

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work

## eSupplement 1. Search strategy for Medline (using PubMed)

### Index tests

Medical history taking[mesh] OR medical history[tiab] OR family history[tiab] OR history taking[tiab] OR patient history[tiab] OR clinical evaluation[tiab] OR clinical assessment[tiab] OR clinical presentation[tiab] OR clinical sign[tiab] OR clinical signs[tiab] OR clinical symptom\*[tiab] OR clinical manifestation[tiab] OR clinical manifestations[tiab] OR clinical features[tiab] OR clinical characteristics[tiab] OR clinical finding[tiab] OR clinical findings[tiab] OR presenting symptoms[tiab] OR Gastrointestinal symptomatology[tiab] OR gastrointestinal symptoms[tiab] OR gastrointestinal manifestations[tiab] OR scoring system[tiab] OR symptom criteria[tiab] OR symptom score[tiab] OR symptom scores[tiab] **OR** Abdominal pain[mesh] OR abdominal pain[tiab] OR abdominal complaint\*[tiab] OR bloating[tiab] OR Flatulence[mesh] OR flatulence[tiab] OR abdominal distension[tiab] OR abdominal distention[tiab] OR abdominal cramp[tiab] OR abdominal cramps[tiab] OR abdominal tenderness[tiab] **OR** Diarrhea[mesh] OR diarrhea[tiab] OR diarrhoea[tiab] OR Constipation[mesh] OR constipation[tiab] OR ((feces[mesh] OR feces[tiab] OR faeces[tiab] OR fecal[tiab] OR faecal[tiab] OR stool[tiab]) AND (form[tiab] OR consistency[tiab])) OR (((Intestines[mesh] OR bowel[tiab] OR bowels[tw]) AND (habits[tiab] OR movement[tiab] OR movements[tiab] OR motility[tiab] OR pattern[tiab] OR patterns[tiab] OR frequency[tiab])) OR Peristalsis[mesh] OR Defecation[mesh] OR defecation[tiab] OR defaecation[tiab] OR Gastrointestinal motility[mesh:noexp] OR Gastrointestinal transit[mesh]) AND (altered[tiab] OR alteration[tiab] OR disordered[tiab] OR change[tiab] OR changes[tiab] OR changed[tiab])) OR steatorrhea[tiab] **OR** Physical examination[mesh:noexp] OR physical examination[tiab] OR Auscultation[mesh:noexp] OR auscultation[tiab] OR Palpation[mesh] OR palpation[tiab] OR Percussion[mesh] OR percussion[tiab] OR abdominal examination\*[tiab] OR abdominal evaluation\*[tiab] **OR** Weight loss[mesh:noexp] OR weight loss[tiab] OR weight reduction[tiab] OR anemia[mesh:noexp] OR Hypochromic anemia[mesh:noexp] OR Anemia, iron-deficiency[mesh:noexp] OR iron deficiency anemia[tiab] OR nocturnal symptoms[tiab]

OR

((ultrasonography[mesh:noexp] OR ultrasonography[sh] OR ultrasonography[tiab] OR ultrasonographic[tiab] OR ultrasound[tiab] OR ultrasonic[tiab] OR echography[tiab] OR echographic[tiab] OR sonography[tiab] OR sonographic[tiab] OR hydrosonography[tiab] OR hydrosonographic[tiab]) NOT ((staging[ti] OR resection[ti] OR preoperative[ti]) NOT (diagnosis[ti] OR detection[ti]))) NOT ((intraoperative ultrasound[tiab] OR intraoperative ultrasonography[tiab] OR intraoperative sonography[tiab] OR endosonography[tiab] OR endoscopic ultrasound[tiab] OR endoscopic ultrasonography[tiab] OR endoscopic sonography[tiab] OR endorectal ultrasound[tiab] OR endorectal ultrasonography[tiab] OR endorectal sonography[tiab]) NOT (conventional ultrasound[tiab] OR conventional ultrasonography[tiab]))

