptoms From Oberhuber 1999	N/A
Poddar et al, 2008 (31) N= 333 Children < 14 yrs	Prospective	CD: 180 Non-CD: 126 (suspected CD w/o VA)	Suspected CD Unclear if consecutive subjects 2000-2002	Chronic diarrhea, FTT, pallor.	IgA tTG (Gp)	> 4 U/Ml > 10 U/ml > 20 U/ml	Blinding unclear Site and # of duodenal biopsies NR # pathologists: NR	Unclear	VA + unequivocal response to GFD From ESPGAN1990 VA put on GFD regardless of tTG status	Children w/o GFD response or incomplete f-up excluded, N=27)
Rashtak et al, 2008 (45) N= 216 Adults and children	Retrospective cohort 1 centre	CD: 92 Non-CD: 124 (random sample of Marsh 0, age and sex-matched subjects)	Referred to GI clinic. Suspected CD Unclear if consecutive subjects 1999-2006 (biopsy)	GI symptoms, unexplained weight loss, anemia, or referred to rule out CD GFD > 2 wks before test excluded	IgA AGA IgG AGA IgA DGP IgG DGP IgA tTG (Hu) IgG tTG (Hu)	> 30 EU > 30 EU > 20 EU > 20 EU > 6 U/ml > 4 U/ml	Blinding unclear duodenal biopsy N. unknown N. pathologist unknown	Blood test 6 months before or 3 months after CD diagnosis (biopsy)	VA (Marsh 3a, b, c) From ESPGAN 1990 and NASPGHAN 2005	N/A
Santaolalla, 2008 (43) N= 315 Adults and children	Prospective 1 centre	CD: 42 Non-CD: 39 (normal duodenal biopsy, DQ2 neg., 5 DQ8 postive)	Recruited from outpatient clinic Unclear if consecutive subjects 2003-2005	GI or extraintestinal symptoms, or CD-risk group. Excludes IgA deficient	IgA tTG (substrate NR) Total serum IgA	> 2 U/ml	Blinding unclear D2 and D3 4 biopsies No. pathologists unclear	Performed at the same time.	Definite: DQ2 or DQ8 positive + VA (Marsh 3¦) + histological/ serological response to GFD From American Gastroenterological Association 2006	N/A

Study, N Cases/ control	Type of study	N. diseased / N. non-diseased	Recruitment, Period	Symptoms	Interventions	Blood test Cut-off levels,	Biopsy blinded to serology Procedure	Time lag btw blood test and biopsy	Biopsy criteria # biopsies	Withdrawals
Barker 2005 (32) N=103 Children	Retrospective cohort 1 centre	CD: 58 Non-CD: 45	Children with previous biopsy and blood test 2000-03	Symptomatic or not, DM 1, IBD, thyroid autoimmune disease, MS	IgA tTG (Hu)	≥ 20 U/ml	Blinded Biopsy site and N. pathologists: NR	Test before or on the same day as biopsy	Marsh 2 or 3 (Oberhuber 1999)	Yes
Wolters et al. (2002) (42) N=101 Children	Retrospective cohort 1 centre	CD: 52 Non-CD: 49 (no abnormalities or non-specific changes)	Subjects seen at GI clinic, suspected CD Unclear if consecutive subjects 1996-2000	Abdominal pain/distentio, growth failure, diarrhea, anemia	IgA tTG (Hr) IgA tTG (gp) IgA EMA (Me) IgA AGA IgG AGA	> 8 U/ml > 1 U/ml Dilution ≥ 1:5 > 4 U/ml > 150 U/ml	Blinding unclear D2 or D3 Several biopsies	Unclear	Subtotal or total VA + crypt hyperplasia, inflammatory infiltrate in lamina propria.	N/A
Reeves et al. (2006) (33) N=254 Adults and children	Prospective Multicentre	CD: 26 Non-CD: 228 (no CD on biopsy)	Referred for GI clinic Suspected CD Consecutive subjects 2003-2004	Symptoms consistent with CD.	IgA tTG (Hr) IgA EMA (Me) IgA AGA IgG AGA	> 10 U/ml ≥ 1:10 dilution > 20 U/ml > 15 U/ml	Blinded D2 3 biopsies 2 pathologists	Performed at the same time	According to modified Marsh criteria	N/A
Niveloni et al. (2007) (34) N= 141 Adults	Prospective 1 centre	CD: 60 Non-CD: 81 (Marsh 0)	Attending 1st clinic visit Suspected CD Consecutive subjects 2004-2005	Classic, atypical, asymptomatic	IgA tTG (Hu) IgA DGP IgG DGP EMA only in false + or – Inova	> 20 U/ml > 20 U/ml > 20 U/ml	Blinded Distal duodenum ≥ 3 biopsies	Performed at the same time.	Marsh 3a, b,c* From 1992, 1999 + tTG or EMA serology and/or histological response to GFD.	N/A
Teesalu et al. (2009) (35) N=270 Children	Prospec tive	CD: 173 Non-CD: 97 (normal biopsy)	Children investigated for CD Not consecutive 1996-2007	Abdominal pain, GI symptoms	IgA tTG (Hr) IgG tTG (Hu)	≥ 12 AU/ml ≥ 16 AU/ml	Unclear	Unclear	ESPGAN (1990) Marsh 1-3	N/A
Parizade et al. (2009) (36) N=116 Children	Prospective	CD: 85 Non-CD: 31	Suspected CD, referred to GI clinic Unclear if consecutive subjects	Symptoms (FTT, anemia, GI, abdominal pain), conditions associated, relatives of CD patients	IgA tTG (NR) IgG tTG (NR) IgA/G DGP IgA/G EMA (Me)	> 8 U/ml > 4 U/ml > 10 U/ml > 20 U/ml > 1:5 dilution	Blinded Distal duodenum ≥ 5 biopsies	Performed at the same time.	Marsh criteria Marsh 1-3 When discrepancy btw biopsy and serology DQ2 and DQ8 tested.	N/A
Dahlbom et al. (2008) (37) N=150 Children	Retrospective cohort	CD: 108 Non-CD: 42 (normal biopsy)	Suspected CD, referred for biopsy Consecutive subjects 2002-2006	Suspected CD	IgA tTG (Hr) IgG tTG (Hr) IgA EMA (Me)	> 3 U/ml > 6 U/ml > 1:10 dilution	Unclear (ESPGAN) 2 pathologists	Unclear	ESPGAN (1990)	N/A
Basso et al. (2009) (38) (2006 publ. assumed to be part of	Retrospective cohort 1 centre	CD: 161 Non-CD: 129	Suspected CD referred for endoscopy Consecutive	Suspected CD	IgA tTG (Hu) IgG tTG (Hu) N=28/16 for tTG IgA DGP IgG DGP	> 20 AU/ml > 20 AU/ml > 20 AU/ml	NR (Marsh-Oberhuber)	Performed at the same time.	Marsh-Oberhuber type 1-3c	N/A

