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# BMJ Open

## A panel of serum biomarkers (GastroPanel) in diagnosis of atrophic gastritis and helicobacter pylori infection: a protocol of systematic review and meta-analysis

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Complete List of Authors:	Wu, Dan; People' s Hospital of Xinjin District, Chengdu Shi, Anya; Lanzhou University Wang, Haiping; Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine; Lanzhou University First Affiliated Hospital Yu, Xiuzhong; People's Hospital of Xinjin District, Chengdu
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Manuscripts

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4 1 **A panel of serum biomarkers (GastroPanel) in diagnosis of**  
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6 2 **atrophic gastritis and helicobacter pylori infection: a protocol of**  
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8 3 **systematic review and meta-analysis**

11 4 Dan Wu <sup>1</sup>, Anya Shi <sup>2</sup>, Haiping Wang <sup>3,4</sup>, Xiuzhong Yu <sup>5,\*</sup>  
12  
13 5

15 6 <sup>1</sup>People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

17 7 <sup>2</sup>The Second Clinical Medical Hospital, Lan Zhou University, Lanzhou, Gansu, 730000,  
18 8 China

21 9 <sup>3</sup>Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine, Lanzhou,  
22 10 Gansu, 730000, China

25 11 <sup>4</sup>The First Hospital of Lanzhou University, Lanzhou, Gansu, 730000, China

27 12 <sup>5</sup>People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China  
28  
29 13

31 14 \*Correspondence:

33 15 Xiuzhong Yu

35 16 E-mail: [yxzh768019@163.com](mailto:yxzh768019@163.com)

37 17 People' s Hospital of Xinjin District, NO. 149, Wujin West Road, Chengdu, Sichuan  
38 18 610500, China

41 19 Tel: +86 13608076810  
42  
43 20  
44 21

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- 1  
2  
3  
4 28 E-mail address of all authors  
5  
6 29 Dan Wu: dan101412@163.com  
7  
8  
9 30 Anya Shi: shiay18@lzu.edu.cn  
10  
11 31 Haiping Wang: wanghp2016@hotmail.com  
12  
13  
14 32 Xiuzhong Yu: yxzh768019@163.com  
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4 **34 Strengths and limitations of this study**  
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6 ● This study will be the first systematic review and meta-analysis to synthetically  
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9 36 investigate the diagnostic accuracy of GastroPanel ® test for helicobacter pylori  
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12 37 infection.  
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14 ● This research will be conducted in strict accordance with the relevant  
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17 39 methodological guidelines of systematic review and meta-analysis to minimize  
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19  
20 40 bias.  
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22 ● The majority of included studies may be cross-sectional study, which may  
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24  
25 42 compromise the results of our study.  
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27 ● The publication bias is still of concern because this study will be limited to the  
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30 44 English- and Chinese-language publications.  
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## 46 ABSTRACT

47 **Introduction** The etiology of gastric cancer is still unclear but helicobacter pylori (HP)  
48 infection and chronic atrophic gastritis recognized as two major risk factors for gastric  
49 cancer. GastroPanel ® test (GP) is the first non-invasive diagnostic tool to detect  
50 atrophic gastritis and helicobacter pylori infection.

51 The aim of the study is to conduct a systematic review and meta-analysis to review  
52 published literature about the GP test for diagnosing atrophic gastritis (AG) and HP  
53 infection. With the objective to estimate the diagnostic performance indices of GP for  
54 atrophic gastritis and helicobacter pylori infection.

55 **Methods and analysis** This protocol of systematic review and meta-analysis is  
56 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-  
57 Analyses (PRISMA) Protocols statement guidelines. PubMed, Embase, Web of Science,  
58 Cochrane Library databases will be systematically searched to identify eligible studies.  
59 No language limitations were imposed. The studies will be downloaded into the  
60 Endnote X9 software and duplicates will be removed. Two review authors  
61 independently screened the full text against the inclusion criteria, extracted the data  
62 from each included study by using a piloted data extraction form, and conduct risk of  
63 bias assessment, resolving disagreement by discussion. Results will be synthesized  
64 narratively in summary tables, using a random effect bivariate model and we fit a  
65 summary hierarchical receiving operating characteristic (HSROC) curve.

66 **Ethics and dissemination** This systematic review will include data extracted form  
67 published studies, therefore, does not require ethics approval. The results of this study  
68 will be submitted to a peer-reviewed journal.

69 **PROSPERO registration number** CRD42021282616.

70

## 71 INTRODUCTION

72 Gastric cancer (GC) is the sixth most common cancer and the fourth most common  
73 cause of cancer-related deaths worldwide in 2020.<sup>1</sup> Although the incidence of the GC  
74 has decreased constantly over the past five years due to a decreasing prevalence of  
75 helicobacter pylori (HP) infection, GC still remains particularly high incidence  
76 worldwide.<sup>2</sup> In any case, early gastric cancer is still considered an initial phase of tumor  
77 progression with good prognosis, so early detection of these lesions is important for the  
78 screening of gastric cancer.<sup>3</sup> International guidelines recommend endoscopic  
79 surveillance with chromoendoscopy and guided biopsies to detect early gastric cancer  
80 and reduce mortality of subjects with atrophic gastritis, even after HP eradication.<sup>4</sup>  
81 However, the methods was invasive diagnostic tests, and was not cost-effective in  
82 regions with low incidence of gastric cancer and stepwise- or individualized screening  
83 according to the risk factors of gastric cancer.<sup>5</sup> Therefore, novel diagnostic tests were  
84 urgently needed to detect early GC.<sup>6</sup>

85 The etiology of GC is still unclear but is known to involve the complex interplay of  
86 host and environment, with HP infection and its associated chronic atrophic gastritis  
87 (CAG) were recognized as two major risk factors for gastric cancer.<sup>7-9</sup> The Taipei  
88 global consensus supports the proposal that at an individual level, eradication of HP  
89 reduces the risk of GC in asymptomatic subjects.<sup>10</sup> Thus, the non-invasive diagnostic  
90 test for detection of AG and HP was promising tools for systematic screening of GC  
91 risk groups.<sup>11 12</sup> However, it is still a matter that identifying subjects with an underlying  
92 atrophic gastritis or HP infection.

93 Gastroscopy and histology are the gold standards for diagnosis of atrophic gastritis,  
94 but as a screening test, endoscope is expensive for the majority, especially in low-come  
95 countries.<sup>13</sup> Meantime, there were also studies showed that traditional endoscopy  
96 cannot reliably diagnose HP gastritis, atrophy or intestinal metaplasia.<sup>14-16</sup> Endoscope  
97 is an invasive test, it may make subjects to be uncomfortable and does not have good  
98 patient's compliance.<sup>17</sup> For the screening of HP infection, the current non-invasive  
99 method is urea breath tests, serology and stool antigen tests, urea breath tests had high

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4 100 diagnostic accuracy while serology and stool antigen tests were less accurate.<sup>18 19</sup>  
5  
6 101 However the urea breath tests also have some limitations, for instance the <sup>14</sup>C-UBTs  
7  
8 102 are radioactive, and people should know the potential risks, so <sup>14</sup>C-UBTs cannot be  
9  
10 103 performed in children or pregnant women, and repeated tests should be avoided.<sup>20</sup> The  
11  
12 104 major drawback to use of <sup>13</sup>C-UBTs is the cost of the equipment to measure <sup>13</sup>CO<sub>2</sub> in  
13  
14 105 expired breath.<sup>21</sup> Therefore, novel diagnostic measures are urgently needed to allow  
15  
16 106 detection of early AG and HP infection. The novel non-invasive tool alleviates the  
17  
18 107 patients' pain during testing and at the same time improve patient's compliance. In  
19  
20 108 addition, an accurate non-invasive test would be very helpful to improve our knowledge  
21  
22 109 on the epidemiology of atrophic gastritis or HP infection in the general population. The  
23  
24 110 global consensus report has agreed that serological tests (pepsinogen I and II and HP  
25  
26 111 antibody) are useful for identifying individuals at increased risk for gastric cancer and  
27  
28 112 for the diagnosis of chronic gastritis and gastric atrophy.<sup>22</sup> International guidelines and  
29  
30 113 the Maastricht V/Florence Consensus Report also recommend that serological tests may  
31  
32 114 be useful to the patients with HP infection.<sup>4 13</sup>

33 115 GastroPanel ® test (GP) is the non-invasive diagnostic tool based on physiology  
34  
35 116 of three biomarkers specific to stomach structure and function, complemented by  
36  
37 117 ELISA (IgG) testing for pepsinogen I and II, Gastrin-17, and HP antibody.<sup>23-25</sup> Over  
38  
39 118 the last decade, GP had been proposed as a non-invasive test for the diagnosis of  
40  
41 119 atrophic gastritis and HP infection.<sup>23 26</sup> Moreover, recent original studies showed that  
42  
43 120 this test is a useful non-invasive diagnostic tool in an individual patient, and as a  
44  
45 121 population screening and surveillance tool.<sup>12 27</sup> Two systematic reviews and Meta-  
46  
47 122 analyses were conducted to confirmed the accuracy of GP for diagnosing AG in 2016  
48  
49 123 and 2017.<sup>25 28</sup> But all the previous Meta-analyses were limited by the few studies with  
50  
51 124 a small sample size for assessing the reliability of the test for the diagnosis. The limited  
52  
53 125 number of studies also eroded the power of the subgroup analysis. To our knowledge,  
54  
55 126 no meta-analysis on diagnostic accuracy of GP for HP infection. New evidence was  
56  
57 127 published for the diagnostic performance indices of GP for both AG and HP  
58  
59 128 infection.<sup>29-32</sup>  
60



## 129 **OBJECTIVES**

130 This study aims to present a protocol for systematic review and meta-analysis to  
131 estimate the diagnostic performance indices of GP for atrophic gastritis and HP  
132 infection.