OR

(serologic tests[mesh:noexp] OR serological markers[tiab] OR serum antigliadin[tiab] OR antigliadin antibodies[tiab] OR anti gliadin antibodies[tiab] OR IgA antigliadin[tiab] OR IgA anti-gliadin[tiab] OR IgG antigliadin[tiab] OR IgG anti-gliadin[tiab] OR ((IgA[tiab] OR IgG[tiab] OR AGA[tiab] OR EMA[tiab] OR ARA[tiab] OR tTG[tiab] OR TTGA[tiab] OR AEA[tiab]) AND (antibody[tiab] OR antibodies[tiab])) OR antiendomysial antibodies[tiab] OR anti-endomysial antibodies[tiab] OR antiendomysium antibodies[tiab] OR anti-endomysium antibodies[tiab] OR antireticulin antibodies[tiab] OR anti-reticulin antibodies[tiab] OR tissue transglutaminase[tiab]) NOT (screening[ti] NOT (Primary health care[mesh] OR Family practice[mesh] OR family physicians[mesh] OR physicians[mesh:noexp] OR family practice\*[tiab] OR general practice\*[tiab] OR physician\*[tiab] OR outpatient[tiab] OR hospital[tiab] OR clinic[tiab]))

OR

Gluten challenge[tiab]

### Target disease

Celiac disease[mesh] OR celiac disease[tiab] OR coeliac disease[tiab] OR gluten enteropath\*[tiab] OR gluten sensitive enteropath\*[tiab] OR gluten intolerance[tiab] OR celiac sprue[tiab] OR coeliac sprue[tiab] OR nontropical sprue[tiab]

**Study design**

Diagnosis[ti] OR diagnostic[ti] OR diagnosing[ti] OR diagnosis[mesh:noexp] OR diagnostic errors[mesh] OR "Diagnosis, differential"[mesh] OR "Sensitivity and specificity"[mesh] OR sensitivit\*[tiab] OR specificit\*[tiab] OR accuracy[tiab] OR likelihood ratio\*[tiab] OR index test[tiab] OR reference test[tiab] OR pretest[tiab] OR pre-test[tiab] OR posttest[tiab] OR post-test[tiab] OR gold standard[tiab] OR roc[tiab] OR false positive[tw] OR false negative[tw] OR predictive value\*[tw] OR reference value\*[tw] OR (celiac disease/diagnosis[mesh:noexp] AND prevalence[tiab])

**Exclude**

((child[mesh] OR infant[mesh]) NOT (adult[mesh])) OR review[pt] OR case reports[pt] OR comment[pt] OR letter[pt] OR meta-analysis[pt] OR news[pt] OR guideline[pt] OR (animals[mesh] NOT humans[mesh])

**Combine: (index test AND target disease AND study design) NOT exclude**

## **eSupplement 2. Search strategy for EMBASE (using Embase.com)**

### **Index tests**

anamnesis/exp OR symptomatology/de OR clinical-feature/exp OR symptom/exp OR scoring-system/exp **OR** abdominal-pain/exp OR flatulence/exp OR abdominal-distension/exp OR abdominal-cramp/exp OR abdominal-tenderness/exp **OR** diarrhea/exp OR constipation/exp OR abnormal-feces/exp OR abnormal-feces-composition/exp OR feces-composition/exp OR feces-impaction/exp OR hard-feces/exp OR liquid-feces/exp OR loose-feces/exp OR ((gastrointestinal-motility/de OR peristalsis/de OR intestine-motility/de OR defecation/exp OR defecation-habit/exp) AND (altered:ti,ab OR alteration:ti,ab OR disordered:ti,ab OR change:ti,ab OR changed:ti,ab OR changes:ti,ab)) OR defecation-disorder/exp OR gastrointestinal-motility-disorder/exp OR intestinal-dysmotility/exp OR ileum-dysfunction/exp OR steatorrhea/exp **OR** physical-examination/de OR percussion/exp OR auscultation/de OR palpation/exp OR digital-rectal-examination/exp **OR** weight-reduction/de OR anemia/de OR iron-deficiency-anemia/exp

