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Serological Testing in Management of *Dyspeptic Patients* and in Screening of *Gastric Cancer* Risks

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Abstract

The two major risk factors of gastric cancer (GC) are *Helicobacter pylori* (HP) infection and Atrophic gastritis (AG). It is currently possible to diagnose HP gastritis and AG reliably by using serological testing with a marker panel (GastroPanel, Biohit Oyj, Finland) of pepsinogen-I (PGI), pepsinogen-II (PGII), gastrin-17 (G-17) and HP-antibodies. In this short review, the authors make an introduction to the GastroPanel test as the first non-invasive diagnostic tool of stomach health and disease. The major areas of the test application, i.e.,

1. In the first-line diagnosis of dyspeptic symptoms, and
2. In screening of the GC risks (HP and AG) are presented.

A short reference is made to the most recent studies validating the use of GastroPanel in different settings, including a summary of a timely meta-analysis summarizing the whole GastroPanel literature.

Pepsinogen levels and their ratio is decreased in corpus atrophy, accompanied by elevated G-17. G-17 level also gives indication of gastric acid secretion, being low with high acid output and high when stomach is acid-free (due to PPI treatment or AG). In antrum atrophy, G-17 is low and does not respond to protein stimulation (lack of G-cells). The two main indications of GastroPanel test are:

1. First-line diagnostic test for dyspeptic complaints, and
2. Screening of asymptomatic subjects for risks of GC (HP and AG).

GastroPanel is a test for stomach health, with excellent longitudinal negative predictive value. On the other hand, abnormal test results implicating AG do predict a significantly increased long-term risk for GC. The first meta-analysis of GastroPanel literature corroborates the statement of an international expert panel, advocating the use of GastroPanel in diagnosis and screening of AG. Noteworthy, the risk of autoimmune AG is markedly increased in patients suffering from other autoimmune diseases, including type-I diabetes, autoimmune thyroiditis, rheumatoid arthritis, inflammatory bowel disease (IBD), celiac disease and systemic lupus erythematosus. Altogether, 95 million people are estimated to suffer from these diseases in Europe alone.

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Introduction

Gastric cancer (GC) remains to be one of the most common cancers and causes of global cancer mortality; about one million new cases and 736.000 annual cancer deaths[1]. In many Western countries, GC incidence has been steadily declining, and e.g. in our country (Finland), the number of new cases has dropped since the early 1960's from 877 to 335 among males and from 680 to 246 among women 2014[2]. The reasons for this steady decline are primarily due to life-style changes and

through reduced exposure to the known risk factors of GC[2]. These known risk factors for GC include smoking, use of alcohol, dietary factors, occupational exposures, exposure to radiation and/or radiotherapy, as well as genetic predisposition in certain rare inherited syndromes[3,4]. Their different distribution among different populations explains, at least in part, the large geographic variation in the incidence of GC[1,3,4]. It is estimated that nearly 80% of GC cases among males and 70% in women are due to different life-style and environmental factors. The mediterranean type of diet has been considered as particularly healthy and clearly linked to a reduced risk of GC[5].

In addition to the above listed (common) risk factors, there are two specific risk factors that far exceed in importance all the others in pathogenesis of GC: *Helicobacter pylori* (HP) infection and atrophic gastritis (AG)[3,6,7]. Both of these risk factors can be identified in a simple blood test, which is based on the simultaneous measurement of four stomach-specific biomarkers that characterize the structure and function of the gastric mucosa. This same marker panel is equally applicable as the first-line diagnostic test in patients with dyspeptic symptoms, with potential to replace the invasive gastroscopy in this diagnostic algorithm[8,9].

H. pylori and atrophic gastritis

As early as in 1994, the International Agency for Research on Cancer (IARC, Lyon; a WHO agency) concluded that the accumulated scientific evidence is sufficient to declare HP as a human carcinogen[10]. This bacterium primarily infects the gastric mucosa, which, if uneradicated develops AG in about half of the affected patients. Although HP itself is not directly carcinogenic, AG is the single most potent risk factor of GC[3,7,11]. In some 5 - 10% of the patients with HP infection, mucosal atrophy is moderate or severe, and the risk of GC increases in parallel with the severity of AG: compared with healthy stomach, the risk is 2 - 5 times higher in those with only chronic HP gastritis but up to 90-fold in patients with severe AG both in the corpus and antrum (pan-gastritis)[3].

