

BIOHIT

Innovating for Health



GastroPanel
LABORATORIES



Contents

GastroPanel laboratories	3
Examples of different-sized GastroPanel laboratories	3
Growing need for GastroPanel Laboratories	4
GastroPanel Laboratory	4
Prevention of unnecessary deaths due to peptic ulcer bleedings and gastric cancer	5
The background of the GastroPanel innovation	6
GastroPanel biomarkers and GastroSoft	6
The use of GastroView and GastroPanel examinations	8
Replacement of the ¹³ C urea breath test and the stool antigen test by GastroPanel may avoid malpractice	9
An investment and growth opportunity in diagnosing, screening, and prevention of gastrointestinal disorders and related diseases	11
Contact details	13
References	14

The hummingbird

The sensitive and precise qualities of the hummingbird symbolise Biohit's product groups of liquid handling, diagnostic products, and analysis systems. Biohit's liquid handling products based on the company's innovations and technologies are characterised by accuracy, precision and quality, as well as ergonomics and safety.



GastroPanel LABORATORIES

The comprehensive GastroPanel Laboratories include microplate analyzing systems, programs, pipettes, disposables and reagents for performing the GastroPanel tests, pepsinogen I, pepsinogen II, gastrin-17 and *Helicobacter pylori* antibodies. These turn-key laboratories also include training for the use and service of the equipment pro-

vided. In addition to the GastroPanel tests, the GastroPanel Laboratory is also suited for the running of any other microplate-based immunoassays. GastroPanel Laboratories satisfy the unmet needs of private doctors, health centers, reference and service laboratories as well as research institutions and hospitals.

Examples of different-sized GastroPanel laboratories

GastroPanel Laboratory, Small:

- GastroPanel tests for up to 2,200 patient samples (50 x 96-well microplates)
- BP800 Microplate Photometer including eLISA XL software
- Two sets of five 1-channel eLINE electronic pipettes (0.2-10µl, 5-120µl, 10-300µl, 50-1000µl, 100-5000µl).
- Two 8-channel eLINE electronic pipettes (50-1200µl)
- eLINE charging carousel, disposable tips and reagent vessels
- Installation and user training, 1-2 days on-site

GastroPanel Laboratory, Medium:

- GastroPanel tests for up to 4,400 patient samples (100 x 96-well microplates)
- Two BP800 Microplate Photometers including eLISA XL software
- Two BW50/8 Microplate Strip Washers
- Two sets of five eLINE electronic, 1-channel pipettes (0.2-10µl, 5-120µl, 10-300µl, 50-1000µl, 100-5000µl).
- Two sets of four 8-channel and two sets of four 12-channel eLINE electronic pipettes (0.2-10µl, 5-120µl, 10-300µl, 50-1200µl)
- eLINE charging stands, charging carousels, disposable tips and reagent vessels
- Installation and user training, 1-2 days on-site

GastroPanel Laboratory, Large:

- GastroPanel tests for up to 8,800 patient samples (200 x 96-well microplates)
- Three BP800 Microplate Photometers including eLISA XL software
- Three BW50/8 Microplate Strip Washers
- Two sets of five eLINE electronic, 1-channel pipettes (0.2-10µl, 5-120µl, 10-300µl, 50-1000µl, 100-5000µl).
- Two sets of four 8-channel and four 12-channel eLINE electronic pipettes (0.2-10µl, 5-120µl, 10-300µl, 50-1200µl)
- eLINE charging stands, charging carousels, disposable tips and reagent vessels
- Installation and user training, 1-2 days on-site

GastroPanel Laboratory, Extra Large:

- GastroPanel tests for up to 88,000 patient samples (2.000 x 96-well microplates)
- Fully automated enzyme immunoassay analyser
- Two BP800 Microplate Photometers including eLISA XL software
- Two BW50/8 Microplate Strip Washers
- Two sets of five eLINE electronic, 1-channel pipettes (0.2-10µl, 5-120µl, 10-300µl, 50-1000µl and 100-5000µl).
- Two sets of four 8-channel and two sets of four 12-channel eLINE electronic pipettes (0.2-10µl, 5-120µl, 10-300µl and 50-1200µl)
- eLINE charging stands, charging carousels, disposable tips and reagent vessels
- Installation and user training, 1-2 days on-site



Growing need for GastroPanel Laboratories

Since the 1980's, Biohit and its scientific advisors have taken into account an unmet need by developing safe, ethical and cost-efficient evidence-based preventive medicine for diseases of the gastrointestinal (GI) tract. We have done it with significant investments in numerous innovations, R&D, current in vitro diagnostics (IVD), and diagnostic analyzing systems.