OR

(Serodiagnosis/de OR gliadin-antibody/exp OR endomysium antibody/exp OR immunoglobulin-G-antibody/exp OR immunoglobulin-A-antibody/exp OR protein-glutamine-gamma-glutamyltransferase-antibody/exp) NOT (screening:ti NOT (Primary-medical-care/exp OR Primary-health-care/de OR General-practitioner/exp OR general-practice/exp OR physician/de OR outpatient-department/de OR hospital:ti,ab OR clinic:ti,ab))

OR

((Echography/de OR transrectal-ultrasonography/exp OR ultrasound/exp OR real-time-echography/exp) NOT ((staging:ti OR resection:ti OR preoperative:ti) NOT (diagnosis:ti OR detection:ti))) NOT ((intraoperative-ultrasound:ti,ab OR intraoperative-ultrasonography:ti,ab OR intraoperative-sonography:ti,ab OR endoscopic-ultrasound:ti,ab OR endoscopic-ultrasonography:ti,ab OR endoscopic-sonography:ti,ab OR endorectal-ultrasound:ti,ab OR endorectal-ultrasonography:ti,ab OR endorectal-sonography:ti,ab OR endosonography:ti,ab) NOT (conventional-ultrasound:ti,ab OR conventional-ultrasonography:ti,ab))

### **Target disease**

celiac-disease/exp OR celiac-disease:ti,ab OR coeliac-disease:ti,ab OR coeliaky:ti,ab OR coeliakie:ti,ab OR gluten-enteropathy:ti,ab OR gluten-sensitive-enteropathy:ti,ab OR gluten-intolerance:ti,ab OR celiac-sprue:ti,ab OR nontropical-sprue:ti,ab

### **Study design**

diagnosis/de OR diagnostic-error/exp OR differential-diagnosis/exp OR 'sensitivity and specificity'/exp OR accuracy/exp OR gold-standard/exp OR reference-value/exp OR sensitivity:ti,ab OR specificity:ti,ab OR likelihood-ratio:ti,ab OR index-test:ti,ab OR reference-test:ti,ab OR pretest:ti,ab OR pre-test:ti,ab OR posttest:ti,ab OR post-test:ti,ab OR roc:ti,ab OR reference-values:ti,ab OR diagnostic-accuracy OR diagnostic-value OR predictive-value OR predictive-values OR false-positive OR false-negative

### **Exclude**

((child/exp OR newborn/exp) NOT (adult/exp OR aged/exp)) OR review/exp OR case-report/exp OR letter/exp OR meta-analysis/exp OR ([animals]/lim NOT [humans]/lim)

**Combine: (index test AND target disease AND study design) NOT exclude**

**eTable 1. Results of quality assessment per study†**

Study reference	Spectrum/ selection bias	Test review bias	Incorporation bias	Clinical review bias	Adequate reference test	Partial verification bias	Differential verification bias	Diagnostic review bias	Time to reference test	Withdrawal bias	Bias due to missing values
1	?	?	+	?	+	+	+	?	?	+	+
2	+	?	+	?	+	+	+	+	+	+	+
3	-	+	-	+	-	-	-	-	?	-	?
4	?	?	+	+	+	+	+	?	?	+	+
5	-	+	?	+	+	-	-	-	?	+	?
6	-	-	+	-	+	+	+	-	?	+	+
7	+	+	+	+	+	+	+	+	?	+	+
8	?	+	+	+	+	+	+	?	+	+	+
9,10	?	-	+	?	+	+	+	+	?	+	+
11	-	+	-	?	+	-	+	?	?	-	?
12	?	+	+	?	?	-	-	?	?	?	+
13	-	+	-	-	+	-	+	?	?	-	?
14	+	?	+	?	?	+	+	+	+	+	+
15	-	?	-	?	?	+	+	+	?	+	?
16	-	?	+	-	?	+	+	?	?	+	+
17	-	-	-	+	?	-	+	-	?	-	?

