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Non-invasive Screening by Serological Biomarker Test (Gastro Panel®) and Stomach Protection of High-Risk Individuals Using Slow-Release L-Cysteine (Acetium® Capsule): A Potential Strategy for the Primary Prevention of Gastric Cancer

Kari Syrjänen[1,2*]

[1]SMW Consultants Ltd, Kaarina, Finland

[2]Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil

***Corresponding author:**

Kari J. Syrjänen, MD, PhD, FIAC,
SMW Consultands Ltd, Kylliäisentie 9,
FI-21620 Kuusisto, Finland

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1. Abstract

The two major risk factors of Gastric Cancer (GC) are Helicobacter Pylori (Hp) infection and Atrophic Gastritis (AG). Both of these can be diagnosed by using serological testing with a panel of biomarkers (Gastro Panel®, Biohit Oyj, Finland): pepsinogen I, pepsinogen II, gastrin-17 and Hp IgG antibodies. Severe AG results in acid-free stomach colonized by Hp and other bacteria, producing acetaldehyde (Group I human carcinogen; IARC). Together with other conditions leading to a) acid-free stomach, e.g., chronic users of proton pump inhibitors (PPI) and autoimmune AG, or b) increased exposure to acetaldehyde, e.g., cigarette smokers, alcohol intake, and ALDH2 enzyme mutations, these subjects are at high risk of gastric and esophageal cancer. Acetium® Capsule (Biohit Oyj) is a novel formulation of slow-release L-cysteine, designed for elimination of carcinogenic acetaldehyde in the stomach, thus effectively protecting the stomach against the exposure to acetaldehyde. This communication introduces the dual concept how to i) screen the subjects at high risk for GC using the non-invasive Gastro Panel® test for early diagnosis of AG and Hp, and how to ii) protect the stomach mucosa of these high-risk individuals by a novel formulation (Acetium® Capsule, Biohit Oyj) based on slow-release L-cysteine, effectively eliminating carcinogenic acetaldehyde. The results of Gastro Panel® test are interpreted by a special software (Gastro Soft®) identifying eight diagnostic biomarker profiles. Gastro Panel® has been validated in clinical and screening settings worldwide, and its outstanding clinical performance was confirmed in two recent meta-analyses. Biomarker profiles of AG also have an excellent longitudinal predictive value for incident GC. Acetium® Capsule was designed for elimination of carcinogenic acetaldehyde in the stomach, and its regular use is indicated for all those who have acid-free stomach. In placebo-controlled clinical trials, slow-release L-cysteine effectively (up to 80%) eliminated acetaldehyde in patients with acid-free stomach due to AG or PPI treatment, irrespective of their ALDH2 status. With a rational use of these two medical devices, i) the lesions at high risk for GC can be timely diagnosed and ii) the stomach mucosa effectively protected against the exposure to carcinogenic acetaldehyde.

2. Gastric Cancer

2.1. Epidemiology of Gastric Cancer (GC)

Gastric cancer (GC) represents a major global burden, with over one million new cases and 770,000 annual deaths worldwide [1]. In many Western countries, however, GC incidence shows a declining trend during the past decades [1], attributed to major changes in the lifestyle factors including a reduced exposure to the known risk factors [2]. The well-established risk factors for GC include smoking, alcohol, dietary factors, occupational exposures, radiation and/or radiotherapy, as well as genetic predisposition (certain rare inherited syndromes) [2–4]. According to the current thinking, the different distribution of these risk factors among different populations explains the large geographic variation in the incidence of GC [1,2,4]. It is estimated that nearly 80% of GCs among males and 70% in women are due to lifestyle and environmental factors [2–4]. In contrast, the Mediterranean type of diet seems to be associated with a low risk of GC [5].

2.2. Key Risk Factors

In addition to the above general risk factors [2-4], there are two risk factors specific to GC that far exceed in importance all the others in pathogenesis of GC: i) Helicobacter Pylori (Hp) infection and ii) atrophic gastritis (AG) [3,6,7]. Already in 1994, the International

Agency for Research on Cancer (IARC, Lyon, France) declared Hp as a human carcinogen, based on convincing accumulated scientific evidence [8]. This bacterium primarily infects the gastric mucosa, and if not treated, develops AG in about half of the affected patients [3,6]. A representative example on the global GC trends is Japan, where GC has ranked as the most common cancer for the past several decades, but where the prevalence of Hp infection has dramatically declined as a result of improved general hygiene in childhood [9]. The older generations born before 1950 still show an Hp prevalence of around 80-90%, decreasing progressively with the birth cohorts to reach <10% in those born around the 1990s, and further to <2% among the children born after 2000 [9]. This change has implications in risk-stratified approaches in GC prevention in Japan as well as in other countries with similar GC trends [9,10].

2.3. Pathogenesis (Correa Cascade)

Hp itself is not a directly carcinogenic agent, but Hp-induced AG is the single most potent risk condition of GC [3,7,11]. Some 5-10% of the Hp-infected patients eventually develop moderate to severe AG, and the risk of GC increases in parallel with the severity of AG, up to 90-fold among the patients with severe AG both in the corpus and antrum (pan-gastritis) [3,6,7,12]. The other main histological type of GC (intestinal type) develops in atrophic gastric mucosa through various degrees of dysplasia (mild, moderate, severe), which are often accompanied by Intestinal Metaplasia (IM) [3,7]. This pathogenetic chain of events is known as the Correa cascade referring to its discoverer [3]. This cascade can often (but not always) be interrupted by a curative early treatment of Hp infection [3,4,11,13]. AG is the single most important risk condition for GC [3,7,14,15]. According to the Updated Sydney System classification (USS), AG is classified by its topographic location (antrum, corpus, or both) as AGA, AGC or AGpan, respectively [16]. Hp infection also plays a causative role in the development of peptic ulcer disease [8,11,12]. Similarly, both AG and Hp can be responsible for the upper abdominal symptoms known as dyspepsia [17]. Debate still continues on the value of systematic Hp eradication in relieving the dyspeptic symptoms, however [11,12,17].

3. Acetaldehyde – the Carcinogenic Agent in Common

Hp infection and AG are the two most powerful independent risk conditions of GC [3,7,11,12]. The carcinogenic agent in common to both Hp infection and AG is acetaldehyde, declared as Group I human carcinogen by IARC in 2009 [18]. Apart from Hp it self which is capable of synthesizing acetaldehyde, the other bacteria colonizing in acid-free stomach of AG-patients are an abundant source of this carcinogenic substance [18–20]. Other subjects at increased risk of high acetaldehyde exposure include i) cigarette smokers, and ii) alcohol consumers, both substances being abundant sources of acetaldehyde [18]. The same is true with iii) AG caused by autoimmune disease, and iv) chronic users of PPI (proton pump inhibitor) medication [19,20]. Yet, another special group of people at high risk for acetaldehyde exposure are those (estimated 500 million) people in Asia, who bear a mutation in their Aldehyde Dehydrogenase (ALDH2) enzyme, and who fail to metabolize alcohol to acetic acid, resulting in higher local concentrations of acetaldehyde [18–20]. Indeed, a recent meta-analysis provided evidence that chronic use of PPI medication increases the risk of GC [21], which would be plausibly explained by the PPI-induced acid-free stomach, colonized by acetaldehyde-producing microbial flora [22,23].