Study, N Cases/ control	Type of study	N. diseased / N. non-diseased	Recruitment, Period	Symptoms	Interventions	Blood test Cut-off levels,	Biopsy blinded to serology Procedure	Time lag btw blood test and biopsy	Biopsy criteria # biopsies	Withdrawals
this) N=290 Children			subjects 2002-2007			> 10 AU/ml				
Baviera et al. (2007) (39) N=180 Children	Prospective Multicentre	CD: 103 Non-CD: 103 (no gastrointestinal disease)	Suspected CD, referred for biopsy due to GI symptoms Unclear if consecutive subjects	Symptoms not specified	IgA AGA	> 6 IU/ml	NR (ESPGAN)	< 1 month difference	ESPGAN (1990)	N/A
Agardh et al. (2007) (40) N=176 Children	Prospective 1 centre	CD: 119 Non-CD: 57 (normal biopsy)	Suspected CD referred for biopsy Unclear if consecutive subjects	GI symptoms, FTT	IgA tTG (Hu) IgG tTG (Hu) IgA DGP IgG DGP IgA/G tTG/DGP	> 20 AU for all tests	NR ESPGAN	Unclear	ESPGAN (19 90)	N/A
Poddar et al. (2002) (44) N= 97 Children	Prospective 1 centre	CD: 50 Non-CD: 47 (Not diagnosed with CD)	Children with suspected CD seen at GI clinic 1997-1998	Chronic diarrhea, FTT, pallor	IgA AGA	> 5 U/ml > 10 U/ml	Unclear	Unclear	VA + unequivocal clinical response to GFD. ESPGAN 1990 Children with no good response at 6 wks excluded	N/A
Leach et al. (2008) (41) N= 76 Children	Prospective 1 centre	CD: 32 Non-CD: 44 (no endoscopic/ histologic CD/ inflammation sign + normal systemic inflammatory markers)	Suspected CD referred for endoscopy Consecutive subjects	GI symptoms	IgA tTG (Hr) IgA DGP IgG DGP Combined DGP	> 15 U/ml > 10 U/ml > 25 U/ml > 25 U/ml	No details ESPGAN 1990	Performed at the same time	ESPGAN (1990) + positive serology	Excludes seronegative CD

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hr human recombinant; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

*total IgA < 0.5 g/L

¦ Only the 42 cases with Marsh 3 were included in the table in order to be consistent with other studies, therefore 28/70 excluded.

Appendix 5: Results of Diagnostic Studies Included in the Review

Table A5. Study Results serology tests (tTG IgA)

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Emami et al. (2008) (29) 21 / 329 2004-06	Symptoms Mean age: 31.4 yrs Mixed	0/13 false negatives	Marsh 3 + GFD response (clinical) Seronegative CD included 3a-b: 16 (76%) 3c: 5 (24%)	Marsh 0-2	≥ 4 biopsies D2 0-2 months (author info)	IgA tTG > 10 U/ml (Hr)	8	6	13 (none IgA def)	323	38%	98%
Hopper et al. (2008) (30) 77/ 1,923 2004-06	Symptoms Mean age: 55.8 yrs Adults	14 (0.7%)	Marsh 3 + serology + symptoms Seronegative CD included 3a-b: 59 (77%) 3c: 18 (23%)	No VA	4 biopsies D2 Same time	IgA tTG > 15 U/ml (Hu)	70	175	7	1748	90.9%	90.9%
Poddar et al. (2008) (31) 180/126 2000-02	Symptoms Mean age: 6.4 yrs Children	1 in false negatives	Marsh 3 + GFD response (clinical)	No VA or specific features of disease	NR	IgA tTG (Gp) > 4 U/ml > 10 U/ml > 20 U/ml	 178 170 157	 9 4 2	 2 10 23	 117 122 124	 99% 94% 87%	 93% 97% 98%
Rashtak et al. (2008) (45) 92/ 124 1999-06	Symptoms Mean age: 45 yrs Mixed	NR	Marsh 3 3a-b: 50 (54%) 3c: 42 (46%)	Marsh 0	NR Duodenum Test 6 months before or 3 months after biopsy	IgA tTG > 4 U/ml (Hu)	72	3	20 (1 IgA def)	121	78%	98%
Santaolalla (2008) (43) 42/39 2003-05	Symptoms or not * Age? Mixed	0 (exclusion criteria)	Marsh 3¶ + GFD response (histolgy/serology) + genetic test 3a,b: 31 (73.8%) 3c: 11 (26.2%)	Normal biopsy	4 biopsies D2 and D3 Same time	IgA tTG > 2 U/ml (substrate NR)	39	0	3	39	92.9%	100%
Wolters et al. (2002) (42) 52/49 1996-00	Symptoms Mean age: 4 yrs Children	NR	Marsh 3 + inflammatory infiltrate in lamina propria	No abnormalities or no specific changes	Several biopsies D2 or D3 Unclear	IgA tTG > 8 U/ml (Hr) > 1 U/ml (Gp)	 50 50	 0 4	 2 2	 49 45	 96% 96%	 100% 92%
Reeves et al. (2006) (33) 26/ 228 2003-04	Symptoms Mean age: 47.8 yrs Mixed	27 (10.6%) partial or total 25 (9.4%) - total Part of testing indications	Marsh 3	No CD on biopsy	3 biopsies D3 Same time	IgA tTG > 10 U/ml (Hr) (most accurate of several tests used)	23	37	3	191	88.5% w/o A def.?	83.8%

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Niveloni et al. (2007) (34) 60/ 81 2004-05	Symptoms or not¦ CD detected only in symptomatic Mean age: 37 yrs Adults	NR	Marsh 3 + serology + GFD response (histology/serology) 3a-b: 11 (18.3%) 3c: 49 (81.7%)	Marsh 0	≥ 3 biopsies Distal duodenum Same time	IgA tTG > 20 U/ml (NR)	57	2	3	79	95%	97.5%
Barker et al. (2005) (32) 58/45 2000-03	Symptomatic or not, DM 1, autoimmune thyroid disease etc. Children	2 in false negatives	Marsh 2 or 3	Marsh < 2	NR Blood test before or same day as biopsy	IgA tTG ≥ 20 U/ml (Hu)	55	10	3 (2 IgA def)	35	94.8%	77.8%
Teesalu et al. (2009) (35) N=173/97	Symptoms Children	7 (7.2%) among controls. Part of indications for testing	Marsh 1-3 1-2: 7 (4%) 3a-b: 104 (60%) 3c: 62 (36%)	Normal biopsy	Unclear	IgA tTG ≥ 12 AU/ml (Hr)	154	0	19	97	89%	100%
Parizade et al. (2009) (36) 85/31 2006-08	Symptoms, or relatives Children	5 (4.3%) Part of indications for testing	Marsh 1-3 Marsh 1-2: 8 (9%) 3a-b: 48 (57%) 3c: 29 (34%)	Marsh 0	Distal duodenum ≥ 5 biopsies Same time	IgA tTG > 8 U/ml (substrate NR) Phadia IgA tTG ≥ 4 U/ml	80 79	4 8	5 6	27 23	94.1% 92.9%	87.1% 74.2%
Leach et al. (2008) (41) 32/44	GI symptoms Children	2 (2.6%) in CD group	ESPGAN 1990	no endoscopic/ histologic CD/ inflam. sign + normal systemic inflame. markers	Unclear Same time	IgA tTG > 15 U/ml (Hr)	27	4	5	40	84.4%	90.9%
Dahlbom et al. (2008) (37) 108/42 2002-06	Suspected CD Children	7 (4.2%) Part of indications for testing	ESPGAN 1990	Normal biopsy	Unclear Unclear	IgA tTG > 3 U/ml (Hr)	103	3	5	39	85.4%	92.9%
Basso et al. (2009) (38) 28/16	Suspected CD Children Mean age: 6.5-9 yrs	5 (1.7%)	Marsh Oberhuber type1-3c	No CD	Unclear Same time	IgA tTG > 20 AU/ml (Hu)	26	1	2	15	92.5%	97.6%
Agardh et al. (2007) (40)	Suspected CD Children Mean age: 3.5 - 5.7 yrs	7 (4.0%) Part of indications for testing	ESPGAN	Normal biopsy	Unclear Unclear	IgA tTG > 20 AU/ml (Hu)	115	2	4	55	96.6%	96.5%

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity;TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

* Diabetes mellitus 1, 1st degree relatives, autoimmune thyroiditis. ¦ Diabetes mellitus type 1, 1st degree relatives of cases.

