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ORIGINAL ARTICLE

Serum biomarkers provide an accurate method for diagnosis of atrophic gastritis in a general population: The Kalixanda study

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Abstract

Objective. Serological biomarkers can be used for non-invasive diagnosis of gastritis and atrophic gastritis. The aim of this study was to compare the validity of serum levels of pepsinogen I (PGI) and II (PGII), gastrin-17 (G-17) and *Helicobacter pylori* antibodies (Hpab) with that of the gold standard histology for diagnosis of atrophic gastritis in a population sample from Northern Sweden. ***Material and methods.*** In all, 1000 subjects underwent endoscopies with biopsies. Serum biomarkers were available in 976 subjects for independent diagnosis of gastric mucosal status using a predetermined diagnostic algorithm. ***Results.*** Overall agreement between histology and serological biomarkers in diagnosing corpus atrophy was 96% (CI 95%: 95–97%). Sensitivity and specificity of markers for atrophic gastritis were 71% (CI 68–74%) and 98% (CI 97–99%) respectively, corresponding to 69% (CI 95%: 66–72%) and 98% (95% CI 97–99%) positive and negative predictive values. The positive likelihood ratio was 35.5 (95% CI: 35.0–36.0%). In subgroups with normal stomachs, *H. pylori* non-atrophic gastritis and *H. pylori*-negative gastritis by histology, the prevalence of corpus atrophy diagnosed with the biomarkers was 0.8% and 4.9%, respectively. In total, 6.6% of subjects in the study population had corpus atrophy according to the serological biomarkers. ***Conclusions.*** Serological biomarkers show a high degree of accuracy as a non-invasive method to diagnose corpus atrophy, which is common in the general population.

Key Words: *Atrophic gastritis, biological markers, gastritis, Helicobacter pylori*

Introduction

The accuracy of the diagnosis of gastritis and atrophic gastritis based on histopathology of endoscopic biopsy specimens is limited for several reasons. First, inflammatory lesions, atrophy and intestinal metaplasia are often patchy and focal in the stomach and sampling errors readily occur. Secondly, interobserver and intra-observer variations in the interpretation of the biopsy appearances are well proven [1,2] and, thirdly, an upper endoscopy may not be feasible in all clinical situations. Therefore, a blood-based, non-invasive test to diagnose and evaluate gastritis and atrophic gastritis without such limitations would be ideal.

Serological testing for *Helicobacter pylori* antibodies (Hpab) is the simplest non-invasive test for "gastritis" but has limitations regarding the diagnosis of current or recent *H. pylori* infection. Combined serum assays of pepsinogen I (PGI) and pepsinogen II (PGII), and the ratio (PGI/PGII), with assays of Hpab allow the diagnosis of corpus atrophy and *H. pylori* gastritis [3–5]. Furthermore, combining gastrin, particularly the gastrin-17 (G-17) assay, with these biomarkers enables delineation of patients with

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atrophic pangastritis (of both the antrum and corpus), which carries the highest known risk for gastric cancer [6,7], even after *H pylori* eradication [8,9]. In addition, low and high serum levels of G-17 can be used to delineate patients with antrum-predominant atrophic gastritis and in the verification of atrophic gastritis limited to the gastric corpus [3,5,10]. Thus, combined assays of pepsinogens (PGs) and G-17 with Hpab give a more accurate status of the gastric mucosa than testing for *H. pylori* alone, and these assays reduce the risk and rate of false-negative results obtained by using *H. pylori* tests alone, particularly amongst elderly people with more advanced atrophic gastritis and hypochlorhydric stomach [7,11–13]. Some 5–10% of elderly people in the general population of the Nordic countries have atrophic gastritis [14]. Also, owing to the lower grade of colonization in such cases, direct *H. pylori* tests (breath test, stool antigen test, urease biopsy test, culture or biopsy microscopy) may give false-negative results [15–22].