4. Diagnosis of the Gastric High-Risk Lesions (Hp & AG)

The diagnosis of AG has traditionally been made using histological biopsies on gastroscopy [3,16]. However, gastroscopy is an invasive diagnostic tool, which requires considerable professional expertise, and as a subjective, invasive and expensive method, gastroscopy is not suitable for population-based screening of GC. As to the diagnosis of Hp infections, attempts have been made to standardize the management of these patients since 1996 by the Maastricht Consensus Conferences [11,12]. Unfortunately, however, there has been a common tendency to neglect the limitations of the conventional Hp tests in routine clinical settings, although these caveats have been clearly discussed in all European Consensus Reports [11,12]. This applies to both of the most widely used Hp tests; the 13C-Urea Breath Test (UBT) and Stool Antigen test (SAT), the limitations of which have been discussed in detail recently [22–26]. These caveats of the conventional Hp tests (UBT, SAT) can be avoided by the innovative Gastro Panel® test (Biohit Oyj, Helsinki, Finland), where the Hp IgG antibody (ELISA) measurement is complemented by three other biomarkers: pepsinogen I (PGI), pepsinogen II (PGII) and gastrin-17 (G-17) [25–27]. Apart from being specific biomarkers of gastric corpus (PGI, PGII) and antrum (G-17), respectively, all are also sensitive indicators of mucosal inflammation evoked by Hp infection. This 4-biomarker panel makes Gastro Panel® the most comprehensive Hp test [27], devoid of the known shortcomings (false negative and false positive results) of the conventional Hp tests [22–24]. Given that this bacterium is the single most important risk factor of GC [3,4,8,11,13], it sounds timely to move a step forwards in diagnosis of Hp infections, using the test that is i) free from the shortcoming of the conventional Hp tests [22–24], and ii) provides a significant added diagnostic value by accurately detecting also the GC precursor lesions, i.e., AG with all its potentially serious clinical sequelae [25–28].

5. Minimizing the Exposure of Gastric Mucosa to Carcinogenic Acetaldehyde

Because acetaldehyde is ubiquitous, the exposure to it is impossible to avoid completely [18-20]. The only feasible approach is to make every attempt to reduce the acetaldehyde exposure to the minimum [18]. Apart from systematically avoiding the foodstuffs and beverages that contain acetaldehyde [19,20], there is a novel approach based on active elimination of acetaldehyde in the stomach and in the saliva. This innovation is based on the biochemical characteristics of a natural amino acid L-cysteine, recently patented by Biohit Oyj (Helsinki, Finland), with the proprietary names Acetium® Capsule and Acetium® Lozenge. Both are using the slow-release L-cysteine formulation that reacts covalently

with acetaldehyde to form an inert compound, 2-methylthiatsolidne-4-carboxyl acid (MTCA) [29]. These Acetium® preparations reduce the concentration of acetaldehyde in the stomach and in saliva, thus protecting these two mucosal sites against the harmful effects of this carcinogenic compound [30–32].

6. The rationale for the Combined use of GastroPanel® and Acetium® Capsule

The combined use of Gastro Panel® test and Acetium® Capsule is rational as recently emphasized [33,34]. The former is for diagnosis of the high-risk conditions in the stomach, whereas the latter provides an effective and unique means for minimizing the exposure of the stomach mucosa to carcinogenic acetaldehyde. In brief, the most important high-risk conditions of the stomach include Hp infection and AG, readily diagnosed by Gastro Panel® [25–28] as will be detailed in the following sections. Acetium® Capsule is a novel formulation of slow-release L-cysteine, being a unique medical device designed for elimination of carcinogenic acetaldehyde in the stomach [29]. The most common high-risk groups include the following: 1) AG associated with Hp infection; 2) AG caused by autoimmune mechanisms; 3) cigarette smokers; 4) alcohol consumers; 5) chronic users of PPI medication, and 6) those (500 million) people in Asia who have a mutation of the ALDH2 enzyme, failing to metabolize acetaldehyde and exposed to extremely high local concentrations of acetaldehyde [30–32]. We believe that a regular use of Acetium® Capsule is indicated for all those who have acid-free stomach, irrespective of its origin [33,34]. With a rational use of these two medical devices, one can diagnose the GC precursor lesions advocating the protection of the stomach against acetaldehyde exposure. This document discusses the evidence-based rational for the combined use of these two unique medical devices; one for early diagnosis of high-risk lesions and the other one for the primary prevention of gastric carcinogenesis.

7. Gastro Panel® Test Responds to an Unmet Global Need

Because of the above listed obstacles (Section 3) in diagnosis of both AG and Hp infection [11,12,22–24], the global need to develop reliable non-invasive diagnostic tests has increased in parallel with the increasing understanding of the importance of Hp and AG as the key risk factors of GC, emerging e.g., from the long-term follow-up studies conducted since the 1960s [7,15]. To meet this increasing global demand, the Gastro Panel® was designed in the late 1990s by Biohit Oyj (Helsinki, Finland), representing the first non-invasive diagnostic test for stomach health and disease [35–38]. This biomarker panel is readily applicable as the first-line diagnostic test in patients with dyspeptic symptoms, with potential to replace invasive gastroscopy in this diagnostic algorithm [25–28,37,38].

7.1. Basic principles of the Gastro Panel® test

Gastro Panel® is intended for the 1) first-line diagnostic test for Hp infection (5-80% of the world population), for 2) the examination of all patients with dyspepsia (20-40% of the Western population), as well as 3) for the population-based screening of AG [38–40]. Apart from being the key risk factor of GC, AG also increases the risk of malabsorption of vitamin-B12, calcium, iron, magnesium, zinc, and some medicines [36,37]. It is important to recall that Gastro Panel® is not a test for GC itself [25–28]. This is because the biomarkers of the panel are not by any means specific markers of gastric malignancy but react to functional disturbances in acid output as well as in mucosal pathologies (Hp and AG), and their serum levels are poor markers of GC [22–26,38,41]. Gastro Panel® consists of four stomach-specific biomarkers representing the key regulatory mechanisms of normal stomach physiology. These four biomarkers include pepsinogen I (PGI), pepsinogen II (PGII), amidated gastrin-17 (G-17), and Hp IgG antibodies, designed to give information on both the structure and function of the stomach mucosa [36–43]. Most importantly, this panel gives accurate estimates of 1) the capacity of the corpus and antrum mucosa to produce gastric acid and G-17, respectively, of 2) important gastric pathologies, like inflammation, as well as of 3) the grade and topography of AG [16,27,38,44–46]. Normal plasma levels of all four biomarkers indicate that both the structure and function of the stomach mucosa are normal. In contrast, abnormal biomarker levels are signs of a non-healthy stomach, reflecting disturbances in the feedback mechanisms between the corpus (PGI, PGII, acid output) and antrum (G-17). For G-17, Gastro Panel® offers two assessments: G-17 basal (G-17b) values and G-17 stimulated (G-17s) values. The latter are particularly useful while making the distinction between functional disturbance in acid output (high/low) (G-17b low/high; G-17s normal) and AGA (G-17s does not increase upon protein stimulation) [38,47,48]. Apart from being the first non-invasive diagnostic test for stomach mucosa in health and disease, Gastro Panel® is also unique in that the test results are interpreted by a special software application (Gastro Soft®) [25–28]. Based on the specified biomarker profiles, Gastro Soft® classifies the results into one of five possible diagnostic categories that have a morphological equivalent in the gastric biopsy: 1) normal mucosa, 2) superficial or non-atrophic (Hp) gastritis, 3) AG in the corpus (AGC), 4) AG in the antrum (AGA), and 5) AG in both antrum and corpus (AGpan)(Figure 1) [15,25–28,38,48]. Gastro Panel® is optimized for use together with the Updated Sydney System (USS) for the classification of gastritis, which is based on these same five diagnostic categories [16,49]. In addition, there are three other biomarker profiles that are associated with functional disturbances of gastric acid output (and its interference by PPI), where mucosal morphology is normal (details to follow). Gastro Panel® has been validated in a large number of biopsy-confirmed clinical studies [39,50,51], all summarized in a recent meta-analysis [52]. These studies have been invaluable in validating the reference (cut-off) values of each biomarker to the histological endpoints. These studies also confirm the high accuracy of Gastro Panel® in detecting the most important endpoint, moderate-to-severe AG [52]. Thus, normal values of PGI, PGII and their ratio (PGI/PGII) preclude AGC with NPV of over 95% [27,28,39]. In turn, the values of PGI and PGII as well as the PGI/PGII ratio below the cut-off levels predict moderate-to-severe AGC (AGC2+) with