## 133 **METHODS AND ANALYSIS**

### 134 **Study registration**

135 This protocol of systematic review and meta-analysis is reported according to the  
136 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
137 Protocols statement guidelines.<sup>33</sup>

138 This protocol has been registered with the International Prospective Register of  
139 Systematic Reviews (PROSPERO) database. PROSPERO registration number is  
140 CRD42021282616.

### 141 **Criteria for study selection**

#### 142 *Population*

143 Population with doing biomarker panel GP test for diagnosing AG and HP infection.

#### 144 *Index test*

145 The index test is mainly biomarker panel GP test. The test is a serological test consisting  
146 of a panel of stomach-specific biomarkers: Pepsinogens I and II, Gastrin-17, and HP  
147 antibodies. Growing demand for non-invasive tests to screen the gastric cancer (GC)  
148 risk, GP was designed by Biohit Oyj and used for stomach health as the first serological  
149 test.<sup>23-25</sup> Over the last decade, GP has been proposed as a non-invasive test for the  
150 diagnosis of atrophic gastritis and HP infection.<sup>23 26</sup>

#### 151 *Reference standards*

152 There is no gold standard for diagnosis of HP infection. Gastroscopy and histology are  
153 the gold standard for diagnosis of atrophic gastritis.<sup>13</sup> Therefore we considered only  
154 gastroscopy and histology as the reference standard/ gold standard for diagnosis of  
155 atrophic gastritis and HP infection.

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4 156 ***Target conditions or diseases***

5 157 Atrophic gastritis (AG), which has two types: a gastric body predominant type in  
6  
7 158 patients with infection of HP, and an autoimmune type, limited to the gastric body and  
8  
9 159 fundus.<sup>34</sup> It is well known that the intestinal-type gastric adenocarcinoma develops in a  
10  
11 160 stepwise manner with a sequence of events that evolves from atrophic gastritis and  
12  
13 161 intestinal metaplasia to dysplasia and carcinoma.

14  
15 162 HP infection remains one of the most prevalent infections worldwide, especially in low-  
16  
17 163 resource countries. HP infection has been clearly correlated with gastric carcinogenesis.

18  
19  
20 164 ***Type of studies***

21 165 All applicable studies that evaluate the accuracy of GP in diagnosis of atrophic gastritis  
22  
23 166 and HP infection for the appropriate patient population regardless whether data were  
24  
25 167 collected prospectively or retrospectively. However, letters, meeting abstracts, notes,  
26  
27 168 comments, editorials, protocols, guidelines, case reports and case series will be  
28  
29 169 excluded. Case-control studies will also be excluded, because these are prone to bias.

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32 170 ***Search strategy***

33  
34 171 A systematic search of PubMed, Embase, Web of Science, and Cochrane Library will  
35  
36 172 be performed. We will use a combination of the search field 'Title/Abstract' and MeSH  
37  
38 173 (alternatively Thesaurus or Subject Headings) for the best possible information retrieval.  
39  
40 174 A search field converting 'Title', 'Abstract' and 'Keywords' will be use in the absence  
41  
42 175 of a MeSH, Thesaurus or Subject Headings.

43  
44 176 We identified eligible studies by searching PubMed, Embase, Web of Science, and  
45  
46 177 Cochrane Library databases from inception to March 2022. The medical subject  
47  
48 178 headings and keywords searched consisted of 'atrophic gastritis' 'helicobacter pylori'  
49  
50 179 'gastric cancer' 'GastroPanel'. The detailed search strategy for PubMed is shown in  
51  
52 180 Table 1. Deduplication and screening details will be reported in a PRISMA flow  
53  
54 181 diagram. No language or publication date limitations were imposed. To identify  
55  
56 182 additional studies, we examined references lists from related reviews and studies that  
57  
58 183 were included in our analysis. A complete search update of all databases will be  
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4 184 performed before the references lists that conduct the final analysis and hand screening  
5  
6 185 in the included studies.

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8 186 **Selection of studies**

9  
10 187 The duplicated studies will be removed. And then two independent review authors will  
11  
12 188 screen the title and abstract to identify relevant studies. The full-text for identified  
13  
14 189 relevant studies will be obtained, two review authors will independently screen the full-  
15  
16 190 text against the eligible criteria. Any disagreement in study selection will be solved by  
17  
18 191 discussion. We will attempt to contact study authors if there were doubts about the  
19  
20 192 eligibility of a study. Primary reasons for exclusion will be documented in a PRISMA  
21  
22 193 flowchart.

23  
24 194 **Data extraction and management**

25  
26 195 Two review authors will extract the data from each included study independently, using  
27  
28 196 a data extraction form. Any disagreement in study selection will be solved by discussion.

29  
30 197 Extracted data should include:

- 31  
32 198 (1) First author;  
33  
34 199 (2) Year of publication;  
35  
36 200 (3) Study design (prospective or retrospective cohort studies, cross-sectional studies or  
37  
38 201 randomized controlled trials);  
39  
40 202 (4) Population characteristics (age, gender, country, etc.);  
41  
42 203 (5) Geographic origin of the study;  
43  
44 204 (6) Inclusion and exclusion criteria for participants;  
45  
46 205 (7) Whether use of proton pump inhibitors (PPIs) over the last week;  
47  
48 206 (8) Number of AG and HP infection;  
49  
50 207 (9) The threshold values used for each test of the panel;  
51  
52 208 (10) Description of the reference/golden standard;  
53  
54 209 (11) Description of the index test;  
55  
56 210 (12) The indications for endoscopy;  
57  
58 211 (13) The number and site of gastric biopsy specimens used for defining the target  
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4 212 condition;

5 213 (14) Grade of severity of atrophic gastritis (atrophy at any grade of severity or  
6  
7 214 moderate-severe atrophy);

8  
9 215 (15) Constructed  $2 \times 2$  tables that contained the precise numbers of true positive (TP),  
10  
11 216 false negative (FN), false positive (FP) and true negative (TN).

12  
13 217 If we suspected an overlap of participants between multiple reports, we will  
14  
15 218 identify multiple reports of the same study using the information provided in the reports.

16  
17 219 We sought further information from study authors, if necessary.

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20 220 **Risk of bias assessment**

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22 221 Two reviewers will independently assess the quality of included studies using the  
23  
24 222 Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) instrument. This  
25  
26 223 instrument consists of four key domains that include patient selection, index test,  
27  
28 224 reference standard, and flow of patients through the study and timing of the index and  
29  
30 225 reference standard test. Each domain will be assessed in terms of risk of bias, and the  
31  
32 226 first three domains will also be assessed in terms of applicability. Using this instrument,  
33  
34 227 the risk of bias may be categorized as “low”, “high”, or “unclear”. Discrepancies in the  
35  
36 228 interpretation were resolved by consensus between the two reviewers, if necessary,  
37  
38 229 arbitration by a third reviewer.

39  
40 230 **Data synthesis and analysis**

41  
42 231 Using  $2 \times 2$  tables, we will calculate summary estimates of sensitivity and specificity,  
43  
44 232 positive and negative likelihood ratio and diagnostic odds ratio (DOR) with 95%  
45  
46 233 confidence intervals (95% CI) using a random effect bivariate model.

47  
48 234 We will explore the heterogeneity between studies through visual examination of the  
49  
50 235 hierarchical receiving operating characteristic (HSROC) curve. Heterogeneity across  
51  
52 236 the studies will be determined by correlation coefficient between logit transformed  
53  
54 237 sensitivity and specificity by bivariate model and asymmetry parameter,  $\beta$  (beta), where  
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56 238  $\beta=0$  corresponds to a symmetric ROC curve in which the DOR does not vary along the  
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58 239 curve by HSROC model. To determine the final meta-analytic model, we used

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4 240 likelihood ratio tests to assess model fit. Likelihood ratio tests were also used to  
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6 241 determine the statistical significance of differences in test accuracy. When  
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8 242 heterogeneity was present, the degree was quantified using the  $I^2$  statistic. Values of  
9  
10 243 less than 25% are considered as homogenous and 25% to <50% are considered as  
11  
12 244 having low heterogeneity. For values of 50% or more, significant heterogeneity is  
13  
14 245 assumed. And heterogeneity will also be assumed at significance level of  $P < 0.05$  and  
15  
16 246 tested by chi-square.