† '+' = no bias; '-' = potential bias; '?' = insufficient information

Spectrum or selection bias: valid selection of study participants (consecutive patients or random sample, selection criteria do not jeopardize representativeness)

Test review bias: index test results are interpreted blind to the results of reference test

Incorporation bias: index tests do not form part of reference test

Clinical review bias: clinical data are available when interpreting the results of the index test as would be available in clinical practice

Adequate reference test: reference test is likely to correctly classify celiac disease (small bowel biopsy + histology, and positivity criteria are clearly described)

Partial verification bias: all or a random selection of patients who receive the index test go on to receive a reference test

Differential verification bias: all patients who receive the index test are subjected to the same reference standard

Diagnostic review bias: reference test results are interpreted blind to the results of index test

Time to reference test: time between index and reference test is one month or less

Withdrawal bias: all patients who enrol in the study receive both index test and reference standard, or low risk of bias due to withdrawals

Bias due to missing values: no bias due to missing values or uninterpretable test results.

**eTable 2. Diagnostic performance of serological tests – test combinations \***

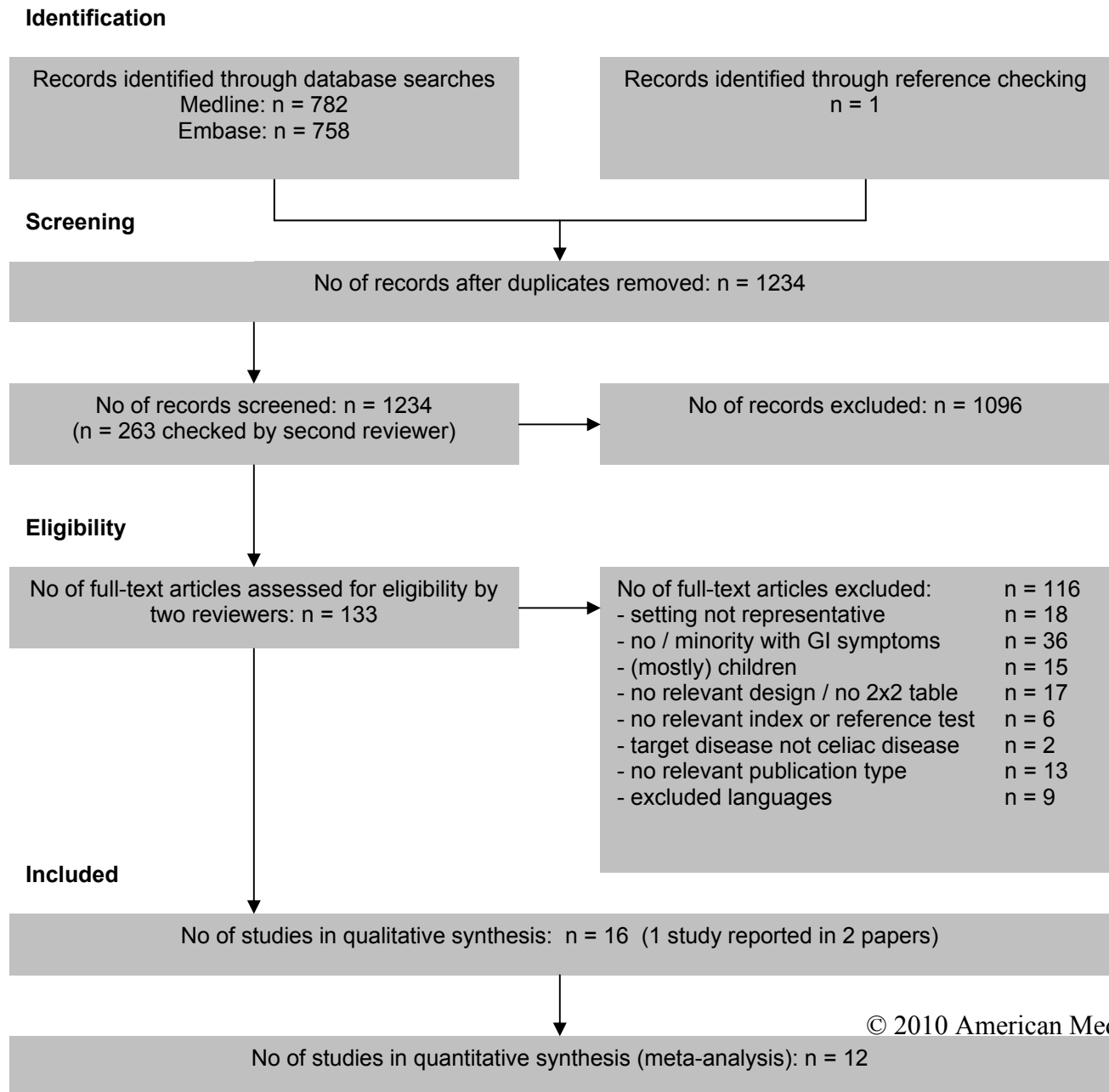
Study ref	Relevant test combinations	TP	FP	FN	TN	Sensitivity [95% CI]	Specificity [95% CI]	LR+ [95% CI]	LR- [95% CI]
16	IgA-AGA or IgA-tTG	29	5	1	140	0.97 [0.83 – 1.00]	0.97 [0.92 – 0.99]	28.0 [11.8 – 66.5]	0.04 [0.01 – 0.24]
