META-ANALYSIS

Diagnostic and clinical significance of antigen-specific pancreatic antibodies in inflammatory bowel diseases: A meta-analysis

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Abstract

BACKGROUND
Non-invasive criteria are needed for Crohn’s disease (CD) diagnosis, with several biomarkers being tested. Results of individual diagnostic test accuracy studies assessing the diagnostic value of pancreatic autoantibodies-to-glycoprotein-2 (anti-GP2) tests for the diagnosis of CD appear promising.
AIM
To systematically review and meta-analyze evidence on the diagnostic accuracy of anti-GP2 tests in patients with suspected/confirmed CD.

METHODS
An electronic search was conducted on PubMed, Cochrane-CENTRAL and grey literature (CRD42019125947). The structured research question in PICPTR format was “Population” including patients with symptoms akin to CD, the “Index test” being anti-GP2 testing, the “Comparator” involved standard CD diagnosis, the “Purpose of test” being diagnostic, “Target disorder” was CD, and the “Reference standard” included standard clinical, radiological, endoscopical, and histological CD diagnostic criteria. Quality was assessed with the Quality Assessment of Diagnostic Accuracy Studies-2 tool and hierarchical models were employed to synthesize the data.

RESULTS
Out of 722 studies retrieved, 15 were meta-analyzed. Thirteen studies had industry-related conflicts-of-interest, and most included healthy donors as controls (spectrum bias). For the combination of IgA and/or IgG anti-GP2 test, the summary sensitivity was 20% (95% confidence interval: 10%-29%) at a median specificity of 97%. If the test was applied in 10000 suspected patients, 9669 would be true negatives and in 26, the diagnosis would be missed. In this hypothetical cohort, the anti-GP2 would fail to produce a diagnosis for 81.3% of the positive cases. Low summary points of sensitivity and high specificity were estimated for the IgG or IgA anti-GP2 test. Analogous results were observed when the analyses were restricted using specific cut-offs, or when ulcerative colitis patients were used as comparators.

CONCLUSION
Anti-GP2 tests demonstrate low sensitivity and high specificity. These results indicate that caution is required before relying on its diagnostic value. Additionally, the need for improving the methodology of diagnostic test accuracy studies is evident.

Key words: Inflammatory bowel disease; Gastrointestinal disease; Evidence-based diagnosis; Sensitivity; Specificity; Ulcerative colitis; Conflicts of interest; Meta-regression; Industry bias

Core tip: The majority of individual studies assessing the diagnostic accuracy of autoantibodies for anti-glycoprotein 2 (anti-GP2) for Crohn’s disease (CD) diagnosis either include asymptomatic participants, or patients with symptoms not akin to CD. Most studies carry industry-related conflicts-of-interest, employing non-blinded evaluation of their assays and CD diagnosis preceding anti-GP2 testing. The pooled analyses performed herein using only symptomatic patients as controls, revealed high heterogeneity and low diagnostic accuracy of the anti-GP2, demonstrating low sensitivity and high specificity. Based on the pooled sensitivity and specificity of the anti-GP2 for CD diagnosis, they do not appear to attain the characteristics to be used per se as a proper non-invasive diagnostic tool.

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INTRODUCTION
Pancreatic secretory granule membrane glycoprotein 2 (GP2) consists of a 78kDa glycoprotein[1]. GP2 is synthesized by the acinus cells[1] in the pancreas, and is considered today as the main target of pancreatic autoantibody[2,3]. Recent data indicate that GP2 is a specific receptor on microfold (M) cells of intestinal Peyer’s patches[4], which consist of the original inflammation site in Crohn’s Disease (CD)[5]. With autoreactive responses being important effectors of immune-mediated inflammation, triggering overt inflammatory bowel diseases (IBD)[6], autoantibodies-to-glycoprotein-2 (anti-GP2) have recently been suggested as possible diagnostic markers of CD.

Today, CD differential diagnosis is based on standard clinical, radiological, endoscopical and histological criteria[8,9,21-25], and a need for less invasive diagnostic tools has been highlighted, especially given the great number of patients with clinical features mimicking CD[10]. This is why recently, many diagnostic test accuracy (DTA) studies have been conducted, assessing the specificity and sensitivity of various biomarkers against standard CD diagnostic procedures[8,9], including the anti-GP2.

Despite the fact that a plethora of DTA studies has recently been conducted assessing the sensitivity and specificity of the GP2 autoantibodies for CD’s differential diagnosis, synthesis of these studies in the form of a systematic review and meta-analysis would undoubtedly produce more valid results, as compared to individual studies, aiding evidence-based diagnosis[11]. Meta-analyses of DTA studies are important to obtain more valid, summary estimates of the diagnostic accuracy of an index test[12]. One such meta-analysis investigating the diagnostic accuracy of anti-GP2 for CD was published during the year 2017[13], missing however, many of the DTA studies published since then. Additionally, this specific meta-analysis[13] also exhibited few methodological shortcomings, like the improper inclusion of healthy controls in the samples analyzed, although for DTA studies, only patients with symptoms akin to the disease investigated are to be used[14,15].

Given the need for less invasive diagnostic tests (preferably serological) to be used in individuals with clinical suspicion of CD, while identifying the literature gap as per relevant state-of-the-art systematic reviews, the aim of the present systematic review and meta-analysis was to synthetize evidence examining the diagnostic accuracy of anti-GP2 tests in patients with suspected or confirmed CD. The PPPICPT or an adapted PICO for systematic reviews of DTA was applied. In further detail, the PICPCTR of the study was Population including patients with gastrointestinal symptoms akin to CD, with the Index test being positive anti-GP2 testing, the Comparator being standard CD diagnosis, the Target disorder being CD, and the Reference standard included the standard clinical, radiological, endoscopical and histological criteria for CD diagnosis[16].

### MATERIALS AND METHODS

#### Literature search

Reporting standards are based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy[17,18]. The protocol of the present systematic review was registered at PROSPERO (CRD42019125947).