area under ROC curve (AUC) values exceeding 0,950 in adequately-powered, biopsy-controlled series [50,52,53]. The AUC values for Hp IgG ELISA to confirm biopsy-verified Hp are close to 0,900 [54]. Taken together, the levels of PGI decrease in AGC and in AGpan, but remain within the normal range in all other conditions (Figure 1). Elevated PGII levels reflect mucosal inflammation, the highest values being detected in Hp-associated non-AG. The G-17b values are highest in AGC, because the missing negative feedback by the acid output from an atrophic corpus results in uninhibited secretion of G-17b by the normal antral mucosa [25–28,35,38,53,54]. G-17b is high also in cases where the acid output is suppressed by long-term use of PPI medication. By definition, when antral mucosa is atrophic, G cells disappear, and G-17 secretion remains very low even after protein stimulation (G-17s) [35]. Hp IgG antibodies provide significant added diagnostic value to the three biomarkers. High IgG antibody levels for Hp reflect two different conditions: 1) an ongoing Hp infection, or 2) a previous exposure to Hp. As the only abnormal marker, elevated Hp IgG antibodies implicate an Hp-associated superficial gastritis (with no AG), while associated with abnormalities in the other three markers, elevated Hp antibody levels are characteristic to Hp-associated AG (AGA or AGC) [22–24,54–56].

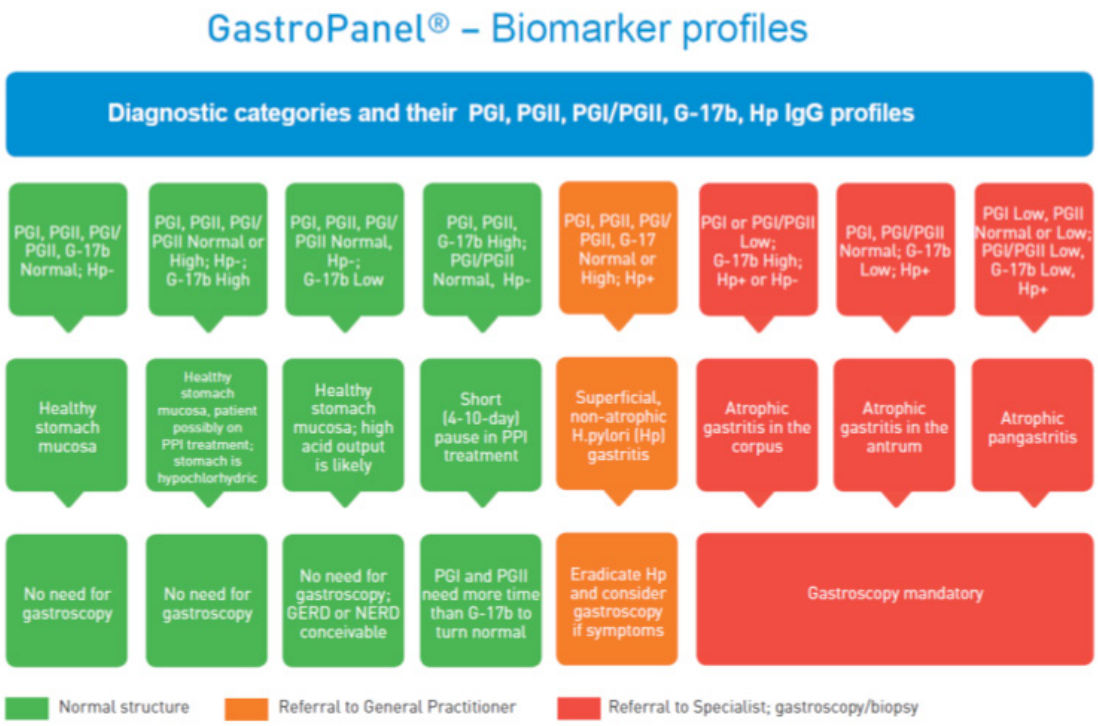

Figure 1: GastroPanel® biomarker profiles and their associated clinical risk

8. GastroPanel® Biomarkers

The combination of the four biomarkers of Gastro Panel®: PGI, PGII, G-17, Hp IgG, was designed to give information on both the structure and function of the stomach mucosa [25–28,36–43]. Following is a brief account on the role of each biomarker as an integral component of the panel.

8.1. Pepsinogen I (PGI)

The role of this biomarker in Gastro Panel® is to identify the patients who have mucosal atrophy in the corpus (AGC), for which the plasma PGI is a highly specific biomarker [25–28,38,52,56–60]. PGI is a precursor enzyme (zymogen) of pepsin, synthesized by the chief cells and neck cells of the gastric corpus (in oxyntic glands). As a pepsin precursor, the major bulk of PGI is secreted into the gastric lumen but a minor fraction is absorbed into the circulation. The circulating PGI concentration closely parallels the quantity of the chief cells in the corpus mucosa, and any loss of these cells (due to atrophy) results in a linear decrease in the plasma levels of PGI [56–60]. For as yet unknown reasons, AG increases the risk of GC [3,6,7,11,12]. Compared with a healthy stomach, this risk is 5-fold among patients with advanced AGC, but up to 90-fold in patients with advanced AG in both the antrum and corpus (AG-pan) [7]. In a screening of middle-aged (50-69 years) males in our country, the circulating PGI level was low (<25 μg/l) in 9.8% of the subjects, of whom 4.7% revealed either a GC or a precancer lesion on gastroscopy [15]. Similar results have been published in a number of similar studies, as summarized in a comprehensive meta-analysis in 2004 [61].

8.2. Pepsinogen II (PG II)

Pepsinogen II is produced by the chief cells and the mucous neck cells of the corpus, as well as in pyloric glands of the antrum, and in Brunner's glands of the proximal duodenum [28,37–40]. The PGII assay is designed for use concomitantly with the PGI assay to determine the PGI/PGII ratio [25–28,38,52,56]. The ratio of PGI to PGII plasma levels in normal subjects levels off between 3-20 [46]. The PGI/PGII ratio decreases linearly with increasing grade of AGC [52,56,57,62]. The ratio falls below 3.0 when AGC is ad-

vanced (i.e., AGC2+) [57]. The risk of GC is increased (5-fold) when the PGI/PGII ratio is low [39,42,45,60,63–68]. This parameter is a valuable adjunct diagnostic indicator for AGC in Gastro Panel®. On the other hand, an elevated PGII level reflects mucosal inflammation, the highest values being constantly detected in Hp-associated, non-atrophic gastritis. Since Hp antibody levels can remain elevated for several months after a successful eradication, PGII is a useful marker for the confirmation of successful eradication, i.e., normal PGII indicates a lack of active inflammation [35,52,56].

8.3. Gastrin-17 (G-17)

Gastrins are linear peptide hormones produced by the G cells in the duodenum, in the pyloric part of the gastric antrum, and in pancreas [38]. The main function of gastrins is to stimulate the output of gastric acid (HCl) of the parietal cells in the corpus, as well as to increase the motility of antrum [69]. In addition, gastrins stimulate gastric chief cells to secrete PGI and PGII and also induce the contraction of the lower esophageal sphincter (LES). The G cells release a mixture of different molecular weight gastrins into the circulation, including gastrin-71, -52, -34, -17, -14, and -6, all of which are carboxy-amidated and circulate in an O-sulfated and non-sulfated form [70]. Amidated G-17 is the most potent form of gastrin, and it is almost exclusively produced by the antral G cells [71]. The amidated G-17 included in the Gastro Panel® test is a direct biomarker of antral structure and function, and through a negative feedback loop, an indirect biomarker of the gastric corpus. G-17 plasma levels within the normal range implicate a normal structure and function of the antrum, whereas low or high values of G-17 also reflect abnormal functions of the corpus. The maximum information is obtained when G-17 testing is done separately for fasting (G-17b) and stimulated (G-17s) levels, combined with PGI, PGII and Hp antibody testing [7,35,62,72–74]. The measurement of plasma G-17b may also be used for the monitoring of the patients who have undergone gastric surgery; secretion of G-17b is practically zero after successful radical antral resection. In Hp-negative subjects, a low fasting level of G-17 indicates high acid output in most cases. This in turn may increase the risk of gastroesophageal reflux disease (GERD) and Barrett's esophagus (up to 3-4–fold risk), whereas a normal or elevated G-17b excludes Barrett's esophagus with high probability [75,76].