The other main histological type of GC (intestinal type) develops in atrophic mucosa through various degrees of dysplasia (mild, moderate, severe), which are often accompanied by intestinal meta-plasia(IM). This pathogenetic chain of events is known as the Correa cascade[3]. It is important to recall that this cascade can often (but not always) be interrupted by appropriate early treatment of HP infection[3,4,11,12]. AG is the single most important risk condition for GC[3,7,13,14]. Based on the Updated Sydney System classification (USS), AG is classified by its topographic location in the stomach (antrum, corpus, or both) as AGA, AGC or AGpan, respectively[15].

The diagnosis of AG has traditionally been made using histological biopsies on gastroscopy. However, gastroscopy is an invasive diagnostic tool, which requires expensive equipment and considerable professional experience. Like other endoscopies, also gastroscopy is a subjective diagnostic method, which is not suitable for population-based screening of GC. Because of this, the need to develop a simple and reliable diagnostic blood test increased in parallel with the increasing understanding of the importance of HP and AG as the key risk factors of GC, as established by long-term follow-up studies conducted e.g., in Finland[7,11,16,17].

GastroPanel test "Serological biopsy"

Since the 1990's, serum pepsinogens (PG) have been evaluated as screening tools for GC[18]. According to a recent meta-analysis, their impact on global GC mortality has been modest, however[19]. To meet the increasing demand, the GastroPanel® test was designed in the late 1990's by Biohit Oyj (Helsinki, Finland), representing the first non-invasive diagnostic test for stomach health[20,21]. This ELISA-based biomarker panel includes 3 markers of mucosal atrophy (PG-I and PG-II for the corpus; G-17 for the antrum), combined with HP IgG antibody assay[8,9,22]. The results of GastroPanel are interpreted by special software (GastroSoft®), another innovation of the company. During the past decade, GastroPanel has been tested in both diagnostic and screening settings[9,22,23-27]. As repeatedly emphasized[22,23,28], GastroPanel is not a test for invasive GC, but designed for disclosing the subjects at risk for GC, i.e., those who present with HP-infection and/or AG.

GastroPanel test is based on Stomach physiology

The marker profile of the GastroPanel test is designed to measure the normal physiology of the stomach and its disturbances, which may be structural or functional. Since the structure and function of the gastric mucosa are closely interlinked, the GastroPanel test is an accurate indicator of both, which makes it a unique diagnostic test[8,9]. In addition to indicating whether the complaint is of functional or structural nature, GastroPanel is capable of localizing the origin of the malfunction, i.e., whether in the antrum or in corpus[20-22,28].

When the mucosa of the gastric corpus undergoes atrophy, glands and their functional cells start reducing in number and eventually disappear completely (severe atrophy). At the same time, the output of hydrochloric acid (HCl from the parietal cells) and the pepsinogens (PG-I and PG-II from the chief cells) is reduced, an acid-free stomach as the end result. The severity of atrophy correlates closely with the HCl output and with the decreased serum levels of PG-I and PG-II[8,9,14,16,28]. As the gastric antrum undergoes atrophy, the G-cells producing G-17 will disappear. This results in a low fasting level of G-17 in the blood that is not responding to protein stimulation[8,9,14,16,17]. Through the negative feedback, the G-17 level is low also in patients with increased gastric acid output. On the other hand, when antral G-cells are not affected by AGA, G-17 level is up-regulated when the acid output is low or absent, either due to AGC or long-term use of PPI-medication[9,17,28]. The discussion of the several important clinical sequels of AGC falls outside the scope of this communication[17,28].

GastroPanel - an Integral Part of the Diagnostic Algorithm for Dyspeptic Complaints

Dyspepsia is a symptom complex including several different complaints of both functional and organic origin. About 20 - 40% of the population suffers from these symptoms at some point of their life. Far too often, gastroscopy is the first-line diagnostic method to investigate these patients, without any real need[8,9,20,21,23]. The same is true for the expensive test medications with PPI, just prescribed as part of the see-and-treat strategy. This strategy results in substantial amount of unnecessary costs and uncomfortable examinations for the patients, both of which would be mostly avoided by adopting an alternative strategy, where GastroPanel testing (instead of gastroscopy or PPI

medication) is used as the first-line diagnostic test for all *dyspeptic patients*[9].