4	total IgA or EmA	29	3	2	284	0.94 [0.79 – 0.99]	0.99 [0.97 – 1.00]	89.5 [28.9 – 276]	0.07 [0.02 – 0.25]
16	IgG-AGA or IgG-tTG	29	52	1	93	0.97 [0.83 – 1.00]	0.64 [0.56 – 0.72]	2.70 [2.15 – 3.38]	0.05 [0.01 – 0.36]
9	IgA-DGP or IgA-tTG	76	6	16	118	0.83 [0.73 – 0.89]	0.95 [0.90 – 0.98]	17.1 [7.78 – 37.5]	0.18 [0.12 – 0.29]
9	IgA-DGP or IgG-AGA	72	7	20	117	0.78 [0.68 – 0.86]	0.94 [0.89 – 0.98]	13.9 [6.70 – 8.70]	0.23 [0.16 – 0.34]
9	IgG-DGP or IgA-tTG	76	2	16	122	0.83 [0.73 – 0.90]	0.98 [0.94 – 0.99]	51.2 [12.9 – 203]	0.18 [0.11 – 0.28]
9	IgA or IgG-DGP or IgA-tTG	77	4	15	118	0.84 [0.74 – 0.91]	0.96 [0.92 – 0.99]	25.5 [9.70 – 67.2]	0.17 [0.11 – 0.27]
9	IgA or IgG-DGP or IgA-tTG or IgG-tTG	77	10	15	114	0.84 [0.74 – 0.91]	0.92 [0.86 – 0.96]	10.4 [5.69 – 18.9]	0.18 [0.11 – 0.28]
7	IgA-AGA or IgG-AGA or IgA-tTG or EmA	13	16	3	431	0.81 [0.54 – 0.96]	0.96 [0.94 – 0.98]	22.7 [13.3 – 38.8]	0.19 [0.07 – 0.54]
17	IgG-AGA or IgG-tTG or EmA Work-up: serology-, no biopsy=no CD	8	159	0	161	1.00 [0.63 – 1.00]	0.50 [0.45 – 0.56]	1.90 [1.58 – 2.31]	0.11 [0.01 – 1.64]
11	IgA-AGA or IgG-AGA or EmA Work-up: serology-, no biopsy=no CD †	14	43	0	224	1.00 [0.77 – 1.00]	0.84 [0.79 – 0.88]	5.96 [4.47 – 7.94]	0.04 [0.01 – 0.61]
9	IgA-tTG and IgG-AGA	23	1	69	123	0.25 [0.17 – 0.35]	0.99 [0.96 – 1.00]	31.0 [4.26 – 225]	0.76 [0.67 – 0.85]
15	IgA-AGA and EmA	13	0	6	125	0.68 [0.43 – 0.87]	1.00 [0.97 – 1.00]	170 [10.5 – 2750]	0.33 [0.17 – 0.61]
7	IgA-AGA and EmA	9	1	7	446	0.56 [0.30 – 0.80]	1.00 [0.99 – 1.00]	251 [33.9 – 1867]	0.44 [0.25 – 0.76]
7	IgA-tTG and EmA	13	3	3	444	0.81 [0.54 – 0.96]	0.99 [0.98 – 1.00]	121 [38.3 – 383]	0.19 [0.07 – 0.52]