In the past, serum/plasma biomarkers have been used in varying combinations in many studies on gastritis and atrophic gastritis. The latest version of available biomarker panels, comprising assays of PGs, G-17 and Hpab, has yielded accurate results in several previous cross-sectional and observational investigations among symptomatic outpatients [3,5]. However, it has never been compared with histology in the unbiased population.

In the present study, we examined the value of these biomarker assays in the diagnosis of atrophic gastritis in a large sample of subjects who represent randomly selected adults in a population sample from Northern Sweden, where the histopathological status of gastric mucosa was also evaluated independently.

Material and methods

Setting

The setting included two adjacent communities, Kalix and Haparanda, in Northern Sweden, with a total of 28,988 inhabitants (December 1998). The distribution of age and gender was similar to the national average [23], while some socio-economic variables were slightly lower, although insignificantly so from an international perspective [23].

Sampling and study design

By using the computerized national population register, covering the entire target population (20–80 years of age, $n=21{,}610$ in September 1998), a representative stratified sample of all adults was drawn (every 7th, $n=3000$, of the study population) [23]. The aim was to perform an endoscopic examination of the upper gastrointestinal tract (EGD) in a third of the study population, i.e. in 1000 adult subjects (4.6% of the target population).

The sampling strategy has been described in detail previously [23]. Briefly, the study population was first approached in subsets of a fifth ($n=600$) per half-year by mail, with a validated postal questionnaire (the Abdominal Symptom Questionnaire, ASQ) [23,24] with up to two reminders. Of the 3000 subjects in the original study population, 2860 were still eligible at the time of the mailing, and 2122 of them replied (response rate 74%, mean age 51.8 years, 49.5% women) [24]. In order to complete the 1001 EGDs with biopsies, 1563 responders then had to be approached. They were invited by telephone in random order, with the caller unaware of any symptoms experienced by the subjects, According to the proper exclusion criteria, 1365 of them were still eligible for the EGD. Of those, 364 refused to participate, and one refused biopsies at EGD. The participation rate for those eligible was thus 73% (mean age 54.0 years, 51.2% women). There was no statistically significant difference in gender distribution compared with in the original study population, but those who underwent endoscopies were significantly older (by a mean of 3.7 years, $p<0.001$). Those who had endoscopies were shown to be representative of the background population, except perhaps for the youngest: those under 35 years of age reported significantly more symptoms compared with the responders in the original study population [23]. The prevalence of positive *H. pylori* serology was 43.0% [25], which is in line with other Northern European countries [26], endorsing the generalizability of the data.

Endoscopy

The EGDs in the survey were done at two endoscopy units which covered the whole catchment area [23]. According to the recommendations of the updated Sydney System [27], two biopsies each were obtained from the cardia just below the Z-line, antrum and corpus. After the first 230 cases, the study protocol was updated and two more biopsies from the angulus were obtained and another two biopsies for the *H. pylori* culture were obtained from the gastric antrum and corpus, respectively. At the time of the EGD, venous blood samples were taken for serology.

Blood sampling procedure

The basal blood samples for measurements of fasting (basal) G-17, PGI, PGII and IgG antibodies to

H. pylori (Hpab) were drawn after an overnight fast. The samples were collected into serum tubes which were centrifuged at 1500*g* for 10 min and the serum samples were stored at −70°C until analysed.

Laboratory tests

G-17 (pmol/l), PG I (microg/l), PG II (microg/l) and IgG class antibodies to *H. pylori* were determined using specific enzyme immunoassay (EIA) tests according to the instructions of the manufacturer (Biohit Plc, Helsinki, Finland). For determination of PGI and G-17 values, second-order fit on standard concentrations were used to interpolate/extrapolate unknown sample concentration automatically, with the help of the BP800 inbuilt software (Biohit Plc). The *H. pylori* antibodies are expressed as enzyme immuno-units (EIUs) according to the formula included in the test kit (sample EIU = $(X(A_{Sample})-X(A_{Blank}))/(X(A_{Calibrator})-X(A_{Blank}))$. EIU levels ≥ 38 are considered to be *H. pylori* positive.