As an alternative to gastroscopy in the diagnostic algorithm of *dyspeptic patients*, GastroPanel test accurately identifies the patients for whom endoscopy or PPI-medication are necessary. Following this practice, only 10 - 20% of all *dyspeptic patients* whose GastroPanel test indicates AG would need gastroscopic confirmation to evaluate the risk of GC[3,8,9,14,15,17,20,21,28]. Similarly, PPI-medication is indicated only for those who demonstrate high acid output in GastroPanel test (i.e., low G-17 without AGA), who are likely to benefit from this medication. However, PPI-medication should be contra-indicated for all those who suffer from acid-free stomach (i.e., high G-17)[9,17,28]. Furthermore, gastroscopy does not give any added value for the patients who have HP-infection without AG, for whom a proper eradication of HP and its adequate control represent a satisfactory management[29]. Accordingly, for the majority (80%) of GastroPanel-tested *dyspeptic patients*, gastroscopy is not necessary[9].

GastroPanel for Screening of the Gastric Cancer Risks

In addition to testing the patients with dyspeptic symptoms, the other main indication of GastroPanel is to screen asymptomatic subjects for detection of the GC risk groups[8,9,1723,28,30]. GastroPanel is a quantitative, ELISA-technique measuring the serum levels of four stomach-specific biomarkers. Using the well-defined thresholds for each marker and by taking into account their combined profile, it is possible to define whether the stomach is healthy or not and whether its function is normal or not[8,9,28]. Due to this complexity, the results are interpreted by a special software (GastroSoft), which classifies the GastroPanel results into eight distinct diagnostic categories[23,28,30]. Of those, five represent purely functional disturbances while three others indicate structural abnormalities (AGA, AGC, AGpan[9,17,28]. For the purpose of clinical management, the GastroPanel test can stratify the subjects into three categories at different risk: A, B, and C.

Group-A: The patient has no HP infection or AG. In this case, the GastroPanel test is perfectly normal, and gastroscopy does not add any significant diagnostic information, because the risk of both GC and peptic ulcer disease is practically non-existent[9,17,23,28].

Group-B: When only the HP-antibodies are elevated and the other markers are normal (or slightly elevated as a result of inflammation), the patient has HP-induced non-atrophic gastritis. In these cases, gastroscopy rarely brings significant additional clinical information[9]. The risk of GC is low, although not nil. After successful HP-eradication, the risk of developing HP-induced disorders (ulcer or cancer) is sharply reduced and soon returns to level of healthy people[3,6,7,9,29,30].

Group-C: When the corpus (PG-I, PG-II) or antrum (G17) markers are below the cut-off values, the patient has atrophic corpus (AGC) or antrum (AGA). In the worst scenario, mucosal atrophy affects both sites, implicating atrophic pan-gastritis (AGpan)[17]. In AGC, HP-antibodies can be elevated or normal, whereas in AGA, HP-antibodies are invariably elevated. The absence of HP-antibodies in otherwise atrophic stomach strongly implicates an autoimmune origin. In all these subjects, gastroscopy is mandatory because of an increased risk of GC[9,17,23,28].

The performance of GastroPanel test has been recently assessed in screening studies of asymptomatic subjects in two countries with high-incidence of GC; Kazakhstan[23] and Russian Federation[30]. GastroPanel results in both studies were very similar, but biopsy confirmation was available only in the second study[30], where the GastroPanel results were verified by gastroscopy and biopsies for all test-positive (AG+) cases and for random 5% (n = 263) test-negatives (to correct for the verification bias)[30]. Of the 918 screened subjects, only 199 (21.7%) tested completely normal, and 76.7% (704/918) had HP-infection. Altogether, in 99 subjects (10.8%) GastroPanel disclosed AG: AGA (n = 21), AGC (n = 69) or AGpan (n = 9). The overall concordance between GP and USS classification was 82.5% (217/263), with weighted kappa ICC = 0.875 (95%CI 0.840-0.901). The sensitivity/specificity balance in ROC analysis for PG-I as a marker of moderate/severe AGC (AGC 2+) had AUC = 0.895 (95% CI 0.837 - 0.953). Using the same AGC 2+ endpoint, the verification bias-corrected specificity of PG-I reached 96.4% (94.7 - 97.9%) and that of PG-I/PG-II ratio 94.6% (92.6 - 96.3%). The authors in both studies[23,30] concluded that, while capable of detecting the subjects at risk for GC, GastroPanel should be the cost-effective means to interrupt the current ominous trend in GC incidence in these two countries. These two studies provide further confirmatory evidence to substantiate the conclusions of an authoritative international expert panel, advocating the use of GastroPanel test in a population-based screening of asymptomatic subjects for the risks of GC[9].