### 17 18 247 **Subgroup analysis**

19  
20 248 If we extract sufficient data, we will perform subgroup analyses for any covariates that  
21  
22 249 showed a statistically significant association with the summary estimates. We will  
23  
24 250 explore the following sources of heterogeneity for the diagnosis of atrophic gastritis  
25  
26 251 and helicobacter pylori infection and adding them as covariates, if appropriate, to a  
27  
28 252 bivariate regression model: country, geographic origin, sample size, time of publication  
29  
30 253 (early, recent), setting, study design.

31  
32 254 Besides, for diagnosis of atrophic gastritis, we will perform subgroup analyses and  
33  
34 255 meta-regressions by GC incidence (high-, intermediate-, low-), grade and extent of AG,  
35  
36 256 activity of mucosal inflammation. For diagnosis of HP infection, subgroup analyses and  
37  
38 257 meta regressions will be performed by application of PPIs, nonsteroidal anti-  
39  
40 258 inflammatory drugs and antibiotic to identify the reasons for heterogeneity.

### 41 42 259 **Sensitivity analysis and publication bias**

43  
44 260 Sensitivity analysis will be performed to assess the stability of the meta-analytical  
45  
46 261 results, using the one-by-one study removal and evaluated by descriptively comparing  
47  
48 262 the magnitude and precision of the random effects summary effect sizes. Publication  
49  
50 263 bias will be analyzed using precision funnel plots and the test statistics.

### 51 52 264 **Patients and public involvement**

53  
54 265 This protocol will use previously published data. No patients or members of public will  
55  
56 266 be included in this study.

### 57 58 267 **DISCUSSION**

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4 268 HP infection and atrophic gastritis have been recognized as two major risk factors for  
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6 269 gastric cancer.<sup>7-9</sup> To identify subjects with an underlying AG and HP infection plays a  
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8 270 vital role in preventing and improving the prognosis for GC. The accurate non-invasive  
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10 271 tool would be very helpful to identify these subjects, especially in the general  
11  
12 272 population. GP test is the non-invasive diagnostic tool based on physiology of three  
13  
14 273 biomarkers specific to stomach structure and function, complemented by ELISA (IgG)  
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16 274 testing for Hp antibodies.<sup>23-25</sup> However, the accuracy of GP is still controversial. And  
17  
18 275 it is necessary to provide a comprehensive review of the relevant studies publish to date.  
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20 276 Therefore, we will conduct this systematic review and meta-analysis to provide more  
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22 277 supportive evidence in diagnosing atrophic gastritis and HP infection by GastroPanel  
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24 278 <sup>®</sup>. This study will synthesize the current literature on the diagnostic performance indices  
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26 279 of GastroPanel <sup>®</sup> for atrophic gastritis and helicobacter pylori infection. However, there  
27  
28 280 will be many limitations for this study. Firstly, the majority of included studies will be  
29  
30 281 cross-sectional study, which might cause bias. Secondly, there may be heterogeneity  
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32 282 due to this test combines four biomarkers which have different evaluation criteria.  
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34 283 Thirdly, publication bias is still of concern because this study will be limited to the  
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36 284 English- and Chinese-language publications.

## 37 285 **ETHICS AND DISSEMINATION**

38  
39 286 Due to this study as a systematic review, ethics approval is not necessary as we are not  
40  
41 287 directly targeting individuals or extracting data without privacy. The results of this  
42  
43 288 study will be submitted to a peer-reviewed journal.

### 44 289 **Contributors**

45  
46 290 XY and DW concepted and designed the study. HW critically revised the design. AS  
47  
48 291 and DW drafted the manuscript. DW, AS, HW, and XY critically revised and edited  
49  
50 292 the manuscript.

51  
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53  
54 294 commercial or not-for-profit sectors.

55  
56 295 **Competing interests** None declared.

57  
58 296 **Patient consent for publication** Not required.

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Table 1 Search strategy used in PubMed

Number	Search terms
1	"helicobacter pylori"[MeSH Terms]
2	"helicobacter nemestrinae"[Title/Abstract]
3	"helicobacter infections"[Title/Abstract]
4	"Helicobacter"[Title/Abstract]
5	"pylori"[Title/Abstract]
6	"H.Pylori"[Title/Abstract]
7	"Campylobacter"[Title/Abstract]
8	"campylobacter pylori"[Title/Abstract]
9	1 or 2-9
10	"gastritis, atrophic"[MeSH Terms]
11	"atrophic gastritides"[Title/Abstract]
12	"atrophic gastritis"[Title/Abstract]
13	10 or 11-12
14	"GastroPanel"[Title/Abstract]
15	"serum biomarkers"[Title/Abstract]
16	"panels"[Title/Abstract]
17	"pepsinogens"[MeSH Terms]
18	"pepsinogen i"[Title/Abstract]
19	"pepsinogen ii"[Title/Abstract]
20	"pepsinogen i ii"[Title/Abstract]
21	"Gastrin-17"[Title/Abstract]
22	"helicobacter pylori antibodies"[Title/Abstract]
23	14 or 15-22
24	9 and 13 and 23

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6, 7
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7, 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8, 16
Study records:			

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Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9, 10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9, 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	10, 11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

NA, not applicable.

# BMJ Open

## A panel of serum biomarkers (GastroPanel) in diagnosis of atrophic gastritis and helicobacter pylori infection: a protocol of systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062849.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Aug-2022
Complete List of Authors:	Wu, Dan; People's Hospital of Xinjin District Chengdu Shi, Anya; Lanzhou University Wang, Haiping; Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine; Lanzhou University First Affiliated Hospital Yu, Xiuzhong; People's Hospital of Xinjin District Chengdu
<b>Primary Subject Heading</b>:	Diagnostics
Secondary Subject Heading:	Gastroenterology and hepatology, Diagnostics, Infectious diseases
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY

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Manuscripts

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4 1 **A panel of serum biomarkers (GastroPanel) in diagnosis of**  
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7 2 **atrophic gastritis and helicobacter pylori infection: a protocol of**  
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9 3 **systematic review and meta-analysis**

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11 4 Dan Wu <sup>1</sup>, Anya Shi <sup>2</sup>, Haiping Wang <sup>3,4</sup>, Xiuzhong Yu <sup>5,\*</sup>  
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15 6 <sup>1</sup>People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China

16  
17 7 <sup>2</sup>The Second Clinical Medical Hospital, Lan Zhou University, Lanzhou, Gansu, 730000,  
18  
19 8 China

20  
21 9 <sup>3</sup>Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative  
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23 10 Medicine, Lanzhou, Gansu, 730000, China

24  
25 11 <sup>4</sup>The First Hospital of Lanzhou University, Lanzhou, Gansu, 730000, China

26  
27 12 <sup>5</sup>People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China  
28  
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31 14 \*Correspondence:

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33 15 Xiuzhong Yu

34  
35 16 E-mail: yxzh768019@163.com

36  
37 17 People' s Hospital of Xinjin District, NO. 149, Wujin West Road, Chengdu, Sichuan  
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47 22 **Running title:** GastroPanel diagnose atrophic gastritis and helicobacter pylori infection

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1  
2  
3  
4 28 E-mail address of all authors  
5

6 29 Dan Wu: dan101412@163.com  
7

8  
9 30 Anya Shi: shiay18@lzu.edu.cn  
10

11 31 Haiping Wang: wanghp2016@hotmail.com  
12

13  
14 32 Xiuzhong Yu: yxzh768019@163.com  
15

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For peer review only



## 34 **ABSTRACT**

35 **Introduction** The etiology of gastric cancer is still unclear but helicobacter pylori (HP)  
36 infection and chronic atrophic gastritis recognized as two major risk factors for gastric  
37 cancer. GastroPanel® test (GP) is the first non-invasive diagnostic tool to detect atrophic  
38 gastritis and helicobacter pylori infection.

39 The aim of the study is to conduct a systematic review and meta-analysis to review  
40 published literature about the GP test for diagnosing atrophic gastritis (AG) and HP  
41 infection. With the objective to estimate the diagnostic performance indices of GP for  
42 atrophic gastritis and helicobacter pylori infection.

43 **Methods and analysis** This protocol of systematic review and meta-analysis is  
44 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-  
45 Analyses (PRISMA) Protocols statement guidelines. PubMed, Embase, Web of Science,  
46 Cochrane Library databases will be systematically searched to identify eligible studies.  
47 No language limitations were imposed. The studies will be downloaded into the  
48 Endnote X9 software and duplicates will be removed. Two review authors  
49 independently screened the full text against the inclusion criteria, extracted the data  
50 from each included study by using a piloted data extraction form, and conduct risk of  
51 bias assessment, resolving disagreement by discussion. Results will be synthesized  
52 narratively in summary tables, using a random effect bivariate model and we fit a  
53 summary hierarchical receiving operating characteristic (HSROC) curve.