The monoclonal antibodies of G-17 and PGI used in the EIA tests are highly specific according to the information from the manufacturer. The G-17 antibody detects only amidated gastrin-17 but no other gastrin molecules or fragments [28]. In immunohistochemistry, for dilutions up to 1/10,000 the G-17 antibodies stain only antral G cells, not other cells or tissues in the stomach, duodenum, small or large bowel, or pancreas. This specificity also applies to the PGI antibody, which stains only chief and neck cells of the gastric corpus (oxyntic gland mucosa).

Classification of patients by serological biomarkers

For delineation of different topographic types of atrophic gastritis with serological biomarkers (GastroPanel®; Biohit Plc), a previously determined algorithm and specific empirically determined cut-offs for serum values of the biomarkers were used [3,5]. This algorithm and different phenotypes of gastritis and atrophic gastritis, delineated by the GastroPanel into four groups, are summarized in Table I.

H. pylori culture

Samples from the antrum and corpus were cultured and analysed as described previously [25,29].

Classification of patients by biopsy histology

The biopsies were routinely processed to paraffin wax and sections cut at 3 μm and stained with haematoxylin and eosin (H&E) and Warthin-Starry silver stain to detect *H. pylori* in samples from the cardia, corpus, antrum and incisura. Histological parameters of the gastric mucosa were assessed using the updated Sydney System [27] where atrophy and intestinal metaplasia were graded as mild, moderate or severe. Based on the histological appearances, the patients were classified into four groups (1–4) by two experienced pathologists (M.V. and M.S.) for a common comparison with biomarkers, and into another two groups (5 and 6) for a separate comparison, as shown in Table II [30–32].

Some of the cases were also diagnosed as corpus-dominant chronic active *H. pylori* gastritis (CDG) whenever the activity of the corpus gastritis was one score or more higher than that of the antrum activity and the antrum activity was scored at least as slight [33], or atrophic autoimmune gastritis was diagnosed whenever there was a total loss of parietal and chief cells, often in combination with focal intestinal metaplasia and hyperplasia of the enterochromaffin-like (ECL) cells [27]. However, owing to a supposed common physiological function as a consequence of mucosal affection, those cases were not analysed separately.

Interobserver study of corpus histology

An independent, experienced pathologist, blinded to the results of the main investigation, reviewed the

Table I. Algorithm for interpretation of serum biomarkers.

Interpretation	Serum biomarkers
1: Normal (healthy gastric mucosa)	All biomarkers are normal
2: Non-atrophic *H. pylori* gastritis	Hpab (IgG) is 38 EIU or more; all other biomarkers are normal
3: Multifocal atrophic gastritis (moderate or severe) both in antrum and corpus – atrophic gastritis is likely *H. pylori* associated – acid output is low and the stomach can be achlorhydric	PGI is less than 25 μg/l and/or PGI/PGII ratio is below 3. G-17 is below 5 pmol/l irrespective of the Hpab level (Hpab is an indicator of whether or not the atrophic gastritis is associated with an ongoing *H. pylori* infection)
4: Atrophic gastritis (moderate or severe) in corpus alone – acid output is low and the stomach can be achlorhydric. Atrophic gastritis is often "autoimmune"	As above but G-17 is 5 pmol/l or more

Abbreviations: Hpab = serum antibody (IgG) level of *H. pylori*; G-17 = fasting serum level of gastrin-17; PGI and PGII = fasting serum level of pepsinogens I and II; EIU = enzyme immuno-units.

Table II. All cases histologically classified into groups 1–4, in accordance with the possible biomarker outcome (as shown in Table I).