8.4. Helicobacter pylori IgG Antibody ELISA

Helicobacter pylori (Hp) infection is the most important cause of chronic gastritis leading to mucosal atrophy. A much more infrequent cause of AG is an autoimmune mechanism [77,78]. In the Gastro Panel® test, this ELISA is designed for detection of Hp infection in the plasma samples, based on IgG antibody detection [25–28,38]. Hp is a spiral-shaped, gram-negative bacterium that colonizes in the human stomach (73) [79]. The organism is found within the mucous layer overlying the gastric epithelium, and also within the mucosal glands, but not within the epithelial cells. The mucosa adjacent to the areas of Hp colonization is invariably inflamed; this condition is referred to as chronic superficial or non-atrophic gastritis which, if untreated, persists for life [16,38,49,79,80]. If not eradicated, this chronic bacterial infection leads to AG [11,12]. AG in turn increases the risk of peptic ulceration and GC, two important sequels of Hp infection [80–84]. Epidemiological evidence also indicates a link between Hp infection and a mucosa-associated lymphatic tissue (MALT) lymphoma [11,22–26,85,86].

9. Interpretation of the Gastro Panel® Results by Gastro Soft® Application

Gastro Panel® test is optimized for use in context with the USS classification of gastritis [16,49]. Both the systems use five diagnostic categories to classify the biopsies and the Gastro Panel® results, respectively: 1) normal mucosa, 2) superficial (Hp) gastritis, 3) AGA, 4) AGC, and 5) AGpan [16,25–28,38,49]. In addition to these five categories with morphological equivalent in the biopsies, Gastro Soft® application uses three other biomarker profiles, specific for defined functional disturbances, with normal stomach morphology (Figure 1). These 8 diagnostic biomarker profiles are depicted in more detail in Table 1 and explained in the subsequent sections.

Table 1: The GastroPanel® biomarker profiles in different diagnostic categories

	GastroPanel® Biomarker Levels ()[1]						**Interpretation**
Marker Profile	PGI (30-160 µg/l)a	PGII (3-15 µg/l)	PGI/ PGII (3-20)	G-17b (1-7 pmol/l)	G-17s (3-30 pmol/l)	Hp IgG antibody titer (<30 EIU)	
1	N	N	N	N	N	N	Healthy mucosa (no atrophy, no Hp infection)
2	N	N	N	L*	N	N	Healthy mucosa. High acid output.
3	N or H^	N or H^	N	H**	N	N	Healthy mucosa. Low acid output due to e.g., PPI medication
4a	N or H^	N or H^	N	N or H^	ND	H	Active Hp infection, not treated
4b	N	N	N	N	ND	N or H†	Hp infection successfully eradicated
4c	N	H	N	H	ND	H	Hp eradication failed
5	L	L	L	H	ND	N^^ or H	Atrophic gastritis in corpus and fundus (AGC)

6	N	N	N	L	L	H	Atrophic gastritis in antrum (AGA)
7	L	L	L	L	L	N^^ or H	Atrophic gastritis in both antrum and corpus (AGpan)
8	H	H	N	H	ND	N	Short (4- to 10-day) interval in continuous PPI treatment. Rebound in gastric acid output.

[1](values in parenthesis indicate the normal reference range of each biomarker); N: Normal; L: low; H: high; Hp: *Helicobacter pylori*; ND: no need for testing; PG: pepsinogen; PPI: proton pump inhibitor. *Test PPI medication for 2 weeks, G-17b should normalize. **Stop medication, G-17b should normalize within 2 weeks; ^Can be elevated due to mucosal inflammation; ^^can disappear in mucosal atrophy with protracted clinical course. aPGI cut-off value 30 μg/l is consonant with moderate/severe atrophic gastritis (AG); †Helicobacter pylori antibody levels can remain elevated for months after successful eradication

9.1. Normal Profile

Given that the function of gastric mucosa is critically dependent on the specific cells responsible for acid output (parietal cells), pepsinogens (chief cells) and G-17 (G cells), normal function necessitates the presence of these cells in normal quantities [38,40,45,48,56]. Accordingly, gastric function and mucosal structure go hand-in-hand, and by definition, a normal Gastro Panel® result is a surrogate marker of a healthy stomach. A normal marker profile does not exclude, however, minor lesions like non-specific inflammation, mild irritation or micro-erosions that have not impact on the marker profiles [28,38,40,56].

9.2. High Acid Output

Gastric acid (HCl) is produced by the highly specialized parietal cells in the corpus. Acid output is controlled by the secretion of G-17 in the antrum as a result of a positive feedback loop after a meal [35,56,69,70]. Acid output results in progressively lower pH in the stomach contents, and the threshold of pH 2.5 triggers a negative feed back to antral G-cells, signalling them to down-regulate the output of G-17 [69–72]. As a result, G-17 output decreases in parallel with the increasing acid output [35,38,40,50]. When, due to any reason, acid content in the corpus remains abnormally high, the result is abnormally low G-17b output [87]. With the Gastro Panel®, this condition is best diagnosed after a test medication with PPI, when G-17b levels should normalize within a couple of weeks on therapy. Under these high-acidic circumstances, however, the post-prandial (stimulated) G-17s will remain within the normal range, because the intact G-cells are capable of G-17 secretion when properly stimulated (e.g., by a protein powder) [56,87].

9.3. Low Acid Output Due to Proton Pump Inhibitor (PPI) Medication

The acid output regulation also works in the other way round. When acid output in the corpus is reduced (for any reason), the positive feedback loop triggers antral G cells to increase their G-17b secretion, resulting in elevated serum levels of G-17b [35,40,56]. The two prime conditions leading to low acid output are: 1) AGC, and 2) long-term use of PPI medication (or H2-receptor blockers). The former is easily excluded by the normal values of PGI, PGII, and PGI/PGII ratio [22–28,38,40,56], while the latter is best confirmed by discontinuing the PPI medication. In that case, the G-17b levels should be normalized within two weeks [40,56,69–73].

9.4. Superficial (non-atrophic), Helicobacter Pylori-Associated Gastritis

Like all bacteria, also Helicobacter pylori induce an acute inflammation in the gastric mucosa, with the usual onset in the antrum [11,12,24,28,38,67,73,74]. To characterize the different outcomes of Hp infection, Gastro Panel® specifies three different biomarker profiles Table 1.

9.4.1. Active Helicobacter pylori infection: In an active Hp infection, Hp IgG antibody levels are raised above the cut-off value (30 EIU), which can be the only abnormal finding in Gastro Panel®. Not infrequently, however, an active ongoing Hp infection causes a severe inflammatory reaction which, due to increased cell permeability, leads to increased leakage of PGI, PGII and G-17 from the secretory cells resulting in elevated serum levels of any or all of these three biomarkers [11,12,28,38,40,44,56].

9.4.2. Successful Helicobacter Pylori Eradication: Successful Hp eradication results in normalized values of Hp IgG antibodies as well as the three "inflammatory" markers (PGI, PGII, G-17). For the latter, this normalization takes place with a delay of some weeks [22–28,40,56]. In contrast, Hp IgG antibody levels remain elevated for a prolonged time which is subject to individual variation and limits the usefulness of Gastro Panel® in the immediate post-treatment control of Hp eradication [28]. Because of this individual variation in the dynamics of these biomarkers, an accurate record of the Hp eradication timing is mandatory while making the re-testing with Gastro Panel® [12,37,56,74].