54 **Ethics and dissemination** This systematic review will include data extracted form  
55 published studies, therefore, does not require ethics approval. The results of this study  
56 will be submitted to a peer-reviewed journal.

57 **PROSPERO registration number** CRD42021282616.

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4 **59 Strengths and limitations of this study**

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7 60 ● This study will be the first systematic review and meta-analysis to synthetically  
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9 61 investigate the diagnostic accuracy of GastroPanel® test for helicobacter pylori  
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12 62 infection.

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14 63 ● This research will be conducted in strict accordance with the relevant  
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17 64 methodological guidelines of systematic review and meta-analysis to minimize  
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20 65 bias.

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22 66 ● The majority of included studies may be cross-sectional study, which may  
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25 67 compromise the results of our study.

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27 68 ● The publication bias is still of concern because this study will be limited to the  
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30 69 English- and Chinese-language publications.  
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## 71 INTRODUCTION

72 Gastric cancer (GC) is the sixth most common cancer and the fourth most common  
73 cause of cancer-related deaths worldwide in 2020.<sup>1</sup> Although the incidence of GC has  
74 decreased steadily over the past five years due to a decreasing prevalence of  
75 helicobacter pylori (HP) infection, GC still remains particularly high incidence  
76 worldwide.<sup>2</sup> In any case, early gastric cancer is still considered an initial phase of tumor  
77 progression with good prognosis, so early detection of these lesions is important for the  
78 screening of gastric cancer.<sup>3</sup> International guidelines recommend endoscopic  
79 surveillance with chromoendoscopy and guided biopsies to detect early gastric cancer  
80 and reduce mortality of subjects with atrophic gastritis, even after HP eradication.<sup>4</sup>  
81 However, the method is an invasive test and is not cost-effective in regions with low  
82 incidence of gastric cancer and stepwise- or individualized screening according to the  
83 risk factors of gastric cancer.<sup>5</sup> Therefore, novel diagnostic tests were urgently needed  
84 to detect early GC.<sup>6</sup>

85 The etiology of GC is still unclear but is known to involve the complex interplay of  
86 host and environment, with HP infection and its associated chronic atrophic gastritis  
87 (CAG) were recognized as two major risk factors for gastric cancer.<sup>7-9</sup> The Taipei  
88 global consensus supports the proposal that at an individual level, eradication of HP  
89 reduces the risk of GC in asymptomatic subjects.<sup>10</sup> Thus, the non-invasive diagnostic  
90 test for detection of AG and HP is a promising tool for systematic screening of GC risk  
91 groups.<sup>11 12</sup> However, the optimal diagnostic test for detection of AG and HP infection  
92 is still under discussion.

93 Gastroscopy and histology are the gold standards for diagnosis of atrophic gastritis, but  
94 as a screening test, endoscope is expensive for the majority, especially in low-income  
95 countries.<sup>13</sup> Several studies have showed that traditional endoscopy cannot reliably  
96 diagnose HP gastritis, atrophy or intestinal metaplasia.<sup>14-16</sup> Endoscopy is an invasive  
97 test, which causes much discomfort, thus reducing patient compliance.<sup>17</sup> For the  
98 screening of HP infection, the current non-invasive methods are urea breath tests,  
99 serology and stool antigen tests. Urea breath tests have to make it have high diagnostic

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4 100 accuracy while serology and stool antigen tests were less accurate.<sup>18 19</sup> However the  
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6 101 urea breath tests also have some limitations, for instance the <sup>14</sup>C-UBTs are radioactive,  
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8 102 and people should know the potential risks, so <sup>14</sup>C-UBTs cannot be performed in  
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10 103 children or pregnant women, and repeated tests should be avoided.<sup>20</sup> The major  
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12 104 drawback to use of <sup>13</sup>C-UBTs is the cost of the equipment to measure <sup>13</sup>CO<sub>2</sub> in expired  
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14 105 breath.<sup>21</sup> Therefore, novel diagnostic methods are urgently needed to allow detection of  
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16 106 early AG and HP infection. The novel non-invasive tool significantly improves  
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18 107 patient's compliance. In addition, an accurate non-invasive test would be very helpful  
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20 108 to improve our knowledge of the epidemiology of atrophic gastritis or HP infection in  
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22 109 the general population. The global consensus report has agreed that serological tests  
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24 110 (pepsinogen I and II and HP antibody) are useful for identifying individuals at increased  
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26 111 risk for gastric cancer and for the diagnosis of chronic gastritis and gastric atrophy.<sup>22</sup>  
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28 112 International guidelines and the Maastricht V/Florence Consensus Report also  
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30 113 recommend that serological tests may be useful to the patients with HP infection.<sup>4 13</sup>

31 114 GastroPanel<sup>®</sup> test (GP) is the non-invasive diagnostic tool based on physiology of  
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33 115 three biomarkers specific to stomach structure and function, complemented by ELISA  
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35 116 (IgG) testing for pepsinogen I and II, Gastrin-17, and HP antibody.<sup>23-25</sup> Over the last  
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37 117 decade, GP had been proposed as a non-invasive test for the diagnosis of atrophic  
38  
39 118 gastritis and HP infection.<sup>23 26</sup> Moreover, recent original studies showed that this test is  
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41 119 a useful non-invasive diagnostic tool in an individual patient, and as a population  
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43 120 screening and surveillance tool.<sup>12 27</sup> Two systematic reviews and Meta-analyses  
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45 121 confirmed the accuracy of GP for diagnosing AG in 2016 and 2017.<sup>25 28</sup> Previous Meta-  
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47 122 analyses were limited by the few studies with a small sample size for assessing the  
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49 123 reliability of the test for the diagnosis. The limited number of studies also eroded the  
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51 124 power of the subgroup analysis. To our knowledge, there are no meta-analysis on  
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53 125 diagnostic accuracy of GP for HP infection. New evidence has been published for the  
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55 126 diagnostic performance indices of GP for both AG and HP infection.<sup>29-32</sup>

## 56 127 **OBJECTIVES**

58 128 This study aims to present a protocol for systematic review and meta-analysis to  
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4 129 estimate the diagnostic performance indices of GP for atrophic gastritis and HP  
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6 130 infection.

## 7 131 **METHODS AND ANALYSIS**

### 8 9 10 132 **Study registration**

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12 133 This protocol of systematic review and meta-analysis is reported according to the  
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14 134 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
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16 135 Protocols statement guidelines.<sup>33</sup>

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18 136 This protocol has been registered with the International Prospective Register of  
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20 137 Systematic Reviews (PROSPERO) database. PROSPERO registration number is  
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22 138 CRD42021282616.

### 23 24 139 **Criteria for study selection**

#### 25 26 27 140 ***Population***

28  
29 141 Population who had biomarker panel GP test for diagnosing AG and HP infection.

#### 30 31 142 ***Index test***

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33 143 The index test is mainly biomarker panel GP test. The test is a serological test consisting  
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35 144 of a panel of gastric-specific biomarkers: Pepsinogens I and II, Gastrin-17, and HP  
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37 145 antibodies. Growing demand for non-invasive tests to screen the gastric cancer (GC)  
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39 146 risk. GP was designed by Biohit Oyj and used for stomach health as the first serological  
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41 147 test.<sup>23-25</sup> Over the last decade, GP has been proposed as a non-invasive test for the  
42  
43 148 diagnosis of atrophic gastritis and HP infection.<sup>23 26</sup>

#### 44 45 46 149 ***Reference standards***

47  
48 150 Compared with other Hp detection methods, histology is the gold standard.  
49  
50 151 Gastroscopy and histology are the gold standard for diagnosis of atrophic gastritis.<sup>13</sup>  
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52 152 Therefore we considered only gastroscopy and histology as the reference standard/ gold  
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54 153 standard for diagnosis of atrophic gastritis and HP infection.

#### 55 56 154 ***Target conditions or diseases***

57  
58 155 There are two types of atrophic gastritis (AG): a gastric body predominant type in  
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4 156 patients with infection of HP, and an autoimmune type, limited to the gastric body and  
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6 157 fundus.<sup>34</sup> It is well known that the intestinal-type gastric adenocarcinoma develops in a  
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8 158 stepwise manner with a sequence of events that evolves from atrophic gastritis and  
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10 159 intestinal metaplasia to dysplasia and carcinoma.

11 160 HP infection remains one of the most prevalent infections worldwide, especially in low-  
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13 161 resource countries. HP infection has been clearly correlated with gastric carcinogenesis.

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15 162 <sup>35</sup>

### 163 ***Type of studies***

164 All applicable studies that evaluate the accuracy of GP in diagnosis of atrophic gastritis  
165 and HP infection for the appropriate patient population regardless whether data were  
166 collected prospectively or retrospectively. However, letters, meeting abstracts, notes,  
167 comments, editorials, protocols, guidelines, case reports and case series will be  
168 excluded. Case-control studies will also be excluded, because these are prone to bias.