1. Normal or *H. pylori*-negative gastritis/gastropathy: Either completely normal antral and corpus mucosa without *H. pylori* in Warthin-Starry (WS) stain, no active gastritis and no *H. pylori* detected by WS stain, and without high-grade atrophy either in the corpus or antrum, and no high-grade intestinal metaplasia in either location or *H. pylori*-negative, non-atrophic gastritis defined by signs of chemical reactive gastritis (normal mucosa in antrum and corpus in association with slight but not active gastritis with foveolar hyperplasia, capillary ectasia and increase of ascending smooth muscle fibres in the lamina propria) [27,30,31] with no concomitant corpus or antrum atrophy as defined above *or* ex-*H. pylori gastritis* with features of former *H. pylori* gastritis as diagnosed whenever basal lymphoid aggregates in antrum or corpus[32] were found besides slight chronic but not active gastritis
2. *H. pylori* gastritis without corpus atrophy: *Non-atrophic gastritis* was defined as chronic active gastritis with lymphocytes, plasma cells and neutrophils within the lamina propria and in some cases with leucopedesis into the surface epithelium, basal lymphoid aggregates or lymphoid follicles and morphological detection of *H. pylori* with the WS silver stain (except for 8 cases with typical signs of a infection but no bacteria seen on histology: 6 of these were also positive on culture and 7 on serology). Also, slight atrophy in the antrum and/or corpus was permitted. *Antrum-limited atrophic gastritis* was defined whenever granulocytosis was seen in the antrum but not in the corpus ($n=11/24$) and/or moderate or high-grade atrophy or moderate or high-grade intestinal metaplasia was seen in the antrum but not in the corpus ($n=23/24$) in subjects with *H. pylori* infection on histology
3. Multifocal (antrum and corpus atrophic) gastritis was defined as moderate or high-grade atrophy or moderate or high-grade intestinal metaplasia in the antrum and in the corpus, irrespective of whether *H. pylori* infection is histologically proven or not (7/15 were *H. pylori* positive on histology, of the remaining 8 subjects, 4 were positive on culture, and of the remaining 4, all were seropositive and 3 of these were diagnosed as ex-*H. pylori* on histology. Only one had no sign of current or previous *H. pylori* infection)
4. Corpus-limited atrophic gastritis was defined as moderate or high-grade atrophy or moderate or high-grade intestinal metaplasia only in the corpus, irrespective of whether or not *H. pylori* infection was histologically proven; 19/47 were *H. pylori* positive on histology, another 4 on culture, another 10 had signs of ex-*H. pylori* infection on histology (of whom 6 were seropositive), another 7 were positive on serology and 7 had no signs at all of a current or past *H. pylori* infection

corpus histology on a random subsample of 105 of the subjects. The Sydney classification for histology was used and identical coding procedures were followed.

Statistics

Non-parametric tests (Wilcoxon–Mann-Whitney test and the Fisher exact test) were used to calculate the significance between the groups. A p-value of less than 0.05 was considered as statistically significant. For prevalence and mean values, 95% CIs were estimated on the basis of binomial distribution. Positive likelihood ratio and receiver operating characteristic (ROC) curves were calculated using standard procedures, as were kappa values on dichotomized data (corpus atrophy and intestinal metaplasia none $=0$, $\geq$slight $=1$) for a second opinion on corpus histology.

Ethics

The study was approved by the Ethics Committee of Umeå University on 29 May 1998 (dnr 98/99) and all participants gave their informed consent.

Results

Of 1001 subjects who underwent endoscopy, only 1 subject refused to undergo a biopsy. Evaluable biopies were missing in 15 cases from the antrum, 9 cases from the corpus and in 1 case from both locations due to technical reasons. Biomarkers were available from all. Thus 976 persons were available for the study. Of those 473 (48.5%) were men, mean age 54 years.

As shown in Table II, subjects with a normal mucosa ($n=351$) were grouped together with those with *H. pylori*-negative non-atrophic gastritis ($n=259$), assuming a common physiological function, and for the same reason those with *H. pylori* non-atrophic gastritis ($n=280$) were grouped together with those who had *H. pylori* gastritis limited to the antrum ($n=24$), thus forming columns 1 and 2 in Table III ($n=610$ and 304, respectively).

A 4×4 cross-tabulation of the applicable diagnoses obtained from histology and those obtained by the serological biomarker assays is presented in Table III, where corpus atrophy is shown in either group 3 or group 4, depending on whether or not concomitant antral atrophy is found.