A systematic search was conducted using the PubMed and Cochrane CENTRAL databases, until February, 28 2019. The grey literature and websites of companies manufacturing anti-GP2 kits were also explored for possible references using the specific tests. The keywords used in the searches included (anti-glycoprotein 2 antibody), (autoantibodies to glycoprotein 2), (anti-gp2), (autoantibodies), (Crohn’s disease), with a combination of MeSH terms wherever possible. In particular, Table 1 details the search strategy used for PubMed and Cochrane-CENTRAL. The keyword “anti-glycoprotein” was used for searches within grey literature sources (Open Grey and National Technical Information Service) and on websites of anti-GP2 manufacturers (Euroimmun, GA Generic Assays, Thermo Fisher, and AMS Biotechnology). Studies were assessed for eligibility independently and in duplicate, by three researchers (Gkiouras K, Grammatikopoulou MG and Bogdanos DP), and any disagreements were resolved by consensus.

#### Inclusion and exclusion criteria

We imposed no restrictions on the age of the study population, language, or the quality of retrieved DTA studies. Studies assessing anti-GP2 levels to diagnose CD in patients with relevant clinical features were selected. Additionally, studies assessing anti-GP2 levels among IBD patients were also considered eligible. The reference standard to verify CD diagnosis was the standard clinical, radiological, endoscopical and histological criteria for CD diagnosis[8,9].

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**Table 1**

| Database            | Search Strategy                                                                 |
|---------------------|--------------------------------------------------------------------------------|
| PubMed              | (anti-glycoprotein 2 antibody), (autoantibodies to glycoprotein 2), (anti-gp2), (autoantibodies), (Crohn’s disease), with a combination of MeSH terms wherever possible. In particular, “anti-glycoprotein” was used for searches within grey literature sources (Open Grey and National Technical Information Service) and on websites of anti-GP2 manufacturers (Euroimmun, GA Generic Assays, Thermo Fisher, and AMS Biotechnology). Studies were assessed for eligibility independently and in duplicate, by three researchers (Gkiouras K, Grammatikopoulou MG and Bogdanos DP), and any disagreements were resolved by consensus. |
| Cochrane CENTRAL    | (anti-glycoprotein 2 antibody), (autoantibodies to glycoprotein 2), (anti-gp2), (autoantibodies), (Crohn’s disease), with a combination of MeSH terms wherever possible. In particular, “anti-glycoprotein” was used for searches within grey literature sources (Open Grey and National Technical Information Service) and on websites of anti-GP2 manufacturers (Euroimmun, GA Generic Assays, Thermo Fisher, and AMS Biotechnology). Studies were assessed for eligibility independently and in duplicate, by three researchers (Gkiouras K, Grammatikopoulou MG and Bogdanos DP), and any disagreements were resolved by consensus. |

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**Table 2**

| Study Details                  |
|-------------------------------|
| Population, including patients with gastrointestinal symptoms akin to CD, with the Index test being positive anti-GP2 testing, the Comparator being standard CD diagnosis, the Target disorder being CD, and the Reference standard included the standard clinical, radiological, endoscopical and histological criteria for CD diagnosis[16]. |

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**Table 3**

| Study Details                  |
|-------------------------------|
| Eligibility criteria, studies assessing anti-GP2 levels to diagnose CD in patients with relevant clinical features were selected. Additionally, studies assessing anti-GP2 levels among IBD patients were also considered eligible. The reference standard to verify CD diagnosis was the standard clinical, radiological, endoscopical and histological criteria for CD diagnosis[8,9]. |

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**Table 4**

| Study Details                  |
|-------------------------------|
| PPPICPT or an adapted PICO for systematic reviews of DTA was applied. In further detail, the PICPCTR of the study was Population including patients with gastrointestinal symptoms akin to CD, with the Index test being positive anti-GP2 testing, the Comparator being standard CD diagnosis, the Target disorder being CD, and the Reference standard included the standard clinical, radiological, endoscopical and histological criteria for CD diagnosis[16]. |

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**Table 5**

| Study Details                  |
|-------------------------------|
| Protocol of the present systematic review was registered at PROSPERO (CRD42019125947). |
Table 1  Search strategy for PubMed and Cochrane-CENTRAL

| Database          | Key words                                                                 |
|-------------------|---------------------------------------------------------------------------|
| PubMed             | No. 1 Anti-glycoprotein 2 antibody                                        |
|                   | No. 2 "Anti-glycoprotein 2 antibody"                                      |
|                   | No. 3 Anti-glycoprotein 2 antibody [Text Words]                           |
|                   | No. 4 Autoantibodies to glycoprotein 2                                   |
|                   | No. 5 "Autoantibodies to glycoprotein 2"                                  |
|                   | No. 6 Autoantibodies to glycoprotein 2 [Text Words]                      |
|                   | No. 7 "Glycoprotein 2 autoantibodies"                                    |
|                   | No. 8 Glycoprotein 2 autoantibodies [Text Words]                         |
|                   | No. 9 Autoantibodies (as a MeSH term)                                    |
|                   | No. 10 OR (No. 1 - No. 9)                                                |
|                   | No. 11 Crohn’s disease                                                   |
|                   | No. 12 Crohn’s disease (as a MeSH term)                                  |
|                   | No. 13 OR (No. 11, No. 12)                                               |
|                   | No. 14 AND (No. 10, No. 13)                                              |
| Cochrane-CENTRAL  | No. 1 Anti-glycoprotein 2 antibody                                        |
|                   | No. 2 Autoantibodies to glycoprotein 2                                   |
|                   | No. 3 Autoantibodies (as a MeSH term)                                    |
|                   | No. 4 OR (No. 1 - No. 3)                                                 |
|                   | No. 5 Crohn’s disease                                                    |
|                   | No. 6 Crohn’s disease (as a MeSH term)                                   |
|                   | No. 7 OR (No. 5, No. 6)                                                  |
|                   | No. 8 AND (No. 4, No. 7)                                                 |

No. means order of the keywords entered on PubMed and CENTRAL. OR and AND are Boolean operators used between keywords.

However, studies were excluded when (1) based on animals or non-human samples; (2) not providing sufficient data to construct a 2 × 2 table; (3) presenting duplicate data already reported in other manuscripts; and (4) not reporting the reference CD diagnostic criteria. When two publications had been identified as using overlapping populations, they were counted as a single study[26].

Data extraction

The main outcomes of interest involved sensitivity, specificity and the diagnostic odds ratio[27,28].

Data were extracted by Gkiouras K and Grammatikopoulou MG on prespecified data extraction sheets for DTA studies, as suggested by the Joanna Briggs Institute[29], which were then checked by Bogdanos DP. For studies reporting sensitivity, specificity, positive and negative predictive values and a total number of included patients, 2 × 2 tables of true positives (TP), false positives, false negatives, and true negatives (TN) were calculated, following the instructions of the Oxford Centre for Evidence-Based Medicine[30].

Quality assessment

Quality of included studies was assessed independently and in duplicate by two reviewers (Theodoridis X and Chatzikyriakou E), using the criteria of the Quality Assessment of Diagnostic Accuracy Studies-2 tool[31].

Meta-analysis

Given the great variability regarding the cut-offs used to define disease status in the primary studies[32,33], the hierarchical summary receiver operating characteristic (HSROC) model[34,35] was employed to synthesize data. SROC curves were constructed, but considering that a summary point of sensitivity or specificity among studies using mixed thresholds would be clinically uninterpretable, we chose to estimate summary sensitivity at its median specificity, based on the SROC curves[34,35]. When more than three primary studies reported similar cut-offs, the analysis was
repeated with the hierarchical Bivariate model in order to obtain summary points of sensitivity and specificity.\(^{[39]}\)

Furthermore, heterogeneity was assessed statistically by including covariates in the HSROC model (meta-regression). Heterogeneity is summarized with the relative diagnostic odds ratios (RDOR) along with their 95% confidence intervals (95%CI). The included covariates involved: Source of funding [state vs other (including private or not stated)], diagnostic kit industry-conflicts-of-interest (COI) [industry (studies either reporting funding from diagnostic kit manufacturers, or having authors employed in the industry) vs other (lack of apparent industry-related COI)], the assay used for detecting autoantibodies (enzyme-linked immunosorbent assay vs indirect immunofluorescence), the manufacturers of the anti-GP2 kits (Generic assays vs other), blinding of the assay (lacking or not stated vs yes), recruitment of consecutive patients (no/not stated vs yes), and the percentage of female participants categorized as ≥ 50% vs < 50%.

When the complete HSROC models failed to converge and/or returned unstable parameters they were simplified with the symmetric HSROC model or the HSROC model with fixed accuracy, as previously described.\(^{[36]}\) Similarly, when the Bivariate model returned unstable parameters, the analysis was repeated with univariate random effects models (UREM), as previously proposed.\(^{[38]}\) The fit of the models was assessed with the -2 Loglikelihood test.\(^{[39]}\) All analyses were repeated twice, once including DTA studies reporting results from CD cases against all patients with relevant symptoms, and the second time including studies reporting CD cases against ulcerative colitis (UC) cases only. In the analyses combining the result of IgA and/or IgG positive antibodies, studies were included only when reporting relevant results in detail.

Estimates of sensitivities and specificities derived for specific cut-off values were expressed as natural frequencies and summarized in a table.\(^{[37]}\) Since the majority of included studies were based in Europe, Germany in particular, and had a case-control design, the estimation of CD prevalence would not have been precise. Subsequently, the prevalence rates used herein were extracted from a recent systematic review.\(^{[39]}\) The prevalence rate used was 322 per 100000 in a hypothetical cohort of 10000 suspected patients. This figure was selected based on its efficiency to produce logical natural frequencies.

Statistical analyses were carried with the SAS PROC NL MIXED procedure and/or the MetaDAS macro on SAS software (SAS Institute Inc., Cary, NC, United States) and the plots were developed with RevMan.\(^{[38]}\) The statistical methods used in this study were reviewed by Dr. Anna-Bettina Haidich, Associate Professor of Medical Statistics and Epidemiology in Aristotle University of Thessaloniki.

RESULTS

Out of the 722 DTA studies retrieved in total, 18 fulfilled the systematic review’s protocol criteria. Figure 1 details the selection process of the primary DTA studies. As three studies did not assess total anti-GP2 but different anti-GP2 isoforms, these were excluded from the meta-analyses, leaving a total of 15 studies.

Study characteristics and quality assessment of studies

Table 2 details the characteristics of the 18 primary DTA studies included in the systematic review. All retrieved studies involved full-text articles, except from the one by Op De Beeck et al\(^{[39]}\), which was in Letter format. None of the studies reported information on the ethnicity of the samples. The Bonaci-Nicolic et al\(^{[42]}\) study was the only one lacking ethical permission disclosure, whereas the DTA by Op De Beeck et al\(^{[39]}\) had reported related ethics in a previous study using part of the same sample.\(^{[39]}\) Cummings and associates\(^{[43-45,49,51]}\) were the only ones recruiting unrelated participants, whereas seven DTA studies in total included children in their samples. Only five studies assured blinding the assays\(^{[41-43,54-58,46-52]}\). Cut-offs used to define positivity in IgA or IgG varied greatly, ranging from 3.7 U/dL to 71.75 U/dL for specific GP2 isoforms.

The quality assessment summary using the QUADAS-2 tool is presented in Figure 2. Risk of bias for the index test was generally unclear since, in most studies, it was uncertain whether the thresholds used had been prespecified by the kit’s manufacturer, or were study-derived.\(^{[38]}\) Additionally, many primary DTA studies failed to report whether the anti-GP2 assay was performed with the results of the CD diagnosis being blind\(^{[38]}\).

Meta-analysis of the diagnostic accuracy of anti-GP2 (IgG) for CD

A total of 15 studies were included in the pooled analyses for evaluation of the diagnostic accuracy of the anti-GP2 IgG (Figure 3), including a pooled sample of 4365
patients, with 665 of them being CD cases and 3700 forming the controls group. The diagnostic sensitivity of the anti-GP2 (IgG) for CD ranged between 10% to 43% (Figure 3A), and the specificity ranged from 80 to 100% (Figure 3B). The summary SROC curve is presented in Figure 3C, indicating that on the median specificity of 93%, summary sensitivity reached 27% (95%CI: 20%-34%). With the UREM models (seven DTA studies), it was estimated that at the cut-off level of 20 U/mL, summary sensitivity reached 22% (95%CI: 15%-30%) and specificity was calculated at 93% (95%CI: 91%-95%). At the cut-off of 15 U/mL (three studies, Bivariate model), summary sensitivity was 28% (95%CI: 16%-43%) and specificity reached 92% (95%CI: 84%-96%).