Biohit offers diagnostics to develop theranostics (=diagnostics+therapy) solutions for gastrointestinal disorders, which are a growing medical, ethical and economic global problem. Theranostics provides the ultimate goal in medicine, which is the basis for safe, ethical and cost-efficient evidence-based and preventive medicine. Visiongain now predicts in its report: *"The markets for IVD and theranostics will exhibit strong growth in revenues from 2008-2023, with significant investments being made by far-sighted companies and health-care providers."* (Visiongain Report & Analysis: In Vitro Diagnostics Market, 2009).

Gastrointestinal disorders are among the most common types of complaints made to primary care physicians worldwide, and are associated with a substantial healthcare and economical burden. Each year, more than 100 million people are diagnosed with a GI disorder, resulting in 200 million sick days, 50 million medical visits, 16.9 million days lost from school, 10 million hospitalizations, and nearly 200 000 deaths per year. In 2005, in the US alone, GI disorders cost the payers and government nearly 110 billion USD in direct healthcare expenditures (IMS Health report. In: IMS Health) - and most probably over 300 billion USD globally.

Despite being one of the world's largest therapeutic areas and presenting huge burdens to health-care systems and economies globally, many of the diseases of the GI tract are still poorly understood, and diagnosis and therapy options are far from optimal, leaving many patients dissatisfied with their current treatment.

In addition, the ageing of the population is accompanied by severe diseases, such as gastric, esophageal and colorectal cancers as well as peptic ulcers, dementia, heart attacks, strokes, anemia and osteoporosis, which are causing an increasing burden for well-being and even a threat to sustainable health care.

Many of the above mentioned medical, ethical and economic problems of gastrointestinal diseases could be alleviated and solved with Biohit's in vitro diagnostics and screening tests for dyspepsia, *Helicobacter pylori* infection, atrophic gastritis with related risks (e.g., gastric- and esophageal cancer, peptic ulcer disease and the deficiency of vitamin B12, iron and calcium), lactose intolerance, celiac disease, inflammatory bowel disease and colorectal cancer, as well as cancers caused by acetaldehyde. Through the GastroPanel Laboratory. Biohit will provide this service and much more.

GastroPanel Laboratory

In addition to Biohit's separate products (www.biohit.com -> Diagnostics and Liquid Handling), there is an opportunity to purchase comprehensive GastroPanel Laboratories of different size and capacity as a "turn-key contract". Governments, health care authorities and the private sector could use this opportunity to improve the laboratory practise and to avoid unnecessary deaths due to gastric cancer, bleeding of peptic ulcer diseases, and save health care costs.

The GastroPanel Laboratory consists of one year's supply of the GastroPanel kits, and, if agreed separately, many other microplate immunoassays, for example, Biohit's SLE, cellular fibronectin, celiac- and inflammatory bowel disease (Crohn's disease and ulcerative colitis) panel as well as any other required microplate immunoassays. The GastroPanel Laboratory has been developed for the needs of private doctors, health centers, reference and service laboratories, research institutions and hospitals.

The Extra Large GastroPanel Laboratory, for example, includes all equipment, plastic consumables, analyzers, programs, installation and training as well as one year's 2,000 GastroPanel diagnostic kits (the reagents and microplates) for approximately 88,000 GastroPanel examinations with the GastroSoft reports (Table, page 10, www.gastropanel.net).

As a primary examination for dyspepsia, *H. pylori* infection and atrophic gastritis with related risks, (Table, page 10), the GastroPanel examinations often save more than 50% of unnecessary gastroscopy and biopsy specimen examinations.



Biohit's different sized and prized comprehensive GastroPanel Laboratories for microplate immunoassays, such as GastroPanel with the GastroSoft interpretation, serve the currently unmet medical, ethical and economic needs by improving the

laboratory practise with diagnostics leading to appropriate evidence-based treatment with savings in health care costs and preventing unnecessary deaths.



Prevention of unnecessary deaths due to peptic ulcer bleedings and gastric cancer

Approximately 200 to 300 persons die in Finland (5.3 million population) each year as a result of gastric and duodenal ulcer bleeding, or consequences thereof. Gastric and duodenal ulcer disease (peptic ulcer disease) is most commonly caused by a *Helicobacter pylori* infection (<http://nobelprize.org/medicine/laureates/2005/press.html>). As we know, the ¹³C- urea breath test (UBT) – or stool antigen test of the “test and treat” strategy - very often fails to detect *H. pylori* infections. In addition, these tests do not indicate, e.g., whether the patient has atrophic gastritis of the corpus and antrum of the stomach (Table, page 10). Atrophic gastritis of the antrum strongly increases the risk of stomach cancer and peptic ulcer disease in connection with a *H. pylori* infection. This may be a significant reason for the above mentioned hemorrhagic deaths, in connection with