Diagnosis by serology-detected corpus atrophy with or without antral atrophy in 3/351 subjects (0.8% 95% CI, 0–1.7%) with normal stomachs and in 2/259 subjects (0.8%; 95% CI: 0–1.9%) with *H. pylori*-negative gastritis, as assessed histologically, i.e. a total of 5/610 (0.8%; 95% CI: 0.1–1.5%) as shown in Table III, column 1. Moreover, column 2 in the same table shows that the same serological outcome was found in 15/304 subjects (4.9%; 95% CI: 2.5–7.3%) with histologically assessed *H. pylori* non-atrophic gastritis (none had *H. pylori*-related antral atrophy). The difference between the 4.9% of subjects with histological *H. pylori* non-atrophic gastritis and the 0.8% (5/610) with normal histology or *H. pylori*-negative non-atrophic gastritis was statistically significant ($p<0.0001$), as for the two histological subgroups.

Table III. Cross-tabulation of the diagnostic interpretations of the histological appearance and the serum biomarker assays (in bold type: cases with corpus atrophy with any or both methods).

Biomarker \ Histology	Normal or *H. pylori*-negative gastritis/ gastropathy	*H. pylori* gastritis without corpus atrophy	Multifocal (antrum and corpus atrophic) gastritis	Corpus limited atrophic gastritis	Total number of cases; histology
Normal	541	34	**0**	**4**	579
H. pylori gastritis without atrophy	64	255	**5**	**19**	333
Multifocal (antrum and corpus) atrophic gastritis	**2**	**3**	**3**	**3**	11
Corpus-limited atrophic gastritis	**3**	**12**	7	**31**	53
Total number of cases; biomarker	610	304	15	47	976

Of subjects with normal stomachs by histology, 311/351 (89%, 95% CI: 86–92%) cases were correctly classified by the biomarker assays, which by definition, however, cannot separate "normal" histology from *H. pylori*-negative non-atrophic gastritis, where 230 cases out of the 259 (89% (95% CI: 85–93%) were detected by the biomarkers. These two groups are thus shown as merged in Table III, column 1.

Among the 304 cases in Table III, column 2, the biomarkers correctly classified 255 (84%; 95% CI: 80–88%) of the subjects with *H. pylori* non-atrophic or antrum-limited atrophic gastritis. None of the 24 cases with *H. pylori*-induced antral atrophy only (not shown separately in the Table) was detected by the biomarker test, indicating its limitations in detecting changes confined to the antrum.

Using histology as the gold standard, and combining corpus atrophy with or without concomitant antral atrophy versus subjects without any corpus atrophy, as shown in Table IV, it appears that the overall rate of agreement of the serological markers to diagnose corpus atrophy compared to histology is 96% (95% CI: 95–97%), i.e. (44+894/976) from Table IV. In this comparison, the sensitivity and specificity of the markers for corpus atrophy are 71% (95% CI: 68–74%) and 98% (95% CI: 97–99%), respectively. This corresponds to a positive predictive value of 69% (CI 95%: 66–72%), and a negative predictive value of 98% (95% CI: 97–99%) for the serum biomarker test panel.

Table IV. Corpus atrophy with histology ("Histo+") as the gold standard versus corpus atrophy with serology ("Panel+").

	Histo+	Histo−	
Panel+	44	20	64
Panel−	18	894	912
	62	914	976

The positive likelihood ratio is 35.5 (95%CI: 35.0–36.0%) and the area under the ROC is 0.84, as shown in Figure 1.

Of the 64 subjects classified to have corpus atrophy by serum biomarkers in Table IV, 20 were considered to be non-atrophic by histology. The rate of "false-positive" results by the biomarker assay is therefore 31% (CI 95%: 28–34%). As 18 of the cases with atrophy on histology were negative on the biomarker, the "false-negative" rate is 2.0% (CI 95%: 1.1–2.9%). Thus, of those with positive biomarkers for corpus atrophy, 69% were positive and 2% negative on histology ($p<0.0001$).