¶ Marsh 1 and 2 excluded from the analyses in order to be consistent with other studies, most studies defined CD as Marsh 3 lesions

Table A6. Study Results serology tests (tTG IgG)

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition, Marsh 3 (%)	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Rashtak et al. (2008) (45) 92/ 124 1999-06	Symptoms Mean age: 45 yrs Mixed	NR	Marsh 3 3a-b: 50 (54%) 3c: 42 (46%)	Marsh 0	NR Duodenum Test 6 mos before or 3 mos after biopsy	IgG tTG > 6 U/ml (Hu)	42	12	50	112	46%	90%
Teesalu et al. (2009) (35) N=173/97	Symptoms Children	7 (7.2%) among controls. Part of indications for testing	Marsh 1-3 1-2: 7 (4%) 3a-b: 104 (60%) 3c: 62 (36%)	Normal biopsy	Unclear	IgG tTG ≥ 16 AU/ml	84	1	89	96	48.6%	99%
Parizade et al. (2009) (36) 85/31 2006- 08	Symptoms, or relatives Children	5 (4.3%) Part of indications for testing	Marsh 1-3 Marsh 1-2: 8 (9%) 3a-b: 48 (57%) 3c: 29 (34%)	Marsh 0	Distal duodenum ≥ 5 biopsies Same time	IgA tTG > 8 U/ml	58	2	27	29	67.7%	93.5%
Dahlbom et al. (2008) (37) 108/42 2002-06	Suspected CD Children	7 (4.7%)	ESPGAN 1990	Normal biopsy	Unclear	IgG tTG > 6 U/ml	86	4	22	38	79.6%	90.5%
Agardh et al. (2007) (40)	Suspected CD Children Mean age: 3.5-5.7 yrs	5 (8.7%) in controls	ESPGAN	Normal biopsy	Unclear	IgG tTG > 20 AU/ml	15	0	104	57	12.6%	100%

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity; TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

Table A7. Study Results serology tests (IgA AGA)

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Hopper et al. (2008) (30) 77/ 1,923 2004-06	Symptoms Mean age: 55.8 yrs Adults	14 (0.7%)	Marsh 3 + serology + symptoms Seronegative CD included	No VA	4 biopsies D2 Same time	IgA AGA > 15 U/ml	38	200	39	1,723	49.4%	89.6%
Rashtak et al. (2008) (45) 92/ 124 1999-06	Symptoms Mean age: 45 yrs Mixed	NR	Marsh 3	Marsh 0	NR Duodenum Test 6 m bef or 3 m after biopsy	IgA AGA > 30 EU	58	12	34	112	63%	90%
Wolters et al. (2002) (42) 52/49 1996-00	Symptoms Mean age: 4 yrs Children	NR	Marsh 3 + inflamm infiltrate in lamina propria	No abnormalities or no specific changes	Several biopsies D2 or D3 Unclear	IgA AGA > 4 U/ml	43	7	9	42	83%	86%
Reeves et al. (2006) (33) 26/ 228 2003-04	Symptoms Mean age: 47.8 yrs Mixed	25 (9.4%) - total Part of indications for testing	Marsh 3	No CD on biopsy	3 biopsies D3 Same time	IgA AGA > 20 U/ml	12	34	14	194	46.2%	85.1%
Poddar et al. (2002) (44) 50/47	Symptoms Mean age: 6.5 yrs Children	NR	ESPGAN + GFD (clinical) Excludes no GFD response	Not diagnosed with CD	NR Unclear	IgA AGA > 5 U/ml > 10 U/ml	47 44	4 0	3 6	43 47	94% 88%	91.5% 100%
Baviera et al. (2007) (39) 103/63 Children	Symptoms	0	ESPGAN criteria	NR	NR < 1 month	IgA AGA > 6IU/ml	77	13	26	50	74.8%	79.4%

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; mos months; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity; TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

¦ Diabetes mellitus type 1, 1st degree relatives of cases.

Table A8. Study Results serology tests (IgG AGA)

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Hopper et al. (2008) (30) 77/ 1,923 2004-06	Symptoms Mean age: 55.8 yrs Adults	14 (0.7%)	Marsh 3 + serology + symptoms Seronegative CD included	No VA	4 biopsies D2 Same time	IgG AGA > 15 U/ml	37	81	40	1,842	48.1%	95.8%
Rashtak et al. (2008) (45) 92/ 124 1999-06	Symptoms Mean age: 45 yrs Mixed	NR	Marsh 3	Marsh 0	NR Duodenum Test 6 m bef or 3 m after biopsy	IgG AGA > 30 EU	39	12	53	112	42%	90%
Wolters et al. (2002) (42) 52/49 1996-00	Symptoms Mean age: 4 yrs Children	NR	Marsh 3 + inflamm infiltrate in lamina propria	No abnormalities or no specific changes	Several biopsies D2 or D3 Unclear	IgG AGA > 150 U/ml	43	10	9	39	83%	80%
Reeves et al. (2006) (33) 26/ 228 2003-04	Symptoms Mean age: 47.8 yrs Mixed	25 (9.4%) - total Part of indications for testing	Marsh 3	No CD on biopsy	3 biopsies D3 Same time	IgG AGA > 15 U/ml	16	36	10	192	61.5%	84.1%

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; mos months; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity; TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

¦ Diabetes mellitus type 1, 1st degree relatives of cases.

Table A9. Study Results serolo gy tests (IgA DGP)

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Rashtak et al. (2008) (45) 92/ 124 1999-06	Symptoms Mean age: 45 yrs Mixed	NR	Marsh 3	Marsh 0	NR Duodenum Test 6 mos before or 3 mos after biopsy	IgA DGP > 20 U	68	6	24	118	74%	95%
Niveloni et al. (2007) (34) 60/ 81 2004-05	Symptoms or not¦ Mean age: 37 yrs Adults	NR	Marsh 3 + serology + GFD (hist/serol)	Marsh 0	≥ 3 biopsies Distal duodenum Same time	IgA DGP > 20 U/ml	59	5	1	76	98.3%	93.8%
Leach et al. (2008) (41) 32/44	GI symptoms Children	2 (2.6%) in CD group	ESPGAN 1990	no endoscopic/ histologic CD/ inflammation sign + normal systemic inflammatory markers	Unclear Same time	IgA DGP > 10 U/ml 0-5 yrs (n= 7/7)	27 4	4 0	5 3	40 7	83.3% 57.1%	91.5% 100%
Basso et al. (2009) (38) (2006 publ. assumed to be part of this) 161/129 2002-07	Suspected CD Children Mean age: 6.5-9 yrs	NR	Marsh Oberhuber type1-3c	No CD	Unclear Serology before biopsy	IgA DGP > 20 AU/ml	130	9	31	120	80.7%	92.9%
Agardh et al. (2007) (40)	Suspected CD Children Mean age: 3.5-5.7 yrs	5 (8.7%) in controls	ESPGAN	Normal biopsy	Unclear Unclear	IgA DGP > 20 AU/ml	108	5	11	52	90.8%	91.2%

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; mos months; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity; TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

Table A10. Study Results serology tests (IgG DGP)