9	IgA-DGP and IgA-tTG	65	2	27	122	0.71 [0.60 – 0.80]	0.98 [0.94 – 1.00]	43.8 [11.0 – 174]	0.30 [0.22 – 0.41]
9	IgA-DGP and IgG-AGA	56	1	36	123	0.61 [0.50 – 0.71]	0.99 [0.96 – 1.00]	75.5 [10.6 – 535]	0.39 [0.31 – 0.51]
9	IgG-DGP and IgA-tTG	58	1	34	123	0.63 [0.52 – 0.73]	0.99 [0.96 – 1.00]	78.2 [11.0 – 554]	0.39 [0.31 – 0.51]
9	IgA and IgG-DGP and IgA-tTG	54	1	38	123	0.59 [0.48 – 0.69]	0.99 [0.96 – 1.00]	72.8 [10.3 – 516]	0.42 [0.33 – 0.53]
9	IgA + IgG-DGP and IgA-tTG and IgG-tTG	19	1	73	123	0.21 [0.13 – 0.30]	0.99 [0.96 – 1.00]	25.6 [3.49 – 187]	0.80 [0.72 – 0.89]
13	IgA-AGA and EmA Work-up: serology-, no biopsy=no CD	3	0	9	93	0.25 [0.06 – 0.57]	1.00 [0.96 – 1.00]	50.6 [2.77 – 925]	0.74 [0.53 – 1.02]
11	IgA-AGA and IgG-	1	0	13	286	0.07 [0.00 – 0.34]	1.00 [0.99 – 1.00]	57.4 [2.44 – 1351]	0.90 [0.76 – 1.07]

	AGA <b>and</b> EmA Work-up: serology-, no biopsy=no CD ‡								
7	IgA-AGA <b>and</b> IgG- AGA <b>and</b> IgA-tTG <b>and</b> EmA	3	0	13	447	0.19 [0.04 – 0.46]	1.00 [0.99 – 1.00]	184 [9.91 - 3431]	0.80 [0.62 – 1.01]
8	High risk score (table 4) <b>and</b> IgA-tTG	64	655	13	1268	0.83 [0.73 – 0.91]	0.66 [0.64 – 0.68]	2.44 [2.17 – 2.75]	0.26 [0.16 – 0.42]
8	High risk score <b>or</b> positive IgA-tTG	77	753	0	1170	1.00 [0.95 – 1.00]	0.61 [0.59 – 0.63]	2.54 [2.39 – 2.69]	0.01 [0.001 – 0.17]

\* For the analyses, 0.5 was added to all cells of 2x2 tables containing at least one 0

† 19 drop-outs (9 seropositives and 10 seronegatives) had to be excluded from analysis, ‡19 drop-outs assumed to have no CD in analysis

**eFigure. Flow of information through the different phases of the review**







## eReferences

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