Among the 41 cases with corpus-dominant gastritis (no. 5 in Table II), corpus and/or antral atrophy was diagnosed by the biomarker in 17 (41%, 95% CI: 26–56%).

The 28 cases diagnosed as autoimmune gastritis by histology (no. 6 in Table II) had atrophy in 24 cases (86%, 95% CI: 73–99%) according to the biomarker.

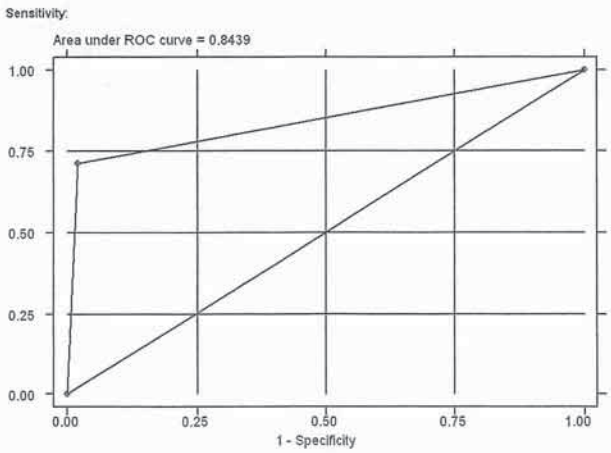

Figure 1. Receiver operating characteristic (ROC) for corpus atrophy as measured with serum biomarkers (Gastropanel) with histology as a gold standard.

In the blinded second opinion, the kappa value for corpus atrophy was 0.71 (95% CI: 0.52–0.90) and for intestinal metaplasia the value was 0.85 (95% CI ± 0.65–1.0) between the two pathologists, and the overall agreement was 82% (95%CI: 75–89%) and 86% (95% CI: 79–93%), respectively, thus confirming the validity of histology for diagnosis in this study

Discussion

This study indicates that biomarkers can diagnose moderate or severe corpus atrophy with a high degree of accuracy in comparison with the histological diagnosis. The apparently high "false-positive" outcome of 31% may actually highlight the inadequacy of relying on histology when standard biopsy routines are used, as these can result in the appropriate tissue areas being "missed". Whilst histological diagnosis is the current "gold standard" for comparison with biomarkers, it has limitations in diagnostic accuracy; for example, significant interobserver errors have been highlighted in previous investigations [1,2]. Thus, the value of validating biomarkers for diagnosis of gastritis and atrophic gastritis is highly dependent on the validity and interpretation of the biopsy histology. In our study, the excellent kappa values for interobserver observations on relevant corpus histology ensure reliable histology data [34,35] but do not exclude possible errors in biopsy sampling. A potential cause of bias in the histological assessment of *H. pylori* is the use of proton-pump inhibitors (PPIs). In this sample, however, only 3.6% of subjects (2.2% continuously) had used PPIs during the previous week [36], and thus with no marked influence on the results.

In this study, the correlation between biomarker assays and biopsy histology was generally good. However, some inaccuracies in defining the correct status of the gastric mucosa by biopsy histology were also obvious in the present study. Corpus atrophy, as diagnosed by biomarkers, was found in 4.9% ((3+12)/304 in Table III) of subjects with histological "*H. pylori* non-atrophic gastritis" but in only 0.8% of both those with "*H. pylori*-negative gastritis" and those with "normal stomach", respectively. The differences were statistically significant ($p<0.0001$), indicating that the accumulation of cases with corpus atrophy into a subgroup of "*H. pylori* non-atrophic gastritis" was not a random phenomenon and cannot be due to technical errors in marker assays. It indicates that some subjects with corpus atrophy were erroneously classified by histology into the group of subjects with "non-atrophic *H. pylori* gastritis". If this is true, it means that the diagnostic accuracy of biomarkers is more than 96%, and that the biomarkers may provide a more reliable view of the presence or absence of atrophic gastritis than the biopsy histology alone. This is most likely explained by sampling errors at endoscopy and shows the value of biomarkers in evaluating the entire gastric mucosal status as compared to small areas sampled by biopsy for histology.