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Rashtak et al. (2008) (45) 92/ 124 1999-06	Symptoms Mean age: 45 yrs Mixed	NR	Marsh 3	Marsh 0	NR Duodenum Test 6 m bef or 3 m after biopsy	IgG DGP > 20 U	60	2	32	122	65%	98%
Niveloni et al. (2007) (34) 60/ 81 2004-05	Symptoms or not¦ Mean age: 37 yrs Adults	NR	Marsh 3 + serology + GFD (hist/serol)	Marsh 0	≥ 3 biopsies Distal duodenum Same time	IgG DGP > 20 U/ml (DGP)	58	0	2	81	96.7%	100%
Leach et al. (2008) (41) 32/44	GI symptoms Children	2 (2.6%) in CD group	ESPGAN 1990	no endoscopic/ histologic CD/ inflammation sign + normal systemic inflammatory markers	Unclear Same time	IgG DGP > 25 U/ml	27	4	5	40	84.4%	90.9%
Basso et al. (2009) (38) (2006 publ. assumed to be part of this) 161/129 2002-07	Suspected CD Children Mean age: 6.5-9 yrs	NR	Marsh Oberhuber type1-3c	No CD	Unclear Serology before biopsy	IgG DGP > 10 AU/ml	129	4	32	125	80.1%	96.9%
Agardh et al. (2007)	Suspected CD Children Mean age: 3.5-5.7 yrs	5 (8.7%) in controls	ESPGAN	Normal biopsy	Unclear Unclear	IgG DGP > 20 AU/ml	113	8	6	49	95.0%	86.0%

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; mos months; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity; TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

Table A11. Study Results serology tests (EMA)

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test Cut-off levels	TP	FP	FN	TN	Sens (%)	Spec (%)
Wolters et al. (2002) 52/49 1996-00	Symptoms Mean age: 4 yrs Children	NR	Marsh 3 + inflamm infiltrate in lamina propria	No abnormalities or no specific changes	Several biopsies D2 or D3 Unclear	IgA EMA ≥ 1:5 dilution	48	5	4	44	92%	90%
Reeves et al. (2006) 21/ 140 2003-04	Symptoms Mean age: 47.8 yrs Mixed	25 (9.4%) - total Part of indications for testing	Marsh 3	No CD on biopsy	3 biopsies D3 Same time	IgA EMA ≥ 1:10 dilution	13	11	8	129	61.9%	92.1%
Parizade et al. (2009) 85/31 2006-08	Symptoms, or relatives Children	5 (4.3%) Part of indications for testing	Marsh 1-3 Marsh 1-2: 8 (9%) 3a-b: 48 (57%) 3c: 29 (34%)	Marsh 0	Distal duodenum ≥ 5 biopsies Same time	EMA > 1:5	81	8	4	23	95.3%	74.2%
Dahlbom et al. (2008) 108/42 2002-06	Suspected CD Children	7 (4.7%)	ESPGAN 1990	Normal biopsy	Unclear Unclear	IgA EMA > 1:10 dilution	103	5	5	37	95.4%	88.1%

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; mos months; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity; TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

* Diabetes mellitus 1, 1st degree relatives, autoimmune thyroiditis.

¦ Diabetes mellitus type 1, 1st degree relatives of cases.

Table A12. Study Results serology tests - Combinations

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test	TP	FP	FN	TN	Sens (%)	Spec (%)
Both tTG (A) and EMA positive												
Hopper et al. (2008) 77/ 1,923 2004-06	Symptoms Mean age: 55.8 yrs Adults	14 (0.7%)	Marsh 3 + serology + symptoms Seronegative CD included	No VA	4 biopsies D2	tTG pos AND EMA pos tTG pos OR EMA pos (ref tTG alone)	66 71	27 187	11 6	1,896 1,736	85.7% 92.2% (ref 90.9%)	98.6% 90.3% (ref. 90.9%)
Both AGA (A) and AGA (G) positive												
Hopper et al. (2008) 77/ 1,923 2004-06	Symptoms Mean age: 55.8 yrs Adults	14 (0.7%)	Marsh 3 + serology + symptoms Seronegative CD included	No VA	4 biopsies D2	AGA (A) + AGA (G) (ref AGA A)	28	23	49	1,900	36.4% (ref 49.4%)	98.8% (ref 89.6%)
tTG and DGP												
Niveloni et al. (2007) 60/ 81 2004-05	Symptoms or not¦ Mean age: 37 yrs Adults	NR	Marsh 3 + serology + GFD (hist/serol)	Marsh 0	≥ 3 biopsies Distal duodenum	Either tTg or DGP (A) pos Either tTG or DGP (G)pos tTG, DGP (A) or DGP (G) pos (ref tTG)	60 60	6 2	0 0	75 79	100% 100% 100% (ref 95%)	92.6% 97.5% 96.3% (ref 97%)
Basso et al. (2009) (2006 publ. assumed to be part of this) 28/16 2002-07	Suspected CD Children Mean age: 6.5-9 yrs	NR	Marsh Oberhuber type1-3c	No CD	Unclear Serology before biopsy	IgA tTG AND IgA DGP IgA tTG AND IgG DGP All 3 tests positive (ref tTG)	23 22 20	0 1 0	5 6 8	16 15 16	80.7% 77.6% 72% (92.5%)	100% 99.2% 100% (97.6%)
Basso et al. (2009) (2006 publ. assumed to be part of this) 28/16 2002-07	Suspected CD Children Mean age: 6.5-9 yrs	NR	Marsh Oberhuber type1-3c	No CD	Unclear Serology before biopsy	IgA tTG OR IgA DGP IgA tTG OR IgG DGP Either or 3 tests positive	26 27 27	1.5 1 2	2 1 1	14.5 15 14	92.5% 95.0% 95.0%	90.6% 95.3% 89.8%
IGA/G DGP												

Study, N Cases/ control Study period	Presentation	N (%) IgA deficient	CD definition	Control definition	# Biopsies, Location, Time lag btw tests	Blood test	TP	FP	FN	TN	Sens (%)	Spec (%)
Agardh et al. (2007)	Suspected CD Children Mean age: 3.5-5.7 yrs	5 (8.7%) in controls	ESPGAN	Normal biopsy	Unclear Unclear	IgA/G DGP > 20 AU/ml	116	6	3	51	97.5% (96.6%) tTG)	89.5% (96.5%) tTG)
Rashtak et al. (2008) 92/ 124 1999-06	Symptoms Mean age: 45 yrs Mixed	?	Marsh 3	Marsh 0	NR Duodenum	DGP (A) OR DGP (G)pos (ref DGP A)	69	7	23	117	75% (ref 74%) (78% tTG)	94% (ref 95%) (98% tTG)
Niveloni et al. (2007) 60/ 81 2004-05	Symptoms or not¦ Mean age: 37 yrs Adults	NR	Marsh 3 + serology + GFD (hist/serol)	Marsh 0	≥ 3 biopsies Distal duodenum	DGP (A) OR DGP (G)pos (ref DGP A)	60	3	0	78	100% (ref 98.3%) (95% tTG)	96.3% (ref 93.8%) (97.5% tTG)
Parizade et al. (2009) 85/31 2006-08	Symptoms, or relatives Children	5 (4.3%) Part of indications for testing	Marsh 1-3 Marsh 1-2: 8 (9%) 3a-b: 48 (57%) 3c: 29 (34%)	Marsh 0	Distal duodenum ≥ 5 biopsies Same time	IgA/G DGP > 39 U/ml (Inova) No ref.	81	8	4	23	95.3% (94.1%)	74.2% (87.1%)
Leach et al. (2008) 32/44	GI symptoms Children	2 (2.6%) in CD group	ESPGAN 1990	no endoscopic/ histologic CD/ inflammation sign + normal systemic inflammatory markers	Unclear Same time	IgA/G DGP > 25 U/ml	29	8	3	36	90.6% (84.4% tTG)	81.9% (90.9%, tTG)
IgA/G tTG/DGP												
Agardh et al. (2007)	Suspected CD Children Mean age: 3.5-5.7 yrs	5 (8.7%) in controls	ESPGAN	Normal biopsy	Unclear Unclear	IgA/G tTG/DGP > 20 AU/ml	119	6	0	51	100% (96.6%, tTG)	89.5% (96.5%, tTG)