### 169 **Search strategy**

170 A systematic search of PubMed, Embase, Web of Science, and Cochrane Library will  
171 be performed. We will use a combination of the search field 'Title/Abstract' and MeSH  
172 (alternatively Thesaurus or Subject Headings) for the best possible information retrieval.  
173 A search field converting 'Title', 'Abstract' and 'Keywords' will be use in the absence  
174 of a MeSH, Thesaurus or Subject Headings.

175 We identified eligible studies by searching PubMed, Embase, Web of Science, and  
176 Cochrane Library databases from inception to March 2022. The medical subject  
177 headings and keywords searched consisted of 'atrophic gastritis' 'helicobacter pylori'  
178 'gastric cancer' 'GastroPanel'. The detailed search strategy for PubMed is shown in  
179 Table 1. Deduplication and screening details will be reported in a PRISMA flow  
180 diagram. No language or publication date limitations were imposed. To identify  
181 additional studies, we examined references lists from related reviews and studies that  
182 were included in our analysis. A complete search update of all databases will be  
183 performed before the references lists that conduct the final analysis and hand screening

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4 184 in the included studies.  
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6 185 **Selection of studies**  
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8 186 The duplicated studies will be removed. And then two independent review authors will  
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10 187 screen the title and abstract to identify relevant studies. The full-text for identified  
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12 188 relevant studies will be obtained, thereafter, two review authors will independently  
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14 189 screen the full-text against the eligible criteria. Any disagreement in study selection will  
15  
16 190 be resolved by consensus. We will attempt to contact study authors if there were doubts  
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18 191 about the eligibility of a study. Primary reasons for exclusion will be documented in a  
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20 192 PRISMA flowchart.  
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22 193 **Data extraction and management**  
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24 194 Two review authors will extract the data from each included study independently, using  
25  
26 195 a data extraction form. Any disagreement in study selection will be solved by discussion.  
27

28 196 Extracted data should include:  
29

- 30 197 (1) First author;  
31  
32 198 (2) Year of publication;  
33  
34 199 (3) Study design (prospective or retrospective cohort studies, cross-sectional studies or  
35  
36 200 randomized controlled trials);  
37  
38 201 (4) Population characteristics (age, gender, country, etc.);  
39  
40 202 (5) Geographic origin of the study;  
41  
42 203 (6) Inclusion and exclusion criteria for participants;  
43  
44 204 (7) Whether use of proton pump inhibitors (PPIs) over the last two weeks;  
45  
46 205 (8) Number of AG and HP infection;  
47  
48 206 (9) The threshold values used for each test of the panel;  
49  
50 207 (10) Description of the reference/golden standard;  
51  
52 208 (11) Description of the index test;  
53  
54 209 (12) The indications for endoscopy;  
55  
56 210 (13) The number and site of gastric biopsy specimens used for defining the target  
57  
58 211 condition;  
59  
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- 1  
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3  
4 212 (14) Grade of severity of atrophic gastritis (atrophy at any grade of severity or  
5  
6 213 moderate-severe atrophy);  
7  
8 214 (15) Constructed  $2 \times 2$  tables that contained the precise numbers of true positive (TP),  
9  
10 215 false negative (FN), false positive (FP) and true negative (TN);  
11  
12 216 (16) Recent antibiotic ingestion;  
13  
14 217 (17) Alcohol ingestion;  
15  
16 218 (18) Bile salts;  
17  
18 219 (19) Time lag between taking the samples and analysis;  
19  
20 220 (20) Whether the samples were transported to a lab for analysis, and under what  
21  
22 221 conditions.

23 222 If we suspected an overlap of participants between multiple reports, we will  
24  
25 223 identify multiple reports of the same study using the information provided in the reports.  
26  
27 224 We sought further information from study authors, if necessary.

#### 225 **Risk of bias assessment**

226 Two reviewers will independently assess the quality of included studies using the  
227  
228 Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) instrument. This  
229  
230 instrument consists of four key domains that include patient selection, index test,  
231  
232 reference standard, and flow of patients through the study and timing of the index and  
233  
234 reference standard test. Each domain will be assessed in terms of risk of bias, and the  
235  
236 first three domains will also be assessed in terms of applicability. Using this instrument,  
237  
238 the risk of bias may be categorized as “low”, “high”, or “unclear”. Discrepancies in the  
239  
240 interpretation were resolved by consensus between the two reviewers, if necessary,  
241  
242 arbitration by a third reviewer.

#### 235 **Data synthesis and analysis**

236 Using  $2 \times 2$  tables, we will calculate summary estimates of sensitivity and specificity,  
237  
238 positive and negative likelihood ratio and diagnostic odds ratio (DOR) with 95%  
239  
240 confidence intervals (95% CI) using a random effect bivariate model.  
241  
242 We will explore the heterogeneity between studies through visual examination of the



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4 240 hierarchical receiving operating characteristic (HSROC) curve. Heterogeneity across  
5  
6 241 the studies will be determined by correlation coefficient between logit transformed  
7  
8 242 sensitivity and specificity by bivariate model and asymmetry parameter,  $\beta$  (beta), where  
9  
10 243  $\beta=0$  corresponds to a symmetric ROC curve in which the DOR does not vary along the  
11  
12 244 curve by HSROC model. To determine the final meta-analytic model, we will use  
13  
14 245 likelihood ratio tests to assess model fit. Likelihood ratio tests will also be used to  
15  
16 246 determine the statistical significance of differences in test accuracy. When  
17  
18 247 heterogeneity is present, the degree will be quantified using the  $I^2$  statistic. Values of  
19  
20 248 less than 25% are considered as homogenous and 25% to <50% are considered as  
21  
22 249 having low heterogeneity. For values of 50% or more, significant heterogeneity is  
23  
24 250 assumed. And heterogeneity will also be assumed at significance level of  $P < 0.05$  and  
25  
26 251 tested by chi-square.

### 252 **Subgroup analysis**

253 If we extract sufficient data, we will perform subgroup analyses for any covariates that  
254 showed a statistically significant association with the summary estimates. We will  
255 explore the following sources of heterogeneity for the diagnosis of atrophic gastritis  
256 and helicobacter pylori infection and adding them as covariates, if appropriate, to a  
257 bivariate regression model: country, geographic origin, sample size, time of publication  
258 (early, recent), setting, study design.

259 Besides, for diagnosis of atrophic gastritis, we will perform subgroup analyses and  
260 meta-regressions by GC incidence (high-, intermediate-, low-), grade and extent of AG,  
261 activity of mucosal inflammation. For diagnosis of HP infection, subgroup analyses and  
262 meta regressions will be performed by application of PPIs, nonsteroidal anti-  
263 inflammatory drugs and antibiotic to identify the reasons for heterogeneity.

### 264 **Sensitivity analysis and publication bias**

265 Sensitivity analysis will be performed to assess the stability of the meta-analytical  
266 results, using the one-by-one study removal and evaluated by descriptively comparing  
267 the magnitude and precision of the random effects summary effect sizes. Publication

1  
2  
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4 268 bias will be analyzed using precision funnel plots and the test statistics.  
5

#### 6 269 **Patients and public involvement**

7  
8 270 This protocol will use previously published data. No patients or members of public will  
9  
10 271 be included in this study.

## 11 272 **DISCUSSION**

12  
13  
14 273 HP infection and atrophic gastritis have been recognized as two major risk factors for  
15  
16 274 gastric cancer.<sup>7-9</sup> To identify subjects with an underlying AG and HP infection plays a  
17  
18 275 vital role in preventing and improving the prognosis for GC. The accurate non-invasive  
19  
20 276 tool would be very helpful to identify these subjects, especially in the general  
21  
22 277 population. GP test is the non-invasive diagnostic tool based on physiology of three  
23  
24 278 biomarkers specific to stomach structure and function, complemented by ELISA (IgG)  
25  
26 279 testing for Hp antibodies.<sup>23-25</sup> However, the accuracy of GP is still controversial. And  
27  
28 280 it is necessary to provide a comprehensive review of the relevant studies published to  
29  
30 281 date. Therefore, we will conduct this systematic review and meta-analysis to provide  
31  
32 282 more supportive evidence in diagnosing atrophic gastritis and HP infection by  
33  
34 283 GastroPanel<sup>®</sup>. This study will synthesize the current literature on the diagnostic  
35  
36 284 performance indices of GastroPanel<sup>®</sup> for atrophic gastritis and helicobacter pylori  
37  
38 285 infection. However, there will be many limitations for this study. Firstly, the majority  
39  
40 286 of included studies will be cross-sectional study, which might cause bias. Secondly,  
41  
42 287 there may be heterogeneity with because this test combines four biomarkers which have  
43  
44 288 different evaluation criteria. Thirdly, publication bias is still of concern because this  
45  
46 289 study will be limited to the English- and Chinese-language publications.