In the present study, we have chosen to compare histology results with possible biomarker outcomes in Table III to simplify the interpretation, but the individual results for a more detailed histology are provided in the text. However, atrophic antrum-limited gastritis or antrum-predominant non-atrophic *H. pylori* gastritis was not separately diagnosed and delineated by histology. By using biomarkers, this phenotype of gastritis is characterized by normal levels of serum PGs (PGI = or >25 μg/l PGI/PGII ratio = or >3 – indicates that the corpus mucosa is normal) and with low serum G-17 (<1 pmol/l – indicates loss of gastrin secreting G cells and/or high intragastric acidity that inhibits the release of G-17 from antral G cells) [3,5]. Some 2% of all subjects in the present study population could be classified as this gastritis type by the serum biomarker assays. As expected, these subjects tended to accumulate in the subgroup of subjects with "*H. pylori* non-atrophic gastritis" by histology [14,37].

The combination of the G-17 assay with assays of PGs and Hpab enables separation of subjects with atrophic gastritis in the corpus mucosa alone (PGI <25 μg/l and G-17 is high) from those with atrophic gastritis in both the antrum and corpus (PGI is <25 μg/l and G-17 is low). This separation is noteworthy from some clinical viewpoints. Atrophic gastritis occupying both the antrum and corpus carries the highest risk for gastric cancer known so far, and this phenotype of atrophic gastritis is most likely to be caused by *H. pylori* infection [38,39]. Consequently, it has been considered clinically relevant to eliminate the risk for future gastric cancer by eradicating the organism before gastric atrophy occurs [8,9].

In the present study population, 69% of subjects with atrophic gastritis in the corpus, or in both antrum and corpus, showed *H. pylori* antibodies, indicating that an ongoing or recent infection is indeed common in these subjects even though it is not evident in all. In the present study population some 20% of subjects with corpus atrophy have concomitant atrophic antral gastritis according to the biomarker assays.

The "cut-off" used for the presence of atrophy on corpus histology could be questionable, as we used "moderate" and not "mild" for both atrophy and intestinal metaplasia. However, as the comparison is with physiological parameters as measured by the Gastropanel, it seems more appropriate to use a

histological grade that corresponds reasonably with these physiological parameters. Applying the lower "cut-offs" would give another 27 cases of atrophy on histology, 9 of whom had corpus atrophy, 15 had *H. pylori* gastritis without atrophy, and 3 were "normal" on the biomarkers. This would double the false-negative rate of the biomarkers from 1.8% to 3.6%.

The external validity and the good overall generalizability of the study have been shown before [23,25]. Furthermore, the similar prevalence rates of positive *H. pylori* serology in the endoscopied sample, 43% [25] and in the non-response group, 42% [23] as those of the population-based serology data from Northern Europe [26,40] confirm the comparability of socio-economic status.

The present study population is a population-based sample of individuals and represents the people in general in Northern Sweden, including young, middle-aged and elderly subjects. The assays with serological biomarkers, on the one hand, show that (moderate or severe) corpus atrophy occurs in 6% of people in this general population, while on the other hand more than half (59%) have a normal and healthy gastric mucosa as diagnosed by biomarkers. In this setting, the non-invasive biomarker method is an excellent tool to diagnose patients with atrophic gastritis and those with normal stomachs, without resorting to endoscopies, and thus it is cost efficient.

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Declaration of interest: Dr Pentti Sipponen is a member of the scientific board and a share holder of Biohit Plc, a Finnish company which is producing and marketing laboratory pipets and laboratory tests, including the GastroPanel. Over the decades, he also has been an invited lecturer and participant in several meetings and symposia on gastrointestinal diseases organized by the pharmaceutical industry, including companies like AstraZeneca, Glaxo, Takeda, Cilag Jansen, etc." Lars Agréus has been in the advisory board for Orexo AB.

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