9.4.3. Failed Helicobacter Pylori Eradication: In cases where Hp eradication fails, Hp antibody levels remain elevated, PGI and PGI/PGII ratio usually return to normal values, whereas PGII and/or G-17b may remain slightly elevated as a sign of a continuous inflammatory process. The result can be confirmed after 5-6 months, followed by a new treatment attempt if indicated [11,12,22–28,38,40]. An option is to use another test for the control of Hp eradication, e.g., the Helicobacter pylori Quick Test (fast) or Helicobacter pylori UFT 300 Quick test (ultrafast) (Biohit Oyj) [88].

9.5. Atrophic Gastritis of the Corpus (AGC)

As a result of mucosal atrophy in the corpus, the loss of chief cells leads to a progressively reduced output of PGI and (to a lesser extent) PGII, which is also produced by the same cells in the antral mucosa [28,42]. This unequal reduction of these two markers

will result in a reduced PGI/PGII ratio, which is another excellent signature of AGC [38,40,42–44,46,50,52,56,61]. This progressive reduction in the PGI and PGI/PGII ratio is closely correlated with the severity of AGC, with a total atrophy and acid-free stomach as the end point [74,77]. In the case of intact antral mucosa, this leads to markedly increased output of G-17b [35,40,56]. There is no need to test G-17s in such a situation. In chronic AGC with a protracted clinical course over decades, Helicobacter pylori itself may disappear from the atrophic mucosa, resulting in gradual normalization of the Hp IgG antibody levels [89–91].

9.6. Atrophic Gastritis of the Antrum (AGA)

When the gastric atrophy only affects the antrum, all corpus-derived markers remain within the normal range. By definition, AGA is caused by Hp infection, and Hp IgG antibodies are invariably elevated in the Gastro Panel® testing. In AGA, the G cells are reduced in number and finally disappear, leading to progressively reduced plasma levels of G-17b. In severe AGA, there is no G-17 response to protein stimulation (G-17s), because there are no G cells [35,38,40,50,51,55,56,58,74,76]. The distinction between the two potential causes of low G-17b: i) high acid output, and ii) AGA, is neatly done by using the G-17 testing after protein stimulation (G-17s [22–28,38,40,56]. As pointed out, G-17s will react normally only in the former, but fails to react in severe AGA [28].

9.7. Atrophic Gastritis of the Antrum and the Corpus (AG-pan)

The most severe form of AG is known as atrophic pan-gastritis (AGpan), affecting both the antrum and the corpus [16,22–28,40,49,56]. In the most severe lesions, chief cells in the corpus and G cells in the antrum disappear, leading to a biomarker profile where both PGI and PGII as well as G-17 are significantly reduced [35,38,40,50,51,55,56,77,78]. This applies to both G-17b and G-17s, which remain low even after protein stimulation. Like in AGC, Hp IgG antibody levels can be either within the normal range or elevated. This is because in chronic atrophy, Helicobacteria can disappear from the mucosa, and in the absence of antigen stimulus, a normal decay of IgG antibodies will shift the Hp antibody levels eventually below the 30 EIU cut-off [89–91].

9.8. Biomarker Profile Associated with the PPI use and its Discontinuation

Gastric acid suppressive medication (PPI, H2 blockers) will inevitably interfere with the Gastro Panel® biomarker profiles. Ideally, it is recommended that the patient discontinues any acid-suppressive treatment one week before the sampling [22–28,40,56]. Not infrequently, however, this withdrawal of PPI- or H2-blocker medication is not possible because of severe symptoms. Given this fact, the new version of the Gastro Soft® was modified so as to take into account the eventually continued use of these drugs. Important is an accurate record of i) the PPI/H2-blocker medication, ii) the fact whether or not it was discontinued, and if yes, for iii) how many days before the sampling. With this information accurately recorded, the Gastro Soft® algorithm is capable of interpreting the test results correctly [28].

PPI and H2-blockers effectively reduce gastric acid production in the parietal cells [22–28]. This increases the production of G-17, stimulating the output of pepsinogens. Once the PPI/H2-blocker treatment is discontinued, it takes approximately 4–10 days for HCl production and G-17 levels to normalize. However, pepsinogens respond more slowly, and PGI and PGII levels may remain above the cut-off values for up to 2-3 weeks [22–28,40,56]. An abrupt termination of a long-term PPI medication is typically followed by a rebound acid hypersecretion, frequently accompanied by severe clinical symptoms and very low levels of G-17b [22–28,35,38,40,48,56]. Despite the fact that the effect of PPI use in the GastroPanel® biomarker profile is well established [22–28,40,56], the potential impact of the widespread use of PPI medication on GastroPanel® test results was not surveys until recently [92]. A matched case-control setting was used to estimate i) the impact of PPI use on the Gastro Panel® results, and ii) to disclose the significant predictors of the PPI user status. Of the clinical cohort of 266 gastroscopy-referral patients enrolled at Fortis Hospital (India), age-matched case-control (1:3) pairs were built up, consisting of 68 PPI-non-users as cases and 198 PPI-users as controls. The Gastro Panel® results in the two study arms were compared using weighted kappa ($\varkappa w$) testing, and conditional logistic regression (CLR) models were used to estimate the co-variates of the PPI-user status. The levels of the corpus- (PGI and PGII) ($p<0.001$) and the antrum (G-17b) ($p=0.018$) biomarkers were significantly different between the two groups. The agreement between Gastro Panel® and USS-classified gastric biopsies was significantly different ($p<0.001$) between cases and controls: $\varkappa w=0.868$, and $\square w=0.583$, respectively [92]. In ROC analysis, no difference in the DA of Gastro Panel® in detecting AGC2+ (moderate/severe atrophic corpus gastritis) was disclosed between cases and controls, AUC levels exceeding 0.950 in both study arms. The authors concluded that the PPI-use did not compromise the DA of the Gastro Panel® test in the detection of the most important diagnostic endpoint, AGC2+ [92].

10. Pooled Performance of Gastro Panel® test Confirmed by Random-Effects Bivariate Model and HS-ROC

So far, the published clinical studies have analysed the DA of PGI and PGI/PGII ratio as predictors of AGC2+, reporting AUC values exceeding 0.950 in adequately-powered, biopsy-controlled series [27,28,39,50,52,53]. The AUC values for Hp IgG ELISA to confirm biopsy-verified Hp are close to 0.900 [54]. As discussed above, however, Gastro Panel® test is an entity, i.e., a panel of 4 diagnostic biomarkers, and none of those four can be ignored without significantly interfering with the DA of the test [24–28,38]. Until recently, there has been no report where the DA has been analysed for the Gastro Panel® test as an entity, i.e., pooled performance for all five diagnostic categories (N, Hp, AGA, AGC, AGP), where instead of the AG endpoint, the respective USS-verified five conditions of the stomach are used as the endpoints [93]. Recently, such an analysis was performed based on three previously published clinical validation studies on gastroscopy referral patients

(n=961), using random-effects bivariate model (REBM) and hierarchical summary receiver operating characteristic (HSROC) model to estimate the pooled Se, Sp and summary AUC (SROC) for the Gastro Panel® test in diagnosis of these five target conditions of the stomach [93]. In this analysis, the overall agreement between Gastro Panel® and USS was 0.877 (95%CI 0.86-0.89). The summary Se, Sp, LR+, LR-, and DOR for the five diagnostic categories were 0.62 (95%CI=0.33-0.87), 0.98 (95%CI=0.92-0.99), 26.6 (95%CI=9.2-77.0), 0.37 (95%CI=0.16-0.83) and 73 (95%CI=22-245), respectively. Both REBM- and HSROC models provided an identical summary AUC=0.960 (95%CI=0.93-0.97). Post-test probability is 90% for a correct Gastro Panel diagnosis in a population with 25% pre-test probability of these target conditions. Taken together, these important data confirm that the Gastro Panel® test detects its target disorders of the stomach with an overall diagnostic accuracy of 96% [93].