## 47 290 **ETHICS AND DISSEMINATION**

48  
49  
50 291 Due to this study as a systematic review, ethics approval is not necessary as we are not  
51  
52 292 directly targeting individuals or extracting data without privacy. The results of this  
53  
54 293 study will be submitted to a peer-reviewed journal.

#### 55 294 **Contributors**

56  
57  
58 295 XY and DW concepted and designed the study. HW critically revised the design. AS  
59  
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4 296 and DW drafted the manuscript. DW, AS, HW, and XY critically revised and edited  
5  
6 297 the manuscript.

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8  
9 299 commercial or not-for-profit sectors.

10  
11 300 **Competing interests** None declared.

12  
13 301 **Patient consent for publication** Not required.

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Table 1 Search strategy used in PubMed

Number	Search terms
1	"helicobacter pylori"[MeSH Terms]
2	"helicobacter nemestrinae"[Title/Abstract]
3	"helicobacter infections"[Title/Abstract]
4	"Helicobacter"[Title/Abstract]
5	"pylori"[Title/Abstract]
6	"H.Pylori"[Title/Abstract]
7	"Campylobacter"[Title/Abstract]
8	"campylobacter pylori"[Title/Abstract]
9	1 or 2-9
10	"gastritis, atrophic"[MeSH Terms]
11	"atrophic gastritides"[Title/Abstract]
12	"atrophic gastritis"[Title/Abstract]
13	10 or 11-12
14	"GastroPanel"[Title/Abstract]
15	"serum biomarkers"[Title/Abstract]
16	"panels"[Title/Abstract]
17	"pepsinogens"[MeSH Terms]
18	"pepsinogen i"[Title/Abstract]
19	"pepsinogen ii"[Title/Abstract]
20	"pepsinogen i ii"[Title/Abstract]
21	"Gastrin-17"[Title/Abstract]
22	"helicobacter pylori antibodies"[Title/Abstract]
23	14 or 15-22
24	9 and 13 and 23

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6, 7
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7, 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8, 16
Study records:			

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3	Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
4	Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
5			
6	Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9, 10
7			
8	Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9, 10
9			
10			
11	Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
12			
13	Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
14			
15	Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised	10
16		15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	10, 11
17		15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
18		15d If quantitative synthesis is not appropriate, describe the type of summary planned	NA
19			
20	Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
21			
22	Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA
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24	NA, not applicable.		
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# BMJ Open

## A panel of serum biomarkers (GastroPanel) in diagnosis of atrophic gastritis and helicobacter pylori infection: a protocol of systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-062849.R2
Article Type:	Protocol
Date Submitted by the Author:	08-Sep-2022
Complete List of Authors:	Wu, Dan; People's Hospital of Xinjin District Chengdu Shi, Anya; Lanzhou University Wang, Haiping; Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative Medicine; Lanzhou University First Affiliated Hospital Yu, Xiuzhong; People's Hospital of Xinjin District Chengdu
<b>Primary Subject Heading</b>:	Diagnostics
Secondary Subject Heading:	Gastroenterology and hepatology, Diagnostics, Infectious diseases
Keywords:	Gastrointestinal infections < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Gastrointestinal tumours < GASTROENTEROLOGY

SCHOLARONE™  
Manuscripts

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4 1 **A panel of serum biomarkers (GastroPanel) in diagnosis of**  
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6 2 **atrophic gastritis and helicobacter pylori infection: a protocol of**  
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8 3 **systematic review and meta-analysis**  
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11 4 Dan Wu <sup>1</sup>, Anya Shi <sup>2</sup>, Haiping Wang <sup>3,4</sup>, Xiuzhong Yu <sup>5,\*</sup>  
12  
13 5

14 6 <sup>1</sup>People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China  
15

16 7 <sup>2</sup>The Second Clinical Medical Hospital, Lan Zhou University, Lanzhou, Gansu, 730000,  
17  
18 8 China  
19

20 9 <sup>3</sup>Lanzhou University Gansu Provincial Key Laboratory of Biotherapy and Regenerative  
21  
22 10 Medicine, Lanzhou, Gansu, 730000, China  
23

24 11 <sup>4</sup>The First Hospital of Lanzhou University, Lanzhou, Gansu, 730000, China  
25

26 12 <sup>5</sup>People' s Hospital of Xinjin District, Chengdu, Sichuan 611430, China  
27  
28 13

29  
30  
31 14 \*Correspondence:  
32

33 15 Xiuzhong Yu  
34

35 16 E-mail: yxzh768019@163.com  
36

37 17 People' s Hospital of Xinjin District, NO. 149, Wujin West Road, Chengdu, Sichuan  
38  
39 18 610500, China  
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41 19 Tel: +86 13608076810  
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47 22 **Running title:** GastroPanel diagnose atrophic gastritis and helicobacter pylori infection  
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1  
2  
3  
4 28 E-mail address of all authors  
5

6 29 Dan Wu: dan101412@163.com  
7

8  
9 30 Anya Shi: shiay18@lzu.edu.cn  
10

11 31 Haiping Wang: wanghp2016@hotmail.com  
12

13  
14 32 Xiuzhong Yu: yxzh768019@163.com  
15

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## 34 **ABSTRACT**

35 **Introduction** The etiology of gastric cancer is still unclear but helicobacter pylori (HP)  
36 infection and chronic atrophic gastritis recognized as two major risk factors for gastric  
37 cancer. GastroPanel® test (GP) is the first non-invasive diagnostic tool to detect atrophic  
38 gastritis and helicobacter pylori infection.

39 The aim of the study is to conduct a systematic review and meta-analysis to review  
40 published literature about the GP test for diagnosing atrophic gastritis (AG) and HP  
41 infection. With the objective to estimate the diagnostic performance indices of GP for  
42 atrophic gastritis and helicobacter pylori infection.

43 **Methods and analysis** This protocol of systematic review and meta-analysis is  
44 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-  
45 Analyses (PRISMA) Protocols statement guidelines. PubMed, Embase, Web of Science,  
46 Cochrane Library databases will be systematically searched from inception to March  
47 2022 for eligible studies. No language limitations were imposed. The studies will be  
48 downloaded into the Endnote X9 software and duplicates will be removed. Two review  
49 authors independently screened the full text against the inclusion criteria, extracted the  
50 data from each included study by using a piloted data extraction form, and conduct risk  
51 of bias assessment, resolving disagreement by discussion. Results will be synthesized  
52 narratively in summary tables, using a random effect bivariate model and we fit a  
53 summary hierarchical receiving operating characteristic (HSROC) curve.

54 **Ethics and dissemination** This systematic review will include data extracted from  
55 published studies, therefore, does not require ethics approval. The results of this study  
56 will be submitted to a peer-reviewed journal.

57 **PROSPERO registration number** CRD42021282616.

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4 59 **Strengths and limitations of this study**  
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6 60 ● This study will be the first systematic review and meta-analysis to synthetically  
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9 61 investigate the diagnostic accuracy of GastroPanel® test for helicobacter pylori  
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12 62 infection.  
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14 63 ● This research will be conducted in strict accordance with the relevant  
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17 64 methodological guidelines of systematic review and meta-analysis to minimize  
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20 65 bias.  
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22 66 ● The majority of included studies may be cross-sectional study, which may  
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25 67 compromise the results of our study.  
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27 68 ● The publication bias is still of concern because this study will be limited to the  
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## 71 INTRODUCTION

72 Gastric cancer (GC) is the sixth most common cancer and the fourth most common  
73 cause of cancer-related deaths worldwide in 2020.<sup>1</sup> Although the incidence of GC has  
74 decreased steadily over the past five years due to a decreasing prevalence of  
75 helicobacter pylori (HP) infection, GC still remains particularly high incidence  
76 worldwide.<sup>2</sup> In any case, early gastric cancer is still considered an initial phase of tumor  
77 progression with good prognosis, so early detection of these lesions is important for the  
78 screening of gastric cancer.<sup>3</sup> International guidelines recommend endoscopic  
79 surveillance with chromoendoscopy and guided biopsies to detect early gastric cancer  
80 and reduce mortality of subjects with atrophic gastritis, even after HP eradication.<sup>4</sup>  
81 However, the method is an invasive test and is not cost-effective in regions with low  
82 incidence of gastric cancer and stepwise- or individualized screening according to the  
83 risk factors of gastric cancer.<sup>5</sup> Therefore, novel diagnostic tests were urgently needed  
84 to detect early GC.<sup>6</sup>

85 The etiology of GC is still unclear but is known to involve the complex interplay of  
86 host and environment, with HP infection and its associated chronic atrophic gastritis  
87 (CAG) were recognized as two major risk factors for gastric cancer.<sup>7-9</sup> The Taipei  
88 global consensus supports the proposal that at an individual level, eradication of HP  
89 reduces the risk of GC in asymptomatic subjects.<sup>10</sup> Thus, the non-invasive diagnostic  
90 test for detection of AG and HP is a promising tool for systematic screening of GC risk  
91 groups.<sup>11 12</sup> However, the optimal diagnostic test for detection of AG and HP infection  
92 is still under discussion.