AGA refers to anti-gliadin antibodies; Am GA American Gastroenterological Association; AU arbitrary units; CD celiac disease; D2 2nd part of the duodenum; def deficiency; DGP deamidated gliadin antibody; DM1 diabetes mellitus type 1; EMA endomysial antibody; ESPGAN European Society of Paediatric Gastroenterology and Nutrition; GI gastrointestinal; EU ELISA units; FN false negative; FP false positive; FTT failure-to-thrive; f-up follow-up; GFD gluten-free diet; GP guinea pig; Hu human; IBD irritable bowel disease; IBS irritable bowel syndrome; IgA immunoglobulin A; IgG immunoglobulin G; Me monkey esophagus; N/A not available; NASPGHAN North American Society of Pediatric Gastroenterology Hepatology and Nutrition; NR not reported; Sens sensitivity, Spec specificity; TN true negative; TP true positive; tTG tissue transglutaminase; U units; VA villous atrophy; w/o without.

* Diabetes mellitus 1, 1st degree relatives, autoimmune thyroiditis.

¦ Diabetes mellitus type 1, 1st degree relatives of cases.

Appendix 6: Diagnostic Accuracy of Serologic Tests for Celiac Disease in Chronic Liver Disease

Table A13: Frequency of False Positive Serologic Tests for Celiac Disease in Chronic Liver Disease

Study N Follow-up	Celiac Disease (CD) diagnosis	False Positives IgA tTG (hr substrate)	False Positives IgA tTG (gp substrate)	False Positives IgA EMA	False Positives IgA AGA
Bizzaro et al. (2006) (49) Primary Biliary Cirrhosis (PBC) N=103 (2 with small bowel biopsy-proven celiac disease excluded) Healthy controls, N=40	• Serology: IgA and IgG tTG • Positive results confirmed by IgA EMA • IgA EMA positive confirmed by small bowel biopsy* Different manufacturers' kits used.	• ***tTG (hr)*** 1: 8 (7.8%) 2: 3 (2.9%) • ***tTG Human placenta*** 10 (9.7%) • ***tTG Human RBC*** 18 (17.5%) **False positive in controls** 0 to 4.8% (serologic test not specified)	• ***tTG (gp liver)*** 1: 12 (11.7%) 2: 10 (9.7%)	**IgA EMA** Not applicable	Not reported
Bizzaro et al. (2003) (50) PBC, N=48 Healthy controls, N=120	• Serology: IgA and IgG tTG • Positive results confirmed by EMA • IgA EMA pos. confirmed by small bowel biopsy*	• ***tTG (hr) (> 7AU)*** 5 (10.4%) **Healthy Controls** 1 (0.8%)	Not reported	**IgA EMA** Not applicable	Not reported
Vecchi et al. (2003) (51) Chronic active hepatitis (N=22) Liver cirrhosis (N=19)	• Serology: IgA tTG, IgA EMA • Small bowel biopsy not done	• ***tTG (hr) (> 7 AU)*** 7 (17.0%)	• ***tTG (gp liver > 5 AU)*** Cirrhosis (pos): 11 (26.8%)	• ***IgA EMA*** 0	Not reported
Habior et al. (2003) (52) Liver cirrhosis, N=115 Healthy controls, N=57	• Serology: IgA tTG (gp), EMA, AGA • Small bowel biopsy in positive IgA tTG and/or EMA	Not reported	• ***tTG (gp liver)*** 7 (6%) **Healthy controls** 0 Statistical significance of difference vs. PBC: NR	• ***IgA EMA:*** 0	• ***IgA AGA:*** 8 (6.9%) (assumed) **Healthy controls** • ***IgA AGA*** 6 (10.5%) – NS from PBC patients
Villalta et al. (2005) (53) Liver cirrhosis, N=54 Healthy controls, N=20 Autoimmune diseases, N=20	• CD diagnosis: positive IgA EMA Different manufacturers' kits used. Cut-offs according to manufacturers	• ***tTG (hr)*** 1: 1 (1.9%) 2: 2 (3.8%)¦ 3: 1 (1.9%) 4: 3 (5.6% 5: 1 (1.9%) 6: 0 7: 3 (5.6%) • ***Human native kits*** 1: 2 (3.7%) 2: 1 (1.9%) **Healthy controls and autoimmune diseases** Different kits: 0	• ***tTG (hr cross-linked with gliadin-specific peptides)*** 10 (18.5%) **Healthy controls and autoimmune diseases** NR	• ***IgA EMA (1:10)*** Not applicable • ***EMA and gliadin fragments*** 9 (16.7%)	• ***IgA AGA (3 mg A/L)***: 6 (11.1%) **Healthy controls and autoimmune diseases** NR
Carroccio et al. (2001) (59) Chronic liver disease, N=98 Healthy controls, N=35	• Serology: IgA EMA and tTG • Small bowel biopsy if positive serology	• ***tTG (hr)*** 0 false positives **Healthy Controls**	• ***tTG guinea pig (> 7 AU)*** 15 (15.3%) **Healthy Controls** 0	***IgA EMA:*** 0	Not reported

		0			
Clemente et al. (2002) (58) PBC, autoimmune hepatitis N=10 / N=18 Healthy controls, N=100	• CD diagnosis confirmation unclear • No small bowel biopsy performed.	• ***tTG (hr)*** 0 **Healthy controls** 0	• ***tTG (gp)*** 14 (50%) **Healthy controls** 0	• ***IgA EMA (> 1:5):*** 0 **Healthy controls** 0	***IgA AGA:*** 0 **Healthy controls** 0
Iacono et al. (2005) (54) Unexplained raised liver enzymes, N= 168	• Serology: IgA and IgG tTG • IgA EMA if positive tTG • Small bowel biopsy performed if serology is positive	• ***tTG (hr) (> 7 AU)*** 3 (1.8%)	Not reported	Not reported	Not reported
Germenis et al. (2005) (55) Chronic liver diseases, N=738 Healthy controls, N=1,350	• Serology: IgA tTG, IgA EMA • Small bowel biopsy performed if serology is positive	• ***tTG (hr) (> 7 AU)*** 26/734 (3.5%)‖ **Healthy controls** 0	Not reported	• ***IgA EMA*** 0	Not reported
Chatzicostas et al. (2002) (60) PBC, N=62, Autoimmune cholangitis (AIC) n=17 Healthy controls, N=100	• Serology: IgA AGA, tTG, EMA • Small bowel biopsy performed if serology is positive.	Not reported	• ***tTG (gp liver)*** 8 (10.1%)‡ **Healthy controls** 0	• ***IgA EMA (>1:5):*** 0‡ **Healthy controls** 0	***IgA AGA:*** 11 (13.9%)‡ **Healthy controls** 1 (1.0%)
Floreani et al. (2001) (57) PBC, N=87	• Serology: IgA tTG, EMA • Small bowel biopsy performed if serology was positive. **	Not reported	• ***tTG (gp) (> 10 IU)*** 21 (24.1%)	• ***IgA EMA*** 0	Not reported
Gillett et al. (2000) (56) PBC, N=378	• Serology IgA tTG, EMA • Confirmation with small bowel biopsy performed if IgA EMA was positive.	Not reported	• ***tTG (gp)*** 44 (11.6%)	Not reported	Not reported
Rubio-Tapia et al. (2008) (62) ESALD, N=310	• Serology: IgA tTG, IgA EMA • CD confirmation: positive IgA EMA • No confirmatory small bowel biopsy except in EMA positive patients.	• ***tTG Native human (> 20U/ml)*** 24 (7.7%)	Not reported	Not reported	Not reported
Bardella et al. (2004) (61) NAFLD, N=59	• Serology: IgA tTG and IgA EMA • CD confirmation: positive IgA EMA • Small bowel biopsy confirmation in some patients.	• ***tTG (hr)(> 10 U/ml)*** 4 (6.8%)	Not reported	Not reported	Not reported

AGA refers to anti-gliadin antibody; CD celiac disease; EMA endomysial antibody; ESALD end-stage autoimmune liver disease; gp guinea pig; hr human recombinant; Ig immunoglobulin; NAFLD Non-alcoholic fatty liver disease; PBC primary biliary cirrhosis; RBC red blood cells; tTG tissue transglutaminase

* If IgA tTG positive, igA EMA negative, HLA alleles determination was performed, if positive, patients underwent small bowel biopsy.