10. The Major Recent Studies with the New-Generation Gastro Panel® tests

Two major developments in the Gastro Panel® test have been made by the manufacturer recently. These include the launching of two a new-generation Gastro Panel® tests: i) the unified Gastro Panel harmonizing the ELISA processing conditions of the 4 biomarkers [53,54], as well as ii) the Gastro Panel® Quick Test, intended for point-of-care (POC) diagnosis. The unified test was first validated in patients at high-risk for AG [53] and in those with high Hp-prevalence [54]. Subsequently, three major clinical studies have been conducted, including the validation of both of these new-generation Gastro Panel test [94–96].

The first of these three studies tested unified Gastro Panel® test in a cohort of 522 gastroscopy referral patients at the Gastro Center, Oulu University Hospital, Finland (OUH) [94]. The overall agreement (OA) between the Gastro Panel and the USS classification was 92.4% (95%CI=90.0-94.6%), with the weighted kappa (□w) of 0.861 (95%CI=0.834-0.883). In ROC analysis using AGC2+ as the endpoint, AUC=0.952 (95%CI=0.891-1.000) and AUC=0.998 (95%CI=0.996-1.000) for PGI and PGI/PGII, respectively. Hp IgG antibody ELISA detected biopsy-confirmed Hp-infection with AUC=0.993 (95%CI=0.987-0.999) [94]. The authors concluded that the new generation Gastro Panel® is a precise test for non-invasive diagnosis of AG and Hp-infection in dyspeptic patients referred for diagnostic gastroscopy [94]. More recently, a similarly designed study was conducted in the UK (Homerton Hospital, London) [95]. In this single-centre, prospective DA study, a cohort of 324 patients (median age 57 years: range 39–92 years) was recruited for gastroscopy and Gastro Panel® testing (n=268). The OA between Gastro Panel® and the USS classification was 90% (95% CI=86.7 to 93.8%), with a weighted kappa (kw) of 0.828 (95% CI=0.781 to 0.865). In ROC analysis, using AGC2+ as the endpoint, AUC=0.840 (95% CI 0.630 to 1.000) and 0.960 (95% CI 0.907 to 1.000) for PGI and the PGI/PGII ratio, respectively [95]. These data clearly concur the results from the Finnish study [94] implicating that Gastro Panel is a reliable dyspepsia triage test distinguishing patients who can be safely treated conservatively from those with moderate to severe AGC and at high-risk of developing gastric cancer [95]. The first clinical validation study of the newly introduced Gastro Panel® Quick Test was recently completed in India [96], using a cohort of 266 patients enrolled among the consecutive gastroscopy referrals at Fortis Hospital (Punjab, India). A biopsy-confirmed AG was found in 15.3% (38/249) of the patients. The OA between the Gastro Panel® Quick Test and the USS classification was 71.4% (95% CI 65.4–77.0%), with the weighted kappa (kw) of 0.823 (95% CI 0.773–0.862). Using the AGC2+ endpoint, AUC=0.990 (95% CI 0.979–1.000) and AUC=0.971 (95% CI 0.948–0.995) was obtained for PGI and PGI/PGII, respectively [96]. These Indian data confirm that the Gastro Panel® Quick Test favourably competes in DA of the ELISA test version (unified-GP) in diagnosing AG and Hp in patients referred for diagnostic gastroscopy [96]. Yet further confirmatory evidence on the DA of Gastro Panel® was provided by a recent study evaluating the diagnostic concordance between this biomarker panel, gastroscopy (EGD), and biopsy histology (USS) in gastroscopy-referral patients [97]. This analysis is an extension of the previously reported Oulu cohort of 522 patients [94], now focused on testing the concorddance between the three diagnostic methods, measured using kappa statistics. Of the Gastro Panel® test-negatives (n=447), 60% had normal findings on EGD, 36% (n=161) were diagnosed as inflammatory lesions and 4% (n=19) were classified as having possible or definite AG. Biopsies revealed moderate AG in only three Gastro Panel-negative patients (0.07%). While Gastro Panel and USS showed an excellent agreement (weighted k=0.861) the agreement between Gastro Panel/EGD and EGD/USS was only moderate: kw=0.458 and kw=0.480, respectively. Of the 175 discrepant diagnoses, over 90% were ranked by all gastroenterologists as benign conditions with no need for therapy or follow-up by EGD. Taken together, despite the fact that Gastro Panel®, EGD, and USS do not always provide uniform diagnoses, however, after a negative Gastro Panel® test, the probability of detecting AGC2+ using EGD is extremely low (3/447; 0.07%). Thus, substantial cost savings (90%) in the first-line diagnosis of upper abdominal symptoms could be achieved by preserving EGD only for those (<10%) patients whose Gastro Panel® test indicates AG [96].

11. Clinical Performance Confirmed by Recent Meta-Analyses

Since its introduction in clinical use, the published literature on studies using Gastro Panel® has increased steadily justifying a comprehensive review and meta-analysis [52]. The first meta-analysis was completed in 2016, including all studies where i) Gastro Panel® test (instead of the stand-alone markers) was used to diagnose biopsy-confirmed AGC or AGA, and ii) exact numbers were available to enable calculating the diagnostiv indicators. Altogether, 27 studies were eligible, comprising 8,654 tested patients from different geographic regions [52]. Significant heterogeneity between studies reporting AGC (n=27) or AGA (n=13) warranted random effects (RE) model for the pooled estimates. Gastro Panel® 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 [52]. The results of this first meta-analysis of Gastro Panel® literature corroborate the consensus statement (in 2012) of the international experts [38]. The second meta-analysis was published a year later by gastroenterologists in Italy [98]. Their extensive literature search covered all the key databases between 1995 and end of 2016. Studies were eligible if they assessed the accuracy of the Gastro Panel® test for the diagnosis of AG using the USS [16,49] as the reference. The authors identified 20 eligible studies with a total of 4,241 subjects tested for AG, without considering its topographic location (AGA or AGC). The pooled SE was 74.7% (95%CI 62.0-84.3) and the pooled SP was 95.6% (95%CI, 92.6-97.4). The authors concluded that GastroPanel® test appears to be a reliable tool for the diagnosis of AG, equally applicable for both diagnosis and screening of the subjects at high risk of GC [98]. The third in order (and so far the latest) meta-analysis was reported in 2022 [99]. Core electronic databases were searched until the end of December 2021, following the principles of the PRISMA-P and using the QUADAS-2 quality assessment tool. Altogether, 49 studies were found eligible, comprising 22,597 patients examined by the Gastro Panel test. Significant heterogeneity across the studies was confirmed in Forest plots, HSROC and bivariate boxplot. The pooled Se of Gastro Panel® in diagnosis of AGC was 0.70 (95%CI=0.64-0.76) and pooled Sp was 0.93 (95%CI=0.90-0.95), with AUC=0.900 (95%CI=0.170-1.000) in HSROC. In Fagan's nomogram, positive GP test predicts AGC at population level with the likelihood of 72% [99]. Meta-regression and subgroup meta-analysis disclosed publication year (<2008>) as the only significant source of heterogeneity, geographic study origin being of borderline significance. The results of this most comprehensive meta-analysis confirm the accuracy of Gastro Panel® test in the diagnosis of AGC, advocating its applicability i) in screening for gastric cancer risk conditions (AG, Helicobacter pylori) as well as ii) in non-invasive diagnosis of dyspeptic patients, and iii) in follow-up of AG-patients [99].