93 Gastroscopy and histology are the gold standards for diagnosis of atrophic gastritis, but  
94 as a screening test, endoscope is expensive for the majority, especially in low-income  
95 countries.<sup>13</sup> Several studies have showed that traditional endoscopy cannot reliably  
96 diagnose HP gastritis, atrophy or intestinal metaplasia.<sup>14-16</sup> Endoscopy is an invasive  
97 test, which causes much discomfort, thus reducing patient compliance.<sup>17</sup> For the  
98 screening of HP infection, the current non-invasive methods are urea breath tests,  
99 serology and stool antigen tests. Urea breath tests has high diagnostic accuracy while

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4 100 serology and stool antigen tests were less accurate.<sup>18 19</sup> However the urea breath tests  
5  
6 101 also have some limitations, for instance the <sup>14</sup>C-UBTs are radioactive, and people  
7  
8 102 should know the potential risks, so <sup>14</sup>C-UBTs cannot be performed in children or  
9  
10 103 pregnant women, and repeated tests should be avoided.<sup>20</sup> The major drawback to use of  
11  
12 104 <sup>13</sup>C-UBTs is the cost of the equipment to measure <sup>13</sup>CO<sub>2</sub> in expired breath.<sup>21</sup> Therefore,  
13  
14 105 novel diagnostic methods are urgently needed to allow detection of early AG and HP  
15  
16 106 infection. The novel non-invasive tool significantly improves patient's compliance. In  
17  
18 107 addition, an accurate non-invasive test would be very helpful to improve our knowledge  
19  
20 108 of the epidemiology of atrophic gastritis or HP infection in the general population. The  
21  
22 109 global consensus report has agreed that serological tests (pepsinogen I and II and HP  
23  
24 110 antibody) are useful for identifying individuals at increased risk for gastric cancer and  
25  
26 111 for the diagnosis of chronic gastritis and gastric atrophy.<sup>22</sup> International guidelines and  
27  
28 112 the Maastricht V/Florence Consensus Report also recommend that serological tests may  
29  
30 113 be useful to the patients with HP infection.<sup>4 13</sup>

31 114 GastroPanel<sup>®</sup> test (GP) is the non-invasive diagnostic tool based on physiology of  
32  
33 115 three biomarkers specific to stomach structure and function, complemented by ELISA  
34  
35 116 (IgG) testing for pepsinogen I and II, Gastrin-17, and HP antibody.<sup>23-25</sup> Over the last  
36  
37 117 decade, GP had been proposed as a non-invasive test for the diagnosis of atrophic  
38  
39 118 gastritis and HP infection.<sup>23 26</sup> Moreover, recent original studies showed that this test is  
40  
41 119 a useful non-invasive diagnostic tool in an individual patient, and as a population  
42  
43 120 screening and surveillance tool.<sup>12 27</sup> Two systematic reviews and Meta-analyses  
44  
45 121 confirmed the accuracy of GP for diagnosing AG in 2016 and 2017.<sup>25 28</sup> Previous Meta-  
46  
47 122 analyses were limited by the few studies with a small sample size for assessing the  
48  
49 123 reliability of the test for the diagnosis. The limited number of studies also eroded the  
50  
51 124 power of the subgroup analysis. To our knowledge, there are no meta-analysis on  
52  
53 125 diagnostic accuracy of GP for HP infection. New evidence has been published for the  
54  
55 126 diagnostic performance indices of GP for both AG and HP infection.<sup>29-32</sup>

## 56 127 **OBJECTIVES**

58 128 This study aims to present a protocol for systematic review and meta-analysis to  
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4 129 estimate the diagnostic performance indices of GP for atrophic gastritis and HP  
5  
6 130 infection.

## 7 131 **METHODS AND ANALYSIS**

### 9 10 132 **Study registration**

11  
12 133 This protocol of systematic review and meta-analysis is reported according to the  
13  
14 134 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
15  
16 135 Protocols statement guidelines.<sup>33</sup>

17  
18 136 This protocol has been registered with the International Prospective Register of  
19  
20 137 Systematic Reviews (PROSPERO) database. PROSPERO registration number is  
21  
22 138 CRD42021282616.

### 23 24 139 **Criteria for study selection**

#### 25 26 27 140 ***Population***

28  
29 141 Population who had biomarker panel GP test for diagnosing AG and HP infection.

#### 30 31 142 ***Index test***

32  
33 143 The index test is mainly biomarker panel GP test. The test is a serological test consisting  
34  
35 144 of a panel of gastric-specific biomarkers: Pepsinogens I and II, Gastrin-17, and HP  
36  
37 145 antibodies. Growing demand for non-invasive tests to screen the gastric cancer (GC)  
38  
39 146 risk. GP was designed by Biohit Oyj and used for stomach health as the first serological  
40  
41 147 test.<sup>23-25</sup> Over the last decade, GP has been proposed as a non-invasive test for the  
42  
43 148 diagnosis of atrophic gastritis and HP infection.<sup>23 26</sup>

#### 44 45 46 149 ***Reference standards***

47  
48 150 Compared with other Hp detection methods, histology is the gold standard.  
49  
50 151 Gastroscopy and histology are the gold standard for diagnosis of atrophic gastritis.<sup>13</sup>  
51  
52 152 Therefore we considered only gastroscopy and histology as the reference standard/ gold  
53  
54 153 standard for diagnosis of atrophic gastritis and HP infection.

#### 55 56 154 ***Target conditions or diseases***

57  
58 155 There are two types of atrophic gastritis (AG): a gastric body predominant type in  
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1  
2  
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4 156 patients with infection of HP, and an autoimmune type, limited to the gastric body and  
5  
6 157 fundus.<sup>34</sup> It is well known that the intestinal-type gastric adenocarcinoma develops in a  
7  
8 158 stepwise manner with a sequence of events that evolves from atrophic gastritis and  
9  
10 159 intestinal metaplasia to dysplasia and carcinoma.

11 160 HP infection remains one of the most prevalent infections worldwide, especially in low-  
12  
13 161 resource countries. HP infection has been clearly correlated with gastric carcinogenesis.

14  
15 162 <sup>35</sup>

### 163 ***Type of studies***

164 All applicable studies that evaluate the accuracy of GP in diagnosis of atrophic gastritis  
165 and HP infection for the appropriate patient population regardless whether data were  
166 collected prospectively or retrospectively. However, letters, meeting abstracts, notes,  
167 comments, editorials, protocols, guidelines, case reports and case series will be  
168 excluded. Case-control studies will also be excluded, because these are prone to bias.

### 169 **Search strategy**

170 A systematic search of PubMed, Embase, Web of Science, and Cochrane Library will  
171 be performed. We will use a combination of the search field 'Title/Abstract' and MeSH  
172 (alternatively Thesaurus or Subject Headings) for the best possible information retrieval.  
173 A search field converting 'Title', 'Abstract' and 'Keywords' will be use in the absence  
174 of a MeSH, Thesaurus or Subject Headings.

175 We identified eligible studies by searching PubMed, Embase, Web of Science, and  
176 Cochrane Library databases from inception to March 2022. The medical subject  
177 headings and keywords searched consisted of 'atrophic gastritis' 'helicobacter pylori'  
178 'gastric cancer' 'GastroPanel'. The detailed search strategy for PubMed is shown in  
179 Table 1. Deduplication and screening details will be reported in a PRISMA flow  
180 diagram. No language or publication date limitations were imposed. To identify  
181 additional studies, we examined references lists from related reviews and studies that  
182 were included in our analysis. A complete search update of all databases will be  
183 performed before the references lists that conduct the final analysis and hand screening

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3  
4 184 in the included studies.  
5

6 185 **Selection of studies**  
7

8 186 The duplicated studies will be removed. And then two independent review authors will  
9  
10 187 screen the title and abstract to identify relevant studies. The full-text for identified  
11  
12 188 relevant studies will be obtained, thereafter, two review authors will independently  
13  
14 189 screen the full-text against the eligible criteria. Any disagreement in study selection will  
15  
16 190 be resolved by consensus. We will attempt to contact study authors if there were doubts  
17  
18 191 about the eligibility of a study. Primary reasons for exclusion will be documented in a  
19  
20 192 PRISMA flowchart.  
21

22 193 **Data extraction and management**  
23

24 194 Two review authors will extract the data from each included study independently, using  
25  
26 195 a data extraction form. Any disagreement in study selection will be solved by discussion.  
27

28 196 Extracted data should include:  
29

- 30 197 (1) First author;  
31  
32 198 (2) Year of publication;  
33  
34 199 (3) Study design (prospective or retrospective cohort studies, cross-sectional studies or  
35  
36 200 randomized controlled trials);  
37  
38 201 (4) Population characteristics (age, gender, country, etc.);  
39  
40 202 (5) Geographic origin of the study;  
41  
42 203 (6) Inclusion and exclusion criteria for participants;  
43  
44 204 (7) Whether use of proton pump inhibitors (PPIs) over the last two weeks;  
45  
46 205 (8) Number of AG and HP infection;  
47  
48 206 (9) The threshold values used for each test of the panel;  
49  
50 207 (10) Description of the reference/golden standard;  
51  
52 208 (11) Description of the index test;  
53  
54 209 (12) The indications for endoscopy;  
55  
56 210 (13) The number and site of gastric biopsy specimens used for defining the target  
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58 211 condition;  
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4 212 (14) Grade of severity of atrophic gastritis (atrophy at any grade of severity or  
5  
6 213 moderate-severe atrophy);  
7  
8 214 (15) Constructed  $2 \times 2$  tables that contained the precise numbers of true positive (TP),  
9  
10 215 false negative (FN), false positive (FP) and true negative (TN);  
11  
12 216 (16) Recent antibiotic ingestion;  
13  
14 217 (17) Alcohol ingestion;  
15  
16 218 (18) Bile salts;  
17  
18 219 (19) Time lag between taking the samples and analysis;  
19  
20 220 (20) Whether the samples were transported to a lab for analysis, and under what  
21  
22 221 conditions.