¦ Using the cut-off derived from the ROC curve, there were problems with cut-off suggested by the manufacturer.

‖ In one additional patient, only some of the abnormal features of CD on small bowel biopsy were present, not considered a false positive. 18 refused small bowel biopsy – excluded

‡ Patients without small bowel biopsy excluded.

** Mannitol/lactulose permeability test if small bowel biopsy was refused.

Appendix 7: Quality Appraisal of Systematic Reviews and Observational Studies Included

Table A14: Quality of Studies Included According to the Quadas Tool

	Emami et al. (29)	Hopper et al. (30)	Poddar et al. (31)	Rashtak et al. (45)	Barker et al. (32)	Santaolalla et al. (43)	Wolters et al. (42)	Reeves et al. (33)
1. Spectrum of patients representative of clinical practice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Selection criteria clearly defined ?	Yes	Yes	Yes	No	Yes	No	No	Yes
3. Reference standard likely to correctly classify target condition	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was the time period btw reference and index test appropriate*	No	Yes	Unclear	No	No	Yes	Unclear	Yes
5. Whole sample received reference test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did all receive the same reference test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Reference test independent of index test?	Yes	No	Yes	Yes	Yes	No	Yes	Yes
8. Index test procedure described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Reference test procedure described in detail?	Yes	Yes	No	No	No	Yes	Yes	Yes
10. Blinded index test¦	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Blinded reference test	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes
12. Clinical data available similar to what is done in clinical practice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Uninterpretable/ intermediate results reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Withdrawals explained?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Reference test refers to small intestine biopsy. Index test refers to serology

* Considered appropriate if biopsy and serologic test were performed on the same day.

¦ Index test (serology) was considered blinded in all cases since it is an automated test performed at a laboratory.

Table A15: Quality of Studies Included According to the Quadas Tool

	Niveloni et al. (34)	Teesalu et al. (35)	Parizade et al. (36)	Dahlbom et al. (37)	Basso et al. (38)	Baviera et al. (39)	Agardh et al. (40)	Poddar et al. (44)	Leach et al. (41)
1. Spectrum of patients representative of clinical practice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Selection criteria clearly defined ?	Yes	No	No	Yes	Yes	No	No	No	Yes
3. Reference standard likely to correctly classify target condition	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was the time period btw reference and index test appropriate*	Yes	Unclear	Yes	Unclear	Yes	No	Unclear	Unclear	Yes
5. Whole sample received reference test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did all receive the same reference test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Reference test independent of index test?	No	Yes	No	Yes	Yes	Unclear	Unclear	Yes	No
8. Index test procedure described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Reference test procedure described in detail?	Yes	No	Yes	No	No	No	No	No	No
10. Blinded index test¦	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Blinded reference test	Yes	No	Yes	No	Unclear	Unclear	Unclear	Unclear	Unclear
12. Clinical data available similar to what is done in clinical practice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Uninterpretable/ intermediate results reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Withdrawals explained?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Reference test refers to small intestine biopsy. Index test refers to serology

* Considered appropriate if biopsy and serologic test were performed on the same day.

¦ Index test (serology) was considered blinded in all cases since it is an automated test performed at a laboratory.

Table A16: Quality of Systematic Reviews According to the AMSTAR Tool

Item	NICE (2009) (11)	Rostom et al. (2004) (3)	Lewis et al. (2006) (26)	Zintzaras et al. (2006) (28)	Hill et al. (2005) (27)
1. A priori design provided?	Yes	Yes	Yes	Yes	Yes
2. Duplicate study selection and data extraction?	Unclear	Yes	Unclear	Yes	Unclear
3. Comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes
4. Status of publication used as an inclusion criterion?	Yes	Yes	Yes	Yes	Yes
5. List of studies (included and excluded) provided?	No	Yes	No	No	No
6. Characteristics of the included studies provided?	No	Yes	Yes	Yes	No
7. Scientific quality of studies assessed and documented?	No	Yes	Yes	Yes	No
8. Scientific quality of the included studies used appropriately when formulating the conclusions?	Unclear	Yes	Unclear	Unclear	Unclear
9. Methods used to combine the study findings appropriate?	Yes	Yes	Unclear	Yes	Yes
10. Likelihood of publication bias assessed?	Unclear	Unclear	Unclear	Yes	Unclear
11. Was the conflict of interest included?	Unclear	Unclear	Yes	No	No

NICE refers to National Institute for Health and Clinical Excellence

Appendix 8: Economic Literature Search Strategy

Search date: November 18, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, EconLit

Database: Ovid MEDLINE(R) <1950 to November Week 1 2009>

Search Strategy:

1 exp Celiac Disease/ (12821)
2 (C?eliac or nontropical sprue or non-tropical sprue or (gluten adj2 enteropath*)).ti,ab. (15922)
3 1 or 2 (19545)
4 exp Serologic Tests/ (163641)
5 exp Transglutaminases/ (4215)
6 exp Immunoglobulin G/ (109328)
7 exp Immunoglobulin A/ (31586)
8 exp Enzyme-Linked Immunosorbent Assay/ or exp Antibodies/ or exp Gliadin/ (655823)
9 ((serum or serologic* or blood or antibod*) adj2 (assay* or test* or analysis* or marker*)).ti,ab. (93903)
10 (serodiagnos* or immunoassay* or MIA).ti,ab. (46444)
11 (IgA or IGG or TTG or EMA or IgG-tTG or anti-gliadin or antigliadin or AGA or human leukocyte antigens or HLA).ti,ab. (181753)
12 or/4-11 (909310)
13 3 and 12 (4736)
14 limit 13 to (english language and humans and yr="2003 -Current") (1525)
15 exp Economics/ (418226)
16 exp Models, Economic/ (6943)
17 exp Resource Allocation/ (13162)
18 exp "Value of Life"/ or exp "Quality of Life"/ (84739)
19 (econom$ or cost$ or budget$ or pharmacoeconomic$ or pharmaco-economic$ or valu$).ti. (187655)
20 ec.fs. (265651)
21 ((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab. (62565)
22 or/15-21 (711036)
23 13 and 22 (98)
24 limit 23 to (english language and yr="2003 -Current") (44)

Database: EMBASE <1980 to 2009 Week 46>

Search Strategy:

1 exp celiac disease/ (9455)
2 (C?eliac or nontropical sprue or non-tropical sprue).mp. or (gluten adj2 enteropath*).ti,ab. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (15329)
3 1 or 2 (15329)
4 exp blood examination/ (90941)
5 exp protein glutamine gamma glutamyltransferase/ (3539)
6 ((serum or serologic* or blood or antibod*) adj2 (assay* or test* or analysis* or marker*)).ti,ab. (73724)
7 exp immunoglobulin G/ (56726)
8 "immunoglobulin A"/ (21496)
9 exp enzyme linked immunosorbent assay/ (102547)
10 exp gliadin antibody/ (1090)
11 exp gliadin/ (1174)
12 exp immunoglobulin A antibody/ (3592)
13 exp immunoglobulin G antibody/ (14715)
14 exp antibody blood level/ (9475)
15 (IgA or IGG or TTG or EMA or IgG-tTG or anti-gliadin or antigliadin or AGA or human leukocyte antigens or HLA).ti,ab. (151901)
16 (serodiagnos* or immunoassay* or MIA).ti,ab. (38689)
17 or/4-16 (439905)
18 17 and 3 (4285)

19 limit 18 to (human and english language and yr="2003 -Current") (1634)
20 exp "Health Care Cost"/ (111593)
21 exp Health Economics/ (244650)
22 exp Resource Management/ (15255)
23 exp Economic Aspect/ or exp Economics/ or exp Quality Adjusted Life Year/ or exp Socioeconomics/ or exp Statistical Model/ or exp "Quality of Life"/ (512314)
24 (econom$ or cost$ or budget$ or pharmacoeconomic$ or pharmaco-economic$ or valu$).ti. (113050)
25 ((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab. (55734)
26 or/20-25 (587677)
27 18 and 26 (148)
28 limit 27 to (english language and yr="2003 -Current") (87)

CINAHL

#	Query	Results
S21	S13 and S20	83
S20	S14 or S15 or S16 or S17 or S18 or S19	452072
S19	(cost* N1 benefit*) or costbenefit* or (cost N1 effective*) or costeffective* or econometric* or life value or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc* or sensitivity analys* or "value of life" or "willingness to pay"	17865
S18	(MH "Resource Allocation+")	4595
S17	MW ec	67538
S16	(MH "Quality of Life+")	28394
S15	econom* or cost* or budget* or pharmacoeconomic* or pharmaco-economic* or valu*	239325
S14	(MH "Economics+")	303057
S13	S3 AND S12	280
S12	(S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11)	125969
S11	IgA or IGG or TTG or EMA or IgG-tTG or anti-gliadin or antigliadin or AGA or human leukocyte antigens or HLA	3169
S10	serodiagnos* or immunoassay* or MIA	4324
S9	serum or serologic* or blood or antibod*	120993
S8	"gliadin"	44
S7	(MH "Enzyme-Linked Immunosorbent Assay")	3651
S6	Transglutaminase*	82
S5	(MH "Antibodies")	2065
S4	(MH "Serologic Tests+")	3103
S3	S1 or S2	1168
S2	Celiac or coeliac or nontropical sprue or non-tropical sprue or gluten NEAR enteropath*	1168
S1	(MH "Celiac Disease")	990

Appendix 9: Economic Model - Sensitivity Analyses

Basecase

Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

Prevalence Estimate - One way sensitivity analyses (refer to report for ranges)

Prevalence of Disease	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.267853475	IgGTTG	$177.24		0.51222		0.119837645	0.043635933	0.688510592	0.14801583
	EMA	$208.67	$31.43	0.52829	0.01607	0.227970093	0.044587723	0.687558802	0.039883382
	IgATTG	$224.41		0.5193		0.246800192	0.05791279	0.674233735	0.021053283
	IgGAG	$227.61		0.52257		0.185086751	0.039389483	0.692757042	0.082766724
	IgGDGP	$243.34	$34.67	0.54432	0.01603	0.236648545	0.034923389	0.697223136	0.03120493
	IgAAG	$243.88		0.48509		0.200622253	0.072555721	0.659590804	0.067231222
	IgADGP	$250.70		0.51973		0.238844944	0.05476456	0.677381965	0.029008531
	Panel Combo	$263.35	$20.01	0.57189	0.02757	0.217095241	0.009591119	0.722555406	0.050758234
	Panel Either	$295.97		0.50884		0.254728655	0.069627135	0.66251939	0.01312482
	Biopsy	$396.60	$133.25	0.60778	0.0359	0.267853475	0	0.732146525	0
0.281041532	IgGTTG	$178.95		0.49889		0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12		0.50914		0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42		0.50953		0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74		0.47389		0.210500107	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$34.87	0.53267	0.01592	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30		0.50909		0.250604734	0.053778093	0.665180375	0.030436798
	Panel Combo	$266.86	$19.84	0.55826	0.02559	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74		0.49956		0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$129.74	0.59589	0.03763	0.281041532	0	0.718958468	0
0.294229589	IgGTTG	$180.66		0.48604		0.131638318	0.042063916	0.663706495	0.162591271
	EMA	$215.63	$34.97	0.50577	0.01973	0.250418803	0.042981418	0.662788993	0.043810786
	IgATTG	$231.83		0.49958		0.271103143	0.05582644	0.649943971	0.023126446
	IgGAG	$233.23		0.497		0.203312646	0.037970448	0.667799963	0.090916943
	IgAAG	$249.60		0.46319		0.220377962	0.069941848	0.635828563	0.073851627
	IgGDGP	$250.70	$35.07	0.52161	0.01584	0.259951842	0.033665249	0.672105162	0.034277747
	IgADGP	$257.90		0.49902		0.262364525	0.052791627	0.652978784	0.031865064
	Panel Combo	$270.38	$19.67	0.54521	0.0236	0.238473082	0.009245592	0.696524819	0.055756507
	Panel Either	$303.51		0.49088		0.279812339	0.067118766	0.638651645	0.01441725
	Biopsy	$396.60	$126.22	0.58468	0.03947	0.294229589	0	0.705770411	0

Sensitivity (se) Estimates – One way sensitivity analyses (refer to report for ranges)

p_se_EMA	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.7585	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$203.46	$24.51	0.50782	0.00893	0.213170002	0.043784571	0.675173897	0.06787153
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.8511	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9437	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$220.84	$41.89	0.52837	0.02948	0.265218894	0.043784571	0.675173897	0.015822638
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_se_IgAAG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.6363	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$236.16	$57.21	0.46703	-0.03186	0.178826727	0.071248784	0.647709684	0.102214805
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.74905	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.8618	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	IgAAG	$257.33	$78.38	0.48477	-0.01412	0.242201592	0.071248784	0.647709684	0.03883994
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_se_IgADGP	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.8326	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$248.75	$69.80	0.50232	0.00343	0.23399518	0.053778093	0.665180374	0.047046352
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.8917	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9508	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$259.85	$80.90	0.51695	0.01806	0.267214289	0.053778093	0.665180374	0.013827243
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_se_IgATTG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.88	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$224.23	$45.28	0.5039	0.00501	0.247316548	0.056869615	0.662088853	0.033724984
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9214	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9628	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgATTG	$232.00	$53.05	0.51492	0.01603	0.270586787	0.056869615	0.662088853	0.010454745
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_se_IgGAG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.5602	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgGAG	$218.14	$39.19	0.50434	0.00545	0.157439466	0.038679966	0.680278502	0.123602066
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.691	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.8218	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$242.70	$63.75	0.52013	0.02124	0.230959931	0.038679966	0.680278502	0.050081601
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_se_IgGDGP	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.8208	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgGDGP	$241.14	$62.19	0.52569	0.0268	0.23067889	0.034294319	0.684664149	0.050362643
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.88345	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53266	0.03377	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9461	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$252.90	$73.95	0.54087	0.04198	0.265893394	0.034294319	0.684664149	0.015148139
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_se_IgGTTG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.3027	IgGTTG	$165.37	$0.00	0.5046	0	0.085071272	0.042849925	0.676108543	0.19597026
	EMA	$212.15	$46.78	0.51674	0.01214	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$62.75	0.50914	0.00454	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$65.05	0.50953	0.00493	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$81.37	0.47389	-0.03071	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$81.65	0.53267	0.02807	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$88.93	0.50909	0.00449	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$101.49	0.55826	0.05366	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$134.37	0.49956	-0.00504	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$231.23	0.59589	0.09129	0.281041532	0	0.718958468	0
0.44745	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.5922	IgGTTG	$192.54	$0.00	0.49979	0	0.166432795	0.042849925	0.676108543	0.114608737
	EMA	$212.15	$19.61	0.51674	0.01695	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$35.58	0.50914	0.00935	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$37.88	0.50953	0.00974	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$54.20	0.47389	-0.0259	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$54.48	0.53267	0.03288	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$61.76	0.50909	0.0093	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$74.32	0.55826	0.05847	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$107.20	0.49956	-0.00023	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$204.06	0.59589	0.0961	0.281041532	0	0.718958468	0