12. Biomarker Profiles are of Longitudinal Predictive Value for GC

Apart from the studies that confirmed the utility of Gastro Panel® in the diagnosis of dyspeptic symptoms [22–28,38,52] and in screening of asymptomatic subjects for the risk conditions of GC [38,40,43–47,52,56,100,101], Gastro Panel® has been recently studied also in longitudinal settings to assess the biomarker profiles as long-term predictors of GC [102,103]. The first of these studies was a matched case-control setting nested within a cohort of Caucasian population in Western Siberia (89) [102]. Both the cases (GC) and controls (CO) were derived from a population-based cohort (n=9,360) known as HAPIEE (Health, Alcohol and Psychosocial Factors In Eastern Europe) study, enrolled in Novosibirsk (Siberia) during 2003-2005. Altogether, 156 (52 GCs and 104 COs) serum samples collected at baseline were available for Gastro Panel® analysis. The biomarker levels below cut-off predicted the development of GC as follows: PGI (2.9; 95%CI: 1.3-6.4), PGII (9.0; 95%CI: 1.8-44.3), PGI/PGII (3.3; 95%CI: 1.5-7.3); G-17 (1.8; 95%CI: 0.7-4.8), and Hp IgG Ab (0.4; 95%CI: 0.1-1.3). In a multivariate model adjusted for sex, age, and all four biomarkers, PGI/PGII ratio was the single most powerful independent predictor of GC (OR=2.9; 95% CI: 1.01-8.0). This was the first time in a Caucasian population, where PGI, PGII and PGI/PGII ratio were shown to be reliable longitudinal predictors of incident GC [102]. The second longitudinal study was completed in Northern China [103]. Among 12.112 participants with prospective follow-up from an ongoing population-based screening program, the authors conducted a follow-up, with prediction modelling. In the follow-up, low PGI levels and PGI/II ratios were associated with higher risk of developing GC, similar as low (<0.5 pmol/l) and high (>4.7 pmol/l) G-17 levels [103]. Higher serological biopsy scores based on the five biomarkers at enrolment were associated with higher risk of developing GC during follow-up (p for trend <0,001). According to the authors, Gastro Panel® test could be used to identify the high-risk individuals for further diagnostic gastroscopy, thus guiding a targeted screening and tailored prevention [103]. Together with the published meta-analyses [52,98], these two studies [102,103] implicate that due to its high specificity for atrophic gastritis and due to the longitudinal predictive value of individual biomarker profiles, Gastro Panel® is truly a test for stomach health and disease. Testing Gastro Panel®-negative at any time point during one's lifetime precludes (with >95% probability) a significant gastric pathology for several years ahead [102,103]. In contrast, a Gastro Panel® biomarker profile implicating AGC is an independent predictor of an increased risk of contracting GC within the coming 10 years or so.

13. Acetium® Capsule for Protection of the Stomach in High-Risk Individuals

Acetium® Capsule was designed by Biohit Oyj some 10 years ago for elimination of carcinogenic acetaldehyde in the stomach, intended for regular use for all those who have acid-free stomach [18–20]. Severe AG results in acid-free stomach colonized by Hp and other bacteria, producing acetaldehyde [18–20]. Together with other conditions leading to a) acid-free stomach, e.g., chronic users of PPI and autoimmune AG, or b) increased exposure to acetaldehyde, e.g., cigarette smokers, alcohol intake, and ALDH2 enzyme mutations, these subjects are at high risk of developing GC and EC [19,20,30–32].

13.1. Subjects at High Risk of Exposure to Carcinogenic Acetaldehyde

Whenever Gastro Panel® detects a biomarker profile suggesting AG (any topography) (Figure 1, Table 1), the subject should be referred for gastroscopy to confirm the diagnosis. Gastroscopy is considered as the gold standard to classify the grade and topography of gastritis [16,49]. It is estimated that Hp infection is involved in >90% of all GC cases that develop through the Correa cascade, from intermediate steps of AG, IM, and dysplasia [3,6,7,12]. Accordingly, Hp and AG are currently considered the two most powerful independent risk factors of GC [16,56,61,79]. The carcinogenic agent in common to both Hp and AG is acetaldehyde, classified as Group I human carcinogen by IARC in 2009 [18].

Apart from Helicobacteria itself, which is capable of synthesizing acetaldehyde, the other bacteria colonizing in acid-free stomach, are an abundant source of this carcinogenic substance [19,20]. The same applies to AGC caused by an autoimmune mechanism, which is another well-known causative factor of AG [104–106]. Acetaldehyde is also the major carcinogenic substance in cigarette smoke, predisposing cigarette smokers to acetaldehyde exposure in oral cavity and the upper gastrointestinal tract [18–20,107,108]. The same applies to alcohol intake, because acetaldehyde is the first metabolite of alcohol, also produced in the stomach endogenously from ethanol, e.g., by local microbial or mucosal oxidation of ethanol to acetaldehyde [18–20,28,30–32,109]. Another well-known condition that increases the risk of acetaldehyde exposure is a point mutation in ALDH2-gene resulting in deficient activity of the main acetaldehyde metabolizing mitochondrial ALDH2 enzyme and provides conclusive evidence for the causal relationship between local acetaldehyde exposure and upper digestive tract cancer [110,111]. It has been estimated that some 500 million people (mainly in Asian populations) are affected. When drinking alcohol, the upper digestive tract mucosa of ALDH2-deficients is exposed via saliva to about twofold and via gastric juice, up to 5–6 times higher acetaldehyde concentrations than in persons with active ALDH2-enzyme [110–112]. Parallel to increased local acetaldehyde exposure, the risk of ALDH2-deficient alcohol drinkers for oral, pharyngeal, EC and GC is many-fold compared to ALDH2-actives. Thus, ALDH2-deficiency provides a unique human cancer model for local acetaldehyde exposure in the upper digestive tract [110,111]. Yet another well-defined group of subjects at increased risk of acetaldehyde exposure include all those (estimated >500 million) chronic users of PPI medication. Two recent meta-analyses suggest that a regular and long-term use of PPI medication is associated with an increased risk of GC [21,113]. An acid-free stomach secondary to either AG or PPI treatment is colonized by oral microbes, which effectively produce acetaldehyde from ingested alcohol via their ADH enzymes [107–111]. This was convincingly demonstrated in recent experiments, where PPI treatment for 7 days significantly increased gastric juice acetaldehyde levels in ALDH2-active subjects after intra-gastric infusion of a moderate dose of alcohol. However, the highest gastric juice acetaldehyde concentrations were measured in PPI-treated ALDH2-deficient subjects [112].

13.2. Atrophic Gastritis (AG) and Intestinal Metaplasia (IM)-Always Irreversible?

Whether the gastric carcinogenesis progressing through the stepwise manner from Hp infection, to AG and IM and further to invasive GC, can be arrested or even reverted, is a contradictory subject [3,11,12,114,115]. This issue is of crucial importance from the clinical point of view, because according to our current thinking, both AG and IM are irreversible conditions once established, and without adequate monitoring, inevitably lead to invasive GC [114,115]. However, there is some recent evidence suggesting that an early eradication of Hp infection can slow down or even revert the Correa cascade [11,12,116], suggesting that Hp eradication might have a potential to prevent GC [117]. Among the patients with premalignant lesions, it was shown that curative Hp eradication may prevent their progression [118]. It is thought that a so-called 'point of no return' may exist in the histological cascade from chronic gastritis to GC, however, after which eradication is unlikely to prevent the process from progressing to GC [11,12,116–118]. It appears that once IM has become established, Hp eradication, although retarding the progression of IM, cannot completely prevent GC [119,120]. This is not necessarily true for AG, however, for which there appears to be a discrepancy between the effect of eradication in the corpus and in the antrum. According to a recent meta-analysis of 12 studies comprising 2,658 patients, eradication of Hp infection resulted in significant improvement in AGC but not AGA, and, importantly, had no effect on IM [121].

14. L-Cysteine (Acetium®) Effectively Eliminates Acetaldehyde

L-cysteine is a semi-essential amino acid, which was shown (in 1975) to be capable of eliminating the toxicity of acetaldehyde by reacting covalently with it to form a stable 2-methylthiazolidine-4-carboxylic acid (MTCA) compound [29], resulting in inactivation of the reactive aldehyde group. MTCA is a stable and inert compound that is eliminated from the body through the intestines [29]. This principle was used in the recent innovation of the Biohit Acetium® Capsule, which contains 100 mg L-cysteine [122]. The novelty of this slow-release L-cysteine capsule is based on a highly effective local elimination of carcinogenic acetaldehyde in the stomach [30–32,122]. The other member of the Acetium® products is Acetium® Lozenge (3 ml L-cysteine) that does the same in the saliva in association with cigarette smoking [122].