GastroPanel– a Possibility for Primary Prevention

Substantiated by the meta-analysis of the accumulated vast literature on individual serum biomarkers (PGs and G-17) and their limited utility in GC screening[19], the GastroPanel test was not designed as a cancer screening test[8,13,14,16,17,20,21,28]. Based on several long-term follow-up studies in different countries, the natural history of GC and its development through precursor lesions is well established[3,4,7,12,13,17]. Indeed, these natural history data were exploited in the design of GastroPanel, creating a diagnostic test capable of detecting the cancer precursor lesions (AG) and their causative agent (HP) in a simple blood test. In cancer prevention, detection of the subjects at risk of any target disease falls in the domain of a primary prevention, in contrast to secondary prevention targeted to disease precursors and/or early disease. Most of the implemented population-based cancer screening programs are capable only for the latter, e.g. screening for breast cancer, and very few if any screening test is suitable for a primary prevention. GastroPanel test makes an exception while detecting the subjects at risk for GC years in advance, which makes this test unique among all screening tests[8,9,23,28,30].

This longitudinal predictive power of GastroPanel was firmly confirmed recently in an elegant case-control study nested within a prospective cohort of Caucasian population in Western Siberia and spanning an over 10-year follow-up period[31]. Both the cases and controls were derived from a population-based cohort of 45 - 69 year-old subjects (n = 9.360) in the HAPIEE (Health, Alcohol and Psychosocial Factors in Eastern Europe) study, enrolled in Novosibirsk (Siberia) during 2003 - 2005. Cases represent all GCs reported to the Cancer Registry until

2012, being matched (1:2) with healthy controls (CO). Serum samples of all 156 (52 GCs and 104 COs) study subjects collected at baseline were available for GastroPanel analysis[31].

The biomarker levels below the cut-off at the baseline samples predicted the development of an incident GC during the 10-year follow-up as follows (OR; 95%CI): PGI (2.9; 95%CI: 1.3 - 6.4), PG-II (9.0; 95%CI: 1.8 - 44.3), PG-I/PG-II (3.3; 95%CI: 1.5 - 7.3); G-17 (1.8; 95%CI: 0.7 - 4.8), and HP-Ab (0.4; 95%CI: 0.1 - 1.3). In a multivariate model adjusted for age, sex, and all GastroPanel markers, the PG-I/PG-II ratio was the single most powerful independent predictor of incident GC (OR = 2.9; 95% CI:1.01 - 8.0). This was the first time in a Caucasian population, when PG-I, PG-II and PG-I/PG-II ratio were shown to be significant longitudinal predictors of GC[31].

GastroPanel– the Most Comprehensive Test for *Helicobacter Pylori* and its Clinical Sequels

Diagnosis of infectious diseases is usually based on direct detection of the pathogen (cultivation) or on serological testing. This is not always the case with HP-induced gastritis, however, even though it is a common bacterial infection. Heavily promoted worldwide, the13C-urea breath test (UBT) has gained a wide-spread global use in diagnosis of HP, despite the fact that this test gives both false-negative and false-positive results in up to half of the patients. Also Prof. Barry Marshall who discovered HP[32] made an early warning of these serious limitations of the UBT already 20 years ago[33]. Basically, these false-negative results are due to decreased bacterial loads in the stomach mucosa, and include the following conditions:

1) Use of PPI medication;
2) Use of antibiotics;
3) Bleeding peptic ulcer;
4) AG (with or without IM);
5) GC;
6) MALT lymphoma, and
7) Partial gastrectomy.