p_se_Panel_Combo	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.713	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$257.71	$78.76	0.55019	0.0513	0.200382612	0.009418356	0.709540112	0.08065892
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.81055	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.87	$87.92	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9081	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$276.02	$97.07	0.56934	0.07045	0.255213815	0.009418356	0.709540112	0.025827717
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_se_Panel_Either	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.9215	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$296.97	$118.02	0.49549	-0.0034	0.258979772	0.06837295	0.650585518	0.02206176
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.95095	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.73	$120.78	0.49955	0.00066	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9804	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$302.50	$123.55	0.50388	0.00499	0.275533118	0.06837295	0.650585518	0.005508414
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

Specificity (sp) Estimates - One way sensitivity analyses (refer to report for ranges)

p_sp_EMA	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.9063	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$220.03	$41.08	0.48808	-0.01081	0.239194448	0.067366408	0.651592059	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.93915	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.14	$33.19	0.51679	0.0179	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.972	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$204.25	$25.30	0.54773	0.04884	0.239194448	0.020130837	0.698827631	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_sp_IgAAG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.8626	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	IgAAG	$255.94	$76.99	0.44366	-0.05523	0.210500108	0.098784893	0.620173574	0.070541425
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.90095	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.73	$67.78	0.47393	-0.02496	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.053778093	0.665180374	0.030436798
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9393	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$237.52	$58.57	0.50724	0.00835	0.210500108	0.043640779	0.675317689	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.053778093	0.665180374	0.030436798
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_sp_IgADGP	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.8852	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$263.90	$84.95	0.47557	-0.02332	0.250604734	0.082536432	0.636422036	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9252	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9652	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgADGP	$244.69	$65.74	0.54591	0.04702	0.250604734	0.025019755	0.693938713	0.030436798
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.248300194	0.034294319	0.684664149	0.032741338
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_sp_IgATTG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.8905	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgATTG	$235.42	$56.47	0.48364	-0.01525	0.258951668	0.078725952	0.640232516	0.022089864
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9209	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.258951668	0.078725952	0.640232516	0.022089864
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9513	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$220.82	$41.87	0.53655	0.03766	0.258951668	0.035013277	0.68394519	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.258951668	0.078725952	0.640232516	0.022089864
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_sp_IgGAG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.9235	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$235.87	$56.92	0.48912	-0.00977	0.194199699	0.055000323	0.663958145	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.94625	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.41	$51.46	0.50958	0.01069	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.969	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgGAG	$224.95	$46.00	0.5311	0.03221	0.194199699	0.022287713	0.696670755	0.086841833
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_sp_IgGDGP	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.9233	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$253.99	$75.04	0.50641	0.00752	0.248300194	0.055144114	0.663814353	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.95235	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.01	$68.06	0.53271	0.03382	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9814	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgGDGP	$240.04	$61.09	0.56075	0.06186	0.248300194	0.013372628	0.70558584	0.032741338
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_sp_IgGTTG	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.9056	IgGTTG	$187.31	$0.00	0.46845	0	0.125737981	0.067869679	0.651088788	0.155303551
	EMA	$212.15	$24.84	0.51674	0.04829	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$40.81	0.50914	0.04069	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$43.11	0.50953	0.04108	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$59.43	0.47389	0.00544	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$59.71	0.53267	0.06422	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$66.99	0.50909	0.04064	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$79.55	0.55826	0.08981	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$112.43	0.49956	0.03111	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$209.29	0.59589	0.12744	0.281041532	0	0.718958468	0
0.94045	IgGTTG	$178.94	$0.00	0.49893	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.21	0.51674	0.01781	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.18	0.50914	0.01021	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.48	0.50953	0.0106	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.80	0.47389	-0.02504	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.08	0.53267	0.03374	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.36	0.50909	0.01016	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.92	0.55826	0.05933	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.80	0.49956	0.00063	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.66	0.59589	0.09696	0.281041532	0	0.718958468	0
0.9753	IgGTTG	$170.57	$0.00	0.53193	0	0.125737981	0.017758274	0.701200194	0.155303551
	EMA	$212.15	$41.58	0.51674	-0.01519	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$57.55	0.50914	-0.02279	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$59.85	0.50953	-0.0224	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$76.17	0.47389	-0.05804	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$76.45	0.53267	0.00074	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$83.73	0.50909	-0.02284	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$96.29	0.55826	0.02633	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$129.17	0.49956	-0.03237	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$226.03	0.59589	0.06396	0.281041532	0	0.718958468	0

p_sp_Panel_Combo	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.9805	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$268.40	$89.45	0.55186	0.05297	0.227784162	0.01401969	0.704938778	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.98695	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.85	$87.90	0.55831	0.05942	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9934	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$265.30	$86.35	0.56484	0.06595	0.227784162	0.004745126	0.714213342	0.05325737
	Panel Either	$299.74	$120.79	0.49956	0.00067	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

p_sp_Panel_Either	Strategy	Cost	Incr Cost	Eff	Incr Eff	TP	FP	TN	FN
0.8679	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$308.62	$129.67	0.47	-0.02889	0.267270497	0.094974414	0.623984054	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.90485	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$299.75	$120.80	0.49952	0.00063	0.267270497	0.06837295	0.650585518	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0
0.9418	IgGTTG	$178.95	$0.00	0.49889	0	0.125737981	0.042849925	0.676108543	0.155303551
	EMA	$212.15	$33.20	0.51674	0.01785	0.239194448	0.043784571	0.675173897	0.041847084
	IgATTG	$228.12	$49.17	0.50914	0.01025	0.258951668	0.056869615	0.662088853	0.022089864
	IgGAG	$230.42	$51.47	0.50953	0.01064	0.194199699	0.038679966	0.680278502	0.086841833
	IgAAG	$246.74	$67.79	0.47389	-0.025	0.210500108	0.071248784	0.647709684	0.070541425
	IgGDGP	$247.02	$68.07	0.53267	0.03378	0.248300194	0.034294319	0.684664149	0.032741338
	IgADGP	$254.30	$75.35	0.50909	0.0102	0.250604734	0.053778093	0.665180374	0.030436798
	Panel Combo	$266.86	$87.91	0.55826	0.05937	0.227784162	0.009418356	0.709540112	0.05325737
	Panel Either	$290.88	$111.93	0.53186	0.03297	0.267270497	0.041843383	0.677115085	0.013771035
	Biopsy	$396.60	$217.65	0.59589	0.097	0.281041532	0	0.718958468	0

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