14.1. Acetium® Capsule

The Acetium® Capsule contains 100 mg of L-cysteine as an active ingredient. L-cysteine is bound with matrix granules including Eudragit® RS-PO, Hypromellose (HPMC), calcium hydrogen phosphate (CaHPO4) and titanium dioxide [122]. This multi-particle system ensures that the formulation spreads throughout the stomach, independent of the composition of the stomach content. Granules can also be assumed to remain longer in gastric mucosal folds. The Acetium® Capsule is a CE-marked product and the formulation is registered in many countries as a medical device (class IIa), due to the mode of its action locally in the stomach [30–32]. After the proof-of-concept work in the laboratory, the efficacy of this novel Acetium® formulation has been conclusively documented in three carefully controlled clinical studies in Finland [30], Sweden [123], and Japan [112]. Similarly, the efficacy of Acetium® Lozenge in smokers has been confirmed in randomized controlled trials (RCT), but these data fall outside the scope of this discussion.

14.1.1. Elimination of Ethanol-Derived Acetaldehyde in Acid-free Stomach

In the first of these clinical studies using a placebo-controlled setting, Acetium® Capsule effectively eliminated ethanol-derived acetaldehyde in the gastric juice of patients with acid-free stom-

ach [30]. Altogether, seven volunteers with acid-free AGC were given either slow-release L-cysteine or placebo capsules in a double-blinded randomized fashion, volunteers serving as their own controls. Each study subject ingested placebo or 200 mg of L-cysteine, and ethanol 0.3 g/kg body weight (15 vol%), infused through a nasogastric tube. In the sequential samples of gastric juice aspirated at 5-minute intervals, the mean acetaldehyde level was 2.6-fold higher with placebo than with L-cysteine (13 vs. 4.7 μM, $p < 0.05$, $n = 7$) [30].

14.1.2. Elimination of Acetaldehyde in Patients with AGC

In the second study, patients with AGC received 15% ethanol (0.3 g/kg) through a nasogastric tube on two separate days, accompanied by randomized Acetium® Capsule (2 x 100 mg) or placebo [123]. After intra-gastric infusion of 15% ethanol with placebo, gastric juice acetaldehyde levels increased from zero to mean 36 μM (peak) and remained elevated for up to 100 min. Slow-release L-cysteine decreased gastric juice acetaldehyde by a mean of 68% (max. 87% at 60 min), and the decline persisted for up to two hours. Peak gastric juice L-cysteine level (8370 μM) was seen at 40 min and gastric juice L-cysteine remained elevated up to 160 min (220 μM at 160 min) [123]. Furthermore, the peak gastric juice MTCA level (233 μM) was seen at 80 min and gastric juice MTCA remained elevated for up to 180 min (36 μM at 180 min). These results justified the following conclusions: 1) an exposure of gastric mucosa to acetaldehyde is decreased by a mean of 68% ($p < 0.0001$) with slow-release L-cysteine capsule, and this acetaldehyde-eliminating effect continues for at least two hours; 2) with slow-release L-cysteine, intra-gastric acetaldehyde is inactivated to inert MTCA compound [29] that remains stable in the gastric juice for up to three hours [123].

14.1.3. Acetaldehyde Elimination, ALDH2 Mutation and PPI Treatment

Yet another elegant clinical trial from Japan confirmed that Acetium® Capsule (2 x 100 mg) reduced markedly the gastric juice acetaldehyde levels also in PPI-treated individuals, with either i) an active, or ii) deficient ALDH2 enzyme [112]. In ALDH2-active subjects, L-cysteine administration markedly reduced the gastric juice acetaldehyde concentration from the mean peak value of 26.4±3.7 μM (range 9.3-43.0 μM) at 30 min to a mean peak of 8.4±3.7 μM (range 0.2-35.5 μM) at 30 min [112], and the effect of L-cysteine persisted almost the entire 120-minute follow-up period. Quantitatively, L-cysteine resulted in a mean of 67% (three-fold) decrease in gastric juice acetaldehyde ($p = 0{,}001$). Similarly, in ALDH2-deficient subjects, L-cysteine significantly reduced the gastric juice acetaldehyde concentration, from a mean peak value of 63.9±7.7 μM (range 32.0-96.7 μM) at 30 min (without L-cysteine) to a mean peak of 26.7±8.1 μM (range 3.8-51.2 μM) at 30 min with L-cysteine. also this effect persisted throughout the follow-up period of 120 minutes, and corresponds to a 60% (2.5-fold) reduction in the mean acetaldehyde levels in these ALDH2-deficient subjects [112].

15. Conclusions

This review introduces a novel concept of a combined use of two new innovations: i) a biomarker panel (Gastro Panel®) for non-invasive serological diagnosis and screening of the high-risk lesions (Hp infection and AG) of the stomach, and ii) use of slow-release L-cysteine formulation (Acetium® Capsule) for elimination of carcinogenic acetaldehyde in the stomach in these subjects at high risk of gastric cancer.

15.1. Gastro Panel® Innovation

Gastro Panel® test has been on the market for roughly 15 years by now. The test design was based on long-term natural history studies on gastritis patients run since the 1960s in Finland and Estonia [7,15,16,35,56,57,73,76–78,83,89–91]. This first non-invasive diagnostic test is based on physiology of three stomach-specific biomarkers, supplemented with IgG ELISA testing for Helicobacter pylori, the etiological factor of peptic ulcer disease and GC [11,12,73]. In the current test version (the Unified Gastro Panel®), all 4 biomarkers are being processed under similar conditions [27,28,124]. Gastro Panel® will be soon available in the quick test version as well, particularly suitable for the POC (point-of-care) testing in doctors' offices with limited facilities for blood sample processing [27]. With the sophisticated diagnostic algorithm of the Gastro Soft®, eight specific biomarker profiles are distinguished (Figure 1; Table 1), of which four represent functional disturbances in acid output, three indicate AG and its topographic location, and one is specific for Hp infection. One of the many innovative features of Gastro Panel® is to combine the Hp IgG antibody measurement with three biomarkers (PGI, PGII, G-17), all being sensitive indicators of mucosal inflammation [27,28]. This combination makes this 4-biomarker panel the most comprehensive Hp test, devoid of the known shortcomings (false negative and false positive results) of the conventional Hp tests [22–28]. Given that this bacterium is the single most important risk factor of GC [79], it is time to move to Helicobacter pylori testing that is i) free from the shortcoming of the conventional Hp tests, and ii) provides a significant added value by detecting also the other key risk factor of GC, i.e., atrophic gastritis [28].

15.2. Acetium® Capsule

Acetium® Capsule is another unique innovation, designed for elimination of carcinogenic acetaldehyde in the stomach. This innovation is based on the capacity of L-cysteine to bind with acetaldehyde locally in the stomach, forming a stable MTCA compound [29]. A regular use of this device is indicated for all those who have acid-free stomach, irrespective of its origin. The most common high-risk groups include the following: 1) AG associated with Hp infection; 2) AG caused by autoimmune mechanism; 3) cigarette smokers; 4) alcohol consumers; 5) chronic users of PPI medication, and 6) those (500 million) people in Asia who have a mutation of the acetaldehyde metabolizing enzyme (ALDH2) and thus exposed to extremely high concentrations of this carcinogen [18–20,107–112]. In placebo-controlled clinical trials [30,112,123], slow-release L-cysteine effectively (by 60–80%) eliminated acetaldehyde in patients with acid-free stomach caused by either AGC

or PPI treatment, irrespective of their ALDH2 status. This capacity of slow-release L-cysteine to eliminate acetaldehyde persisted for up to three hours after ingestion of two Acetium® Capsules [30,112,123], indicating a sustained effect. With a rational use of these two medical devices, i) the gastric lesions at high risk for GC can be timely diagnosed, and ii) the stomach mucosa effectively protected against the exposure to carcinogenic acetaldehyde.

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