Since the late 1990's, it has been well established that UBT also gives false-positive results in cases where urease-producing bacterial (non-HP)species are colonizing an acid-free stomach, resulted from AG or long-term use of PPI medication[33].

Furthermore, it is to be emphasized that the UBT is not capable of diagnosing AG (of any type), thus missing the patients at high-risk for its important clinical sequels:

i) GC,
ii) Esophageal cancer,
iii) Vitamin-B12 deficiency, and
iv) Mal-absorption of calcium, iron, magnesium and certain medicines[8,9,34,35].

When performed as an integral part of the GastroPanel marker panel, HP antibody test is independent of these diagnostic errors. In 2012, the International *Helicobacter Pylori* Study Group stated in their Maastricht IV Consensus Conference, that the blood biomarker tests are a reliable means to identify and screen for gastric diseases and their risk status[36]. In the same year, 16 experts from 12 countries in the HSI (Healthy Stomach Initiative, http:\www.hsinitiative.org) drafted a set of recommendations implicating that the biomarker tests are suitable for both screening of asymptomatic patients and for diagnosis of *dyspeptic patients*[9].

To provide an unbiased estimate of the accumulated evidence, we recently performed a systematic review and meta-analysis of all studies published on GastroPanel test since its introduction in the early 2000's[37].

Studies were eligible, if:

i) GastroPanel test (instead of single markers) was used to diagnose biopsy-confirmed AGC or AGA, and
ii) Exact numbers were available to enable calculating the sensitivity (SE) and specificity (SP).

Altogether, 27 studies were eligible, comprising 8.654 tested patients from different geographic regions. Significant heterogeneity between studies reporting AGC (n = 27) or AGA (n = 13) warranted random effects (RE) model for the summary statistics. GastroPanel was shown to perform better in diagnosis of AGC than AGA, with 70.2% vs. 51.6% pooled SE, and 93.9% vs. 84.1% pooled SP, respectively[37]. Limited number of studies erodes the Q test's power to detect true heterogeneity in meta-analysis stratified by geographic origin of the studies. Few hypothetical missing studies had only marginal effect on the pooled estimates of SE and SP. The results of this first meta-analysis of GastroPanel literature corroborate the above cited statement of the international experts[9]. Due to its high specificity for both AGA and AGC[37] as well as its extremely high longitudinal negative predictive value[31], GastroPanel® is truly a test for stomach health. In other words, testing GastroPanel-negative at any time point during one's life-time precludes (with over 95% probability) a significant gastric pathology for several years ahead[31].

Conclusion

GastroPanel test has been on the market for roughly 10 years by now. The test is based on long-term natural history studies on gastritis patients run since the 1960's in Finland and Estonia[14,15]. This test is the first non-invasive diagnostic tool based on physiology of 3 stomach-specific biomarkers both in health and disease. The test also includes testing for HP infection, the key etiological factor in pathogenesis of peptic ulcer disease and GC[32]. In its current version, the unified GastroPanel test is fully automated, and all 4 biomarkers being processed under identical conditions. The test will be soon available in the quick test version as well, particularly suitable for POC (point-of-care) testing in doctor's offices lacking the facilities for blood sample centrifugation. With the refined diagnostic algorithm of the GastroSoft, the results are classified into 8 diagnostic categories[28], of which 5 represent functional disturbances (in acid output) and 3 indicate AG (and its topographic location). In GastroPanel test, the HP antibody measurement is complemented by the other 3 biomarkers (PG-I, PG-II, G-17) which are sensitive indicators of mucosal inflammation. This marker panel makes GastroPanel test the most comprehensive HP test, devoid of the known shortcomings of the conventional HP tests[33-36].

The authors end up by concluding that at the present time when health care savings are the driving force of the public health care in most countries, it would be possible to achieve

substantial savings in these costs by simply implementing a simple, inexpensive and non-invasive GastroPanel test as the first-line diagnostic tool for all patients with dyspeptic symptoms, to replace the systematic use of gastroscopy.

Conflict of Interest

Both authors are employees of Biohit Oyj. Kari Syrjänen is a member of the Management Team, but not a shareholder of the company.

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