Forest plots of sensitivity and specificity and the summary SROC curve for the diagnostic accuracy of anti-GP2 in patients with CD against those with UC (14 studies, total patients: 3947; CD cases: 640; UC cases: 3307) are presented in Figures 3D-F. A potential outlier study, the one conducted by Bonaci-Nicolic and associates [42], was identified from the forest plot and the space of the SROC curve, indicating the need for refitting the HSROC model accordingly, after excluding this study. Based on the -2 Loglikelihood test ($P < 0.001$), the remaining analyses were carried out without this DTA study [42]. Based on the HSROC model, the estimated sensitivity on the SROC curve was estimated at 15% (95%CI: 12%-18%) and median specificity was calculated at 93% (95%CI: 90%-96%). At the cut-off limit of 15 U/mL, summary sensitivity reached 28% (95%CI: 16%-43%) and specificity was estimated at 90% (95%CI: 84%-94%).

**Meta-analysis of the diagnostic accuracy of anti-GP2 (IgA) for CD**
A total of 14 studies were included in the pooled analysis for the diagnostic accuracy of anti-GP2 IgA, involving 3914 patients in total (CD cases: 380; Control cases: 3534). The reported diagnostic sensitivity ranged from 3% to 37% (Figure 4A) and specificity between 75% to 100% (Figure 4B). Using the HSROC model, the estimated sensitivity on the SROC curve was estimated at 15% (95%CI: 12%-18%) and median specificity reached 97% (Figure 4C). Using the cut-off value of 20 U/mL (seven studies, bivariate
Table 2  Characteristics of the included studies evaluating the diagnostic accuracy of glycoprotein 2 antibodies in Crohn’s disease

| Ref. | Country | Multicenter | Recruitment | CD diagnosis and classification | Assays characteristics | Sample characteristics | Funding |
|------|---------|-------------|-------------|--------------------------------|------------------------|-----------------------|---------|
|      |         |             |             |                                |                        |                       |         |
|      |         |             |             |                                |                        |                       |         |
| Bogdanos et al [81] | Germany; United Kingdom | √ | NR | Otto-von-Guericke University; UCL Hospital; and Children’s hospital Technical University Dresden | Standard clinical, radiological, endoscopic and histological criteria | Total No | IgA 20; IgG 20 | CD 60.3%; UC 58.9% |
| Bonaci-Nikolic et al [42] | Serbia | NR | NR | Clinical Center of Serbia | Clinical, endoscopic, histologic, lab findings | Total No | IgA 20; IgG 24 | CD 42.4%; UC 35 (19-63); CD 35 (16-63); UC 34 (24-57); CSE 31 (19-57); HC 41 (22-55) |
| Caneparo et al [43] | Italy | 2008-2014 | Poli clinico San Donato | Clinical, endoscopic and histological criteria | ELISA GA (Dahlewitz/Berlin Germany) | Total No | IgA 10; IgG 15 | CD 47.9%; UC 19.2% |
| Cummings et al [44] | United Kingdom | √ | 2009-2010 Cleveland Clinic | Clinical, endoscopic, radiographic, histopathological criteria | ELISA GA (Dahlewitz/Berlin Germany) | Isoforms GP21 and GP24 | IgA GP21 14; IgA GP24 3.7; IgG GP21 18; IgG GP24 15 | UC 44.4% ± 13.7 |
| Degenhardt et al [45] | Germany | √ | 2000-2006 University Medical Center Regensburg | European Crohn and Colitis Organization criteria | ELISA GA (Dahlewitz/Berlin Germany) | Isoform alpha and beta | CD n = 303; UC n = 308; OGD n = 72; OPC n = 206 | CD 52.8%; UC 39.8%; OGD 36.1% ± 13.8 | Bundesministerium für Bildung & Forschung and Kompetenznetz chronisch entzündliche Darmerkrankungen |
| Study | Location | Year | Institution | Criteria | Technique | Control | Sample Size | Cases | Controls | Percentages | Means | Funds |
|-------|----------|------|-------------|----------|-----------|---------|-------------|-------|----------|-------------|-------|--------|
| Gross et al. | Netherlands | NR | VU University Medical Center Amsterdam | Lennard-Jones criteria | ELISA GA (Dahlewitz/Berlin Germany) | Total | IgA 20; IgG 20 | CD n = 38; UC n = 40 | GA n = 45; CDG n = 54; RCD n = 15 | CD 71.1%; UC 52.5% | CD 36.4 ± 11.8; UC 36.5 ± 9.6 | CD consortium |
| Michaels et al. | Germany | 2005-2013 | University Hospital Schleswig-Holstein | Typical clinical, endoscopic, histological and/or radiological findings of CD/UC | IIF Euroimmun mun Germany | Total | NR | CD n = 224; UC n = 136 | CD 64.3%; UC 54.4%; CD 992; UC 422 | Else-Kröner-Fresenius-Stiftung |
| Op De Beéck et al. | Belgium | NR | University Hospital Gasthuisberg - Leuven | Lennard-Jones criteria | ELISA GA (Dahlewitz/Berlin Germany) | Total | IgA 15; IgG 15 | CD n = 164; UC n = 118 | OGD n = 75 | CD 58.6%; UC 41.7%; CD 43 (19-80); UC 73 (19-98); OGD NR | CD 56.4% ± 15.7; UC 49.7% ± 15.7 | Fund for Scientific Research Flanders and GA GmbH |
| Pavlidis et al. | Hungary | 2005-2010 | Institute of Internal Medicine, University of Debrecen | Lennard-Jones criteria | ELISA GA (Dahlewitz/Berlin Germany) | Total | IgA 20; IgG 20 | CD n = 271; UC n = 187; HC n = 100 | NA | CD 61.5%; UC 54% | CD 25 (19-33); UC 33 (23-43) | Janos Bolyai Research Scholarship; Debrecen University; and IOIBD Research |
| Pavlidis et al. | United Kingdom | NR | UCL Hospital | Lennard-Jones criteria | ELISA GA (Dahlewitz/Berlin Germany) | Total | IgG 20 | CD n = 228; UC n = 225 | NA | CD 56.4%; UC 49.7% | CD 36 ± 14.3; UC 51 ± 15.7 | NIHR; Higher Education Funding Council for England; EASL; and INOVA Diagnostics |
| Pavlidis et al. | United Kingdom | NR | UCL Hospital | Lennard-Jones criteria | ELISA Inova Diagnostics (Research use only) | Total | IgA 20; IgG 25 | CD n = 323; UC n = 294; OPC n = 132; HC n = 103 | NA | CD 54%; UC 47.9% | CD 40 ± 14.3; UC 48.7 ± 15.7 | INOVA Diagnostics |
| Pavlidis et al. | United Kingdom | NR | UCL Hospital | Lennard-Jones criteria | IIF N/A8 | Total | NR | CD n = 212; UC n = 249 | NA | CD 42.4%; UC 51.4% | CD 42.4 (30-49); UC 51.4 (37-61) | Euroimmun |
| Study Authors   | Country         | Institute(s)                          | Criteria                  | ELISA Reagents                                      | IgA IgG | CD n  | UC n  | GE n  | ENDO n | HC n  | Other Notes                        |
|----------------|-----------------|---------------------------------------|---------------------------|------------------------------------------------------|---------|-------|-------|-------|--------|-------|-------------------------------|
| Röber et al[53] | Germany         | Dresden, Leipzig, Giessen             | Porto criteria           | GP21, GP23: (AMS Biotechnology, Abingdon, United Kingdom); GP22: CCS GmbH, Hamburg, Germany; GP24: (Thermo Sci, Braunschweig, Germany) | NR      |       |       |       |        |       | None declared                  |
| Roggenbuck et al[55] | Germany | Charité Berlin                       | Lennard-Jones criteria    | ELISA GA (Dahlewitz/Berlin Germany)                   | NR      |       |       |       |        |       | None declared                  |
| Roggenbuck et al[56] | Germany; Greece; Belgium | Attikon Hospital, UoA; Otto-von-Guericke University; and University Hospital Leuven | Lennard-Jones criteria    | ELISA GA (Dahlewitz/Berlin Germany)                   | NR      |       |       |       |        |       | None declared                  |
| Zhang et al[57] | China           | Peking Union Medical College Hospital | Lennard-Jones criteria    | ELISA GA (Dahlewitz/Berlin Germany)                   | NR      |       |       |       |        |       | None declared                  |
| Zhang et al. China | NR | Peking Union Medical College Hospital | Lennard-Jones criteria | ELISA GA (Dahlewitz/Berlin Germany) | Total NR | IgA 10, IgG 15 | CD n = 171; UC n = 208; BD n = 71; ITB n = 77; HC n = 70 | NR |
|------------------|----|-------------------------------------|------------------------|-----------------------------------|----------|----------------|------------------|----------|
| CD 33%; UC 43%; BD 38%; ITB 43% | CD 33 (10-85); UC 43 (12-77); BD 38 (10-73); ITB 43 (14-58) | NNSFC; Chinese Academy of Medical Sciences; and Chinese Key Research & Development Program |

1Median (minimum–maximum).
2Median.
3Mean (IQR1–IQR3).
4Mean ± standard deviation, or median, IQR.
5Not all participants from the Joossens study were included.
6Not among participants with Crohn’s disease.

Using as substrates IIF chip slides containing sections of unfixed pancreas, recombinantly transformed HEK293 cells-overexpressing GP2.

Healthy controls were not included in the sensitivity and specificity analyses herein. Anti-GP2: Glycoprotein 2 antibodies; BD: Behcet’s disease; CD: Crohn’s disease; CeD: Celiac Disease; EASL: European association for the study of liver; ENDO: Nonspecific gastrointestinal symptoms; ELISA: Enzyme-linked immunosorbent assay; EU: European Union; GA: Generic assays; GE: Acute gastroenteritis; GFD: CeD on gluten-free diet; GP2: Glycoprotein 2; GSE: Gluten-sensitive enteropathy; HC: Healthy controls; IBD: Inflammatory bowel diseases; IIF: Indirect immune-fluorescence; ITB: Intestinal tuberculosis; N/A: Not applicable; NIHR: National Institute for Health Research; NNSFC: National Natural Science Foundation of China; NR: Not reported; OGD: Other gastrointestinal disease; OPC: Other pathological conditions; RCD: Refractory Crohn’s disease; UC: Ulcerative Colitis; UCL: University College London; UoA: University of Athens.

| Zhang et al. [58] China - NR Peking Union Medical College Hospital | Lennard-Jones criteria | ELISA GA (Dahlewitz/Berlin Germany) | Total NR | IgA 10, IgG 15 | CD n = 171; UC n = 208; BD n = 71; ITB n = 77; HC n = 70 | NR |
|------------------|------------------------|-----------------------------------|----------|----------------|------------------|----------|
| CD 33%; UC 43%; BD 38%; ITB 43% | CD 33 (10-85); UC 43 (12-77); BD 38 (10-73); ITB 43 (14-58) | NNSFC; Chinese Academy of Medical Sciences; and Chinese Key Research & Development Program |
model), summary sensitivity was 16% (95% CI: 9%-26%) and specificity was calculated at 96% (95% CI: 86%-99%).

When UC cases were used as the only comparators (Figures 4D and E; Total patients: 3497; CD cases: 324; UC cases: 3173) the estimated sensitivity on the SROC curve was 11% (95% CI: 3%-20%) at the median specificity of 98% (Figure 4F). However, when the analysis was restricted to studies reporting results at the cut-off of 20 U/mL (eight studies, UREM model), pooled summary sensitivity was calculated at 15% (95% CI: 10%-22%) and specificity reached 98% (95% CI: 96%-99%).

**Meta-analysis of the diagnostic accuracy of anti-GP2 (IgA and/or IgG) for CD**

A total of five studies were meta-analyzed during the assessment of the diagnostic accuracy of anti-GP2 IgA and/or IgG antibodies, involving a total of 1693 patients (CD cases: 243; Control cases: 1450). The reported diagnostic sensitivity of the anti-GP2 antibody (IgA and/or IgG) for CD ranged between 10% and 34% (Figure 5A), and the reported specificity ranged from 81% to 98% (Figure 5B). The estimated sensitivity was calculated at 20% (95% CI: 10%-29%) at a median specificity of 97% (Figure 5C). At the cut-off value of 20 U/mL (three studies, UREM model), pooled summary sensitivity reached 22% (95% CI: 12%-39%) and pooled summary specificity was computed at 93% (95% CI: 80%-98%).

When UC cases were used as comparators against patients with CD (Figures 5D and E; Total patients: 1541; CD cases: 203; UC cases: 1338), the estimated sensitivity was 20% (95% CI: 4%-35%) at the median specificity of 97% (Figure 5F).

**Investigation of heterogeneity**

Meta-regression analyses were conducted to explore possible sources of heterogeneity. The results (Table 3) revealed that the assay used to detect the anti-GP2 antibodies was linked with the accuracy of anti-GP2 IgG, both in the pooled patient analysis (RDOR = 4.25, 95% CI: 1.26-14.37), as well as in the analysis using UC cases as

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**Figure 2** Quality assessment of the included studies based on the quality assessment of diagnostic accuracy studies-2 tool.
comparators (RDOR = 3.28, 95%CI: 1.33-8.09). However, these results should be interpreted with caution due to the small number of studies included. The rest of the variables failed to demonstrate significant associations. In the analyses for the anti-GP2 IgA antibodies with the CD vs the UC cases, the models failed to converge, or returned unstable parameters even with the use of alternative models (see aforementioned Meta-analysis paragraph).

**Real-life scenario modeling the present findings**

To “measure” the exact effects of using the anti-GP2 assays for the diagnosis of CD according to the results herein and in a hypothetical pragmatic scenario[60], we used the recent data on IBD prevalence[38] (Table 4). When using the combination of IgG and/or IgA anti-GP2 for the diagnosis of CD in a hypothetical cohort of 10000 suspected patients, 9669 will be the TN cases and for 26 CD diagnosis will be missed (false negatives) although suffering from CD. In contrary, in the same cohort, 32 patients will suffer from CD and the test will correctly identify only 6 CD cases (TP). Analogous results will be observed if this test is implemented with a cut-off value of 20 U/dL, or in patients suspected only for CD vs UC. Likewise, in the analyses of CD vs either all symptomatic patients or UC cases only, using the IgG or IgA anti-GP2 tests would result in similarly increased TN and decreased TP cases.

**DISCUSSION**

The present meta-analysis of DTA studies revealed that the anti-GP2 have a low diagnostic accuracy (low sensitivity and high specificity) in detecting CD true positive cases. In contrast to the published primary DTA research when all relevant DTA studies were pooled together, the autoantibodies did not appear sensitive enough to detect true positive CD cases.

According to Lalkhen et al[61] the ideal diagnostic test is never positive in a disease-free patient, and never negative in a patient with the disease. With the low sensitivity
Figure 4  Pooled forest plots. A-C: Pooled forest plots for sensitivity and specificity, and the summary receiver operating characteristic curves of anti-GP2 antibody (IgA positive) for Crohn’s Disease against all patients with relevant symptoms; D-F: Pooled forest plots for sensitivity and specificity, and the summary receiver operating characteristic curves of anti-GP2 antibody (IgA positive) for patients with Crohn’s Disease against patients with Ulcerative colitis. FN: False negative; FP: False positive; ROC: Receiver operating characteristic; TN: True negative; TP: True positive; CI: Confidence interval.

and high specificity demonstrated herein, it appears that the anti-GP2 fall short in the diagnostic accuracy of CD. According to the rule of thumb suggested by Power et al. in a useful test, the sum of sensitivity + specificity must exceed 1.5, ideally reaching 2.0. In none of the analyses performed herein did the sum of sensitivity + specificity exceed 1.5. When high specificity is detected, the problem of overdiagnosis becomes pivotal. However, low sensitivity and high specificity are ideal characteristics of a screening tool, rather than a diagnostic one. Although different isoforms of the anti-GP2 have been identified since the beginning of the century, it is only until very recently that the diagnostic potential of all four isoforms was investigated and compared. According to some researchers, anti-GP2 isoforms 1 and 4 are considered as the best serological markers for CD diagnosis, superior even to the anti-saccharomyces cerevisiae antibodies (ASCA), which are routinely used, despite their poor specificity and insufficient sensitivity. Among the included DTA studies, Papp et al. reported the use of two different enzyme-linked immunosorbent assay methods employing recombinant human GP2 identified as isoform 4. Degehardt and associates made the distinction between two different isoforms of GP2 synthesized in the pancreas, the larger isoform alpha (analogous to isoforms 1 and 3), and the shorter beta form (analogous to isoforms 1 and 3). However, it is not within the scope of the present paper to further discuss the implications related to antibody reactivities against distinct GP2 isoforms. It should be noted however, that due to the different reported isoforms in the included DTA studies and the small number of studies reporting reactivity against different GP2 isoforms (three), no analyses could be performed to compare the diagnostic accuracy of different anti-GP2 subtypes. However, when more DTA studies of good methodological quality are published using GP2 isoforms, the diagnostic accuracy of the anti-GP2 might be improved in the respective pooled analyses compared to the total anti-GP2 which was evaluated herein.

One important methodological issue identified in the study involves the inclusion of already diagnosed patients, without securing blinding of the index test. The majority of DTA studies on anti-GP2 were performed on already diagnosed CD patients and only five studies reported blinding of the assays. This issue results in two forms of bias, being: (1) Partial verification bias, as only patients with a positive result on the index test (anti-GP2 assay) have actually undergone the reference
standard test for CD diagnosis (although in reverse order); and (2) Test review bias\([15]\), as the results of the reference standard are known to reviewers who interpret the index test. Another important limitation of most primary DTA studies involves the inclusion of healthy controls in their samples, either in the form of healthy donors, or as outpatients. This error was even detected in a recently published meta-analysis of anti-GP2 DTA studies\([14]\). The inclusion of healthy controls, or of patients with a disease having symptoms not akin to CD\([15-17]\) appears to form a systematic error, exhibited by most primary DTA research and has been reported to result in spectrum bias and overestimation of the diagnostic accuracy\([15,65]\). This was corrected in the present analyses, where CD cases were only compared either against symptomatic patients, or against patients with UC.

When compared to the recently published meta-analysis\([14]\) of anti-GP2 diagnostic accuracy for CD, the sensitivity and specificity previously reported is similar to the one calculated herein, despite pooling healthy controls together in the analyses. Still, authors of that meta-analysis\([11]\) acknowledge several of the limitations of applying the anti-GP2 assay as a diagnostic tool and suggest its use for the differentiation of CD patients from controls, although their definition of controls for DTA studies appears to be arbitrary. According to Al Fattani et al.\([66]\), evidence from well-designed thorough systematic reviews indicates the importance of attaining a correct methodological design in DTA studies.

Another concern and possible source of bias that may partly explain the systematic error of using healthy controls, or patients with irrelevant symptoms in the control groups, involves the industry-related COI demonstrated among most primary DTA studies. With 13\([41,43-45,48,49,51-56,58]\) out of 18 primary studies included in the systematic review either reporting direct funding by diagnostic kit manufacturers, receiving the kits for gratis, or including authors with kit-industry affiliations, this may partly explain the methodological mistakes detected in most DTA studies, either in the form of guidance throughout the study’s implementation, or in the form of statistical or interpretation advice provided by the kit industry. Although comparison between DTA studies with industry-related COI vs those lacking any apparent industry-related COI did not differ in terms of anti-GP2 accuracy, further investigation is needed to examine industry-related COI in DTA studies. It is well known that financial competing interests in industry-sponsored research often introduce bias into study design, analyses and interpretation of findings\([67]\), as observed herein. Fairly recently, it was suggested that in several cases the industry might be involved in overdiagnosis, due to underlying financial profits\([68,69]\). Dakubo et al.\([70]\) was the first to identify industry financial interests as a major cause of overdiagnosis, however, to our knowledge, COI in DTA research have never been evaluated, nor has the overall influence of the industry. As many of the primary studies included herein failed to report any funding source\([62,44,43]\), it is highly likely that some might have received the diagnostic kits for gratis by the industry without

![Figure 5](image-url)
Table 3  Investigation of heterogeneity (meta-regression)

| Covariate               | Population         | Ig Type | Number of studies | Relative diagnostic odds ratio (95%CI) |
|-------------------------|--------------------|---------|-------------------|--------------------------------------|
| Funding type            |                    |         |                   |                                       |
|                         | State vs Other     | IgG     | 6 vs 9            | 1.91 (0.87-4.21)                     |
|                         |                    | IgA     | 5 vs 9            | 1.08 (0.38-3.06)                     |
|                         | CD vs UC           | IgG     | 5 vs 8            | 1.21 (0.81-1.80)                     |
|                         |                    | IgA     | 6 vs 8            | 0.73 (0.32-1.66)                     |
|                         | Industry-related COI vs no apparent industry-related COI | IgG | 7 vs 8 | 0.73 (0.32-1.66) |
|                         |                    | IgA     | 6 vs 8            | 0.53 (0.21-1.30)                     |
| Method                  | ELISA vs IFF       | IgG     | 13 vs 2           | 0.84 (0.38-1.85)                     |
|                         |                    | IgA     | 12 vs 2           | 4.25 (1.26-14.37)                    |
| Blind assay             | No/not stated vs Yes | IgG   | 11 vs 2          | 1.60 (0.40-6.54)                     |
|                         |                    | IgA     | 11 vs 3           | 1.77 (0.63-5.00)                     |
|                         | CD vs UC           | IgG     | 10 vs 3           | 1.15 (0.32-4.15)                     |
|                         |                    | IgA     | 10 vs 4           | 1.31 (0.53-3.21)                     |
|                         | Consecutive sampling vs Yes | IgG | 11 vs 4          | 1.47 (0.65-3.32)                     |
|                         |                    | IgA     | 10 vs 4           | 1.31 (0.53-3.21)                     |
|                         | CD vs UC           | IgG     | 9 vs 4           | 1.88 (0.65-5.38)                     |
|                         | Kit manufacturer   | GA vs All other | IgG | 12 vs 3 | 1.04 (0.51-2.11) |
|                         |                    | IgA     | 11 vs 3           | 1.28 (0.80-2.03)                     |
|                         | Female participants | ≥ 50% vs < 50% | IgG | 11 vs 4 | 1.24 (0.79-1.94) |
|                         |                    | IgA     | 10 vs 4           | 0.75 (0.30-1.93)                     |
|                         | CD vs UC           | IgG     | 10 vs 3           | 1.15 (0.54-2.45)                     |

CD: Crohn’s disease; CI: Confidence interval; COI: Conflict of interest; GA: Generic assays; ELISA: Enzyme-linked immunosorbent assay; IFF: Indirect immune-fluorescence; Ig: Immunoglobulin; UC: Ulcerative Colitis.

reporting it, or without disclosing relevant academia-industry funding.

The variety of thresholds used in most studies to identify TP CD cases is yet another issue of concern. Given the high number of industry-related COI demonstrated in the primary DTA studies, one might argue that cut-offs are defined arbitrary, based on the expected TP prevalence in order to fulfill the minimum of positive and negative cases set by the College of American Pathologists[71,72]. Thus, it might be wise to report the diagnostic test thresholds in advance, possibly in the form of a published protocol, before initiating a DTA study.

In the present study we explored many potential sources of heterogeneity extensively and only the assay used to detect the anti-GP2 antibodies was associated with heterogeneity affecting the diagnostic accuracy of anti-GP2 IgG. The high degree of clinical heterogeneity exhibited in the primary DTA studies limits the possibility of making strong conclusions regarding the diagnostic performance of anti-GP2 antibodies. Another issue which needs to be taken into account is the performance of this test in combination with other non-invasive tests, such as fecal calprotectin and the ASCA, which are routinely used for the investigation of cases with a clinical suspicion of CD[73-75].

Undoubtedly, diagnostic tests can aid practitioners in the diagnostic process[76]. It appears that identifying a sensitive test without misclassification of many false positives remains a challenge[77], as most tests are imperfect and can only adjust disease probability[12]. Tests with low sensitivity and high specificity, like the anti-GP2, are better for population screening rather than for diagnosing patients[62,63]. Additionally, it appears that given the methodological pitfalls demonstrated in most anti-GP2 DTA research, high quality DTA cohort studies are required, enrolling consecutive patients, presenting clinical and laboratory features akin to CD, where both the assay and the reference diagnosis will be performed in a double-blind manner, preferably without the industry being involved at any step of the process, other than providing the relevant kits. As per CD diagnosis, we would have to agree with the European Crohn and Colitis Organization[78] that based on the currently available data, serological tests should be used as diagnostic adjuvants in parallel to colonoscopy.

In recap, CD differential diagnosis is important[79,80]. Despite the high accuracy
Table 4  Summary of finding table based on a hypothetical scenario of applying glycoprotein 2 antibodies tests on a cohort of 10000 patients

| Analysis                                      | Diagnostic cut-off (U/dL) | TP (Range) | FP (Range) | TN (Range) | FN (Range) |
|-----------------------------------------------|---------------------------|------------|------------|------------|------------|
| CD vs All symptomatic patients (IgG)         | Mixed                     | 9 (6-21)   | 698 (498-897) | 9270 (9071-9470) | 23 (21-26) |
|                                               | 20                         | 7 (5-10)   | 698 (498-897) | 9270 (9071-9470) | 25 (22-27) |
|                                               | 15                         | 9 (5-14)   | 797 (399-1,595) | 9171 (8373-9569) | 23 (18-27) |
| CD vs UC (IgG)                                | Mixed                     | 10 (8-12)  | 698 (498-897) | 9270 (9071-9470) | 22 (20-24) |
|                                               | 20                         | 8 (5-11)   | 698 (498-897) | 9270 (9071-9470) | 24 (21-27) |
|                                               | 15                         | 9 (5-14)   | 997 (598-1595) | 8971 (8373-9370) | 23 (18-27) |
| CD vs All symptomatic patients (IgA)          | Mixed                     | 5 (4-6)    | 299 (100-1396) | 9669 (8572-9868) | 27 (26-28) |
|                                               | 20                         | 5 (3-8)    | 399 (100-1396) | 9569 (8572-9868) | 27 (24-29) |
| CD vs UC (IgA)                                | Mixed                     | 4 (1-6)    | 199 (100-399) | 9769 (9569-9868) | 28 (26-31) |
|                                               | 20                         | 5 (3-7)    | 199 (100-399) | 9769 (9569-9868) | 27 (25-27) |
| CD vs All symptomatic patients (IgA and/or IgG) | Mixed                     | 6 (3-9)    | 299 (1599-1994) | 9670 (7974-9769) | 26 (20-23) |
|                                               | 20                         | 7 (4-12)   | 698 (199-1994) | 9270 (7974-9769) | 25 (20-28) |
| CD vs UC (IgA and/or IgG)                     | Mixed                     | 6 (1-11)   | 299 (199-1994) | 9669 (7974-9769) | 26 (21-31) |

Mixed diagnostic cut-off includes all cut-offs used as well as studies with unreported cut-offs. A prevalence of 322 per 100000 results in 32 patients with Crohn’s disease in this cohort. FN: False negatives; FP: False positives; TN: True negatives; TP: True positives; UC: Ulcerative colitis; Ig: Immunoglobulin.

reported in individual primary DTA studies, and the gaining residence of the anti-GP2 use in CD diagnosis, the present systematic review and meta-analysis revealed that when the anti-GP2 are used as a proxy for the diagnosis of CD the results should be interpreted with caution, due to its relatively low sensitivity and high specificity.

**ARTICLE HIGHLIGHTS**

**Research background**
Non-invasive criteria are needed for Crohn’s disease (CD) diagnosis, with several biomarkers being tested, including the pancreatic autoantibodies-to-glycoprotein-2 (anti-GP2).

**Research motivation**
Results of individual diagnostic test accuracy (DTA) studies assessing the diagnostic value of the anti-GP2 for the diagnosis of CD appear promising, however, a systematic review and meta-analysis of the studies is still lacking.

**Research objectives**
The aim of the present systematic review and meta-analysis was synthesize all evidence on the diagnostic accuracy of anti-GP2 tests in patients with suspected/confirmed CD.

**Research methods**
An electronic search was conducted on Medline, Cochrane-CENTRAL and grey literature. Quality was assessed with the Quality Assessment of Diagnostic Accuracy Studies-2 tool and hierarchical models were employed to synthesize the data. The hierarchical summary receiver operating characteristic (HSROC) model was employed to synthesize data. SROC curves were constructed and since a summary point of sensitivity or specificity with studies using mixed thresholds would be clinically uninterpretable, the summary sensitivity was estimated at its median specificity, based on the SROC curves. Heterogeneity was assessed statistically by including covariates in the HSROC model (meta-regression) and was summarized with the Relative Diagnostic Odds Ratios.

**Research results**
Out of 722 studies retrieved, 15 were meta-analyzed. Thirteen studies had industry-related conflicts-of-interest, and most included healthy donors as controls. For the combination of IgA and/or IgG anti-GP2 test, the summary sensitivity was 20% at a median specificity of 97%.
Research conclusions

The anti-GP2 demonstrated low sensitivity and high specificity. These results indicate caution before relying on its diagnostic value. However, the anti-GP2 appear to attain all characteristics of a screening tool rather than a diagnostic one. Therefore, based on the available evidence, the use of the anti-GP2 for CD diagnosis is not warranted. Furthermore, overall quality of DTA studies appears low, with many carrying industry-related, spectrum, test-review and partial verification bias. Thus, the need for improving the methodology of DTA studies is evident.

Research perspectives

The majority of DTA studies are lacking a quality design and should be synthesized with caution. Future research should assess differences between industry-funded and non-industry funded DTA studies.

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