23 222 If we suspected an overlap of participants between multiple reports, we will  
24  
25 223 identify multiple reports of the same study using the information provided in the reports.  
26  
27 224 We sought further information from study authors, if necessary.

#### 225 **Risk of bias assessment**

226 Two reviewers will independently assess the quality of included studies using the  
227  
228 Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) instrument. This  
229  
230 instrument consists of four key domains that include patient selection, index test,  
231  
232 reference standard, and flow of patients through the study and timing of the index and  
233  
234 reference standard test. Each domain will be assessed in terms of risk of bias, and the  
235  
236 first three domains will also be assessed in terms of applicability. Using this instrument,  
237  
238 the risk of bias may be categorized as “low”, “high”, or “unclear”. Discrepancies in the  
239  
240 interpretation were resolved by consensus between the two reviewers, if necessary,  
241  
242 arbitration by a third reviewer.

#### 235 **Data synthesis and analysis**

236 Using  $2 \times 2$  tables, we will calculate summary estimates of sensitivity and specificity,  
237  
238 positive and negative likelihood ratio and diagnostic odds ratio (DOR) with 95%  
239  
240 confidence intervals (95% CI) using a random effect bivariate model.  
241  
242 We will explore the heterogeneity between studies through visual examination of the

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4 240 hierarchical receiving operating characteristic (HSROC) curve. Heterogeneity across  
5  
6 241 the studies will be determined by correlation coefficient between logit transformed  
7  
8 242 sensitivity and specificity by bivariate model and asymmetry parameter,  $\beta$  (beta), where  
9  
10 243  $\beta=0$  corresponds to a symmetric ROC curve in which the DOR does not vary along the  
11  
12 244 curve by HSROC model. To determine the final meta-analytic model, we will use  
13  
14 245 likelihood ratio tests to assess model fit. Likelihood ratio tests will also be used to  
15  
16 246 determine the statistical significance of differences in test accuracy. When  
17  
18 247 heterogeneity is present, the degree will be quantified using the  $I^2$  statistic. Values of  
19  
20 248 less than 25% are considered as homogenous and 25% to <50% are considered as  
21  
22 249 having low heterogeneity. For values of 50% or more, significant heterogeneity is  
23  
24 250 assumed. And heterogeneity will also be assumed at significance level of  $P < 0.05$  and  
25  
26 251 tested by chi-square.

### 252 **Subgroup analysis**

253 If we extract sufficient data, we will perform subgroup analyses for any covariates that  
254 showed a statistically significant association with the summary estimates. We will  
255 explore the following sources of heterogeneity for the diagnosis of atrophic gastritis  
256 and helicobacter pylori infection and adding them as covariates, if appropriate, to a  
257 bivariate regression model: country, geographic origin, sample size, time of publication  
258 (early, recent), setting, study design.

259 Besides, for diagnosis of atrophic gastritis, we will perform subgroup analyses and  
260 meta-regressions by GC incidence (high-, intermediate-, low-), grade and extent of AG,  
261 activity of mucosal inflammation. For diagnosis of HP infection, subgroup analyses and  
262 meta regressions will be performed by application of PPIs, nonsteroidal anti-  
263 inflammatory drugs and antibiotic to identify the reasons for heterogeneity.

### 264 **Sensitivity analysis and publication bias**

265 Sensitivity analysis will be performed to assess the stability of the meta-analytical  
266 results, using the one-by-one study removal and evaluated by descriptively comparing  
267 the magnitude and precision of the random effects summary effect sizes. Publication

1  
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4 268 bias will be analyzed using precision funnel plots and the test statistics.  
5

6  
7 269 **Patients and public involvement**

8 270 This protocol will use previously published data. No patients or members of public will  
9  
10 271 be included in this study.

11  
12 272 **DISCUSSION**

13  
14 273 HP infection and atrophic gastritis have been recognized as two major risk factors for  
15  
16 274 gastric cancer.<sup>7-9</sup> To identify subjects with an underlying AG and HP infection plays a  
17  
18 275 vital role in preventing and improving the prognosis for GC. The accurate non-invasive  
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20 276 tool would be very helpful to identify these subjects, especially in the general  
21  
22 277 population. GP test is the non-invasive diagnostic tool based on physiology of three  
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24 278 biomarkers specific to stomach structure and function, complemented by ELISA (IgG)  
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26 279 testing for Hp antibodies.<sup>23-25</sup> However, the accuracy of GP is still controversial. And  
27  
28 280 it is necessary to provide a comprehensive review of the relevant studies published to  
29  
30 281 date. Therefore, we will conduct this systematic review and meta-analysis to provide  
31  
32 282 more supportive evidence in diagnosing atrophic gastritis and HP infection by  
33  
34 283 GastroPanel<sup>®</sup>. This study will synthesize the current literature on the diagnostic  
35  
36 284 performance indices of GastroPanel<sup>®</sup> for atrophic gastritis and helicobacter pylori  
37  
38 285 infection. However, there will be many limitations for this study. Firstly, the majority  
39  
40 286 of included studies will be cross-sectional study, which might cause bias. Secondly,  
41  
42 287 there may be heterogeneity because this test combines four biomarkers which have  
43  
44 288 different evaluation criteria. Thirdly, publication bias is still of concern because this  
45  
46 289 study will be limited to the English- and Chinese-language publications.

47  
48 290 **ETHICS AND DISSEMINATION**

49  
50 291 Due to this study as a systematic review, ethics approval is not necessary as we are not  
51  
52 292 directly targeting individuals or extracting data without privacy. The results of this  
53  
54 293 study will be submitted to a peer-reviewed journal.

55  
56 294 **Contributors**

57  
58 295 XY and DW concepted and designed the study. HW critically revised the design. AS  
59  
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4 296 and DW drafted the manuscript. DW, AS, HW, and XY critically revised and edited  
5  
6 297 the manuscript.

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8  
9 299 commercial or not-for-profit sectors.

10  
11 300 **Competing interests** None declared.

12  
13 301 **Patient consent for publication** Not required.

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For peer review only

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Table 1 Search strategy used in PubMed

Number	Search terms
1	"helicobacter pylori"[MeSH Terms]
2	"helicobacter nemestrinae"[Title/Abstract]
3	"helicobacter infections"[Title/Abstract]
4	"Helicobacter"[Title/Abstract]
5	"pylori"[Title/Abstract]
6	"H.Pylori"[Title/Abstract]
7	"Campylobacter"[Title/Abstract]
8	"campylobacter pylori"[Title/Abstract]
9	1 or 2-9
10	"gastritis, atrophic"[MeSH Terms]
11	"atrophic gastritides"[Title/Abstract]
12	"atrophic gastritis"[Title/Abstract]
13	10 or 11-12
14	"GastroPanel"[Title/Abstract]
15	"serum biomarkers"[Title/Abstract]
16	"panels"[Title/Abstract]
17	"pepsinogens"[MeSH Terms]
18	"pepsinogen i"[Title/Abstract]
19	"pepsinogen ii"[Title/Abstract]
20	"pepsinogen i ii"[Title/Abstract]
21	"Gastrin-17"[Title/Abstract]
22	"helicobacter pylori antibodies"[Title/Abstract]
23	14 or 15-22
24	9 and 13 and 23

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Page
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4, 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6, 7
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7, 8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8, 16
Study records:			

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3	Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
4	Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
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6	Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9, 10
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8	Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9, 10
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11	Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
12			
13	Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
14			
15	Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised	10
16		15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	10, 11
17		15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
18		15d If quantitative synthesis is not appropriate, describe the type of summary planned	NA
19			
20	Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
21			
22	Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA
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24	NA, not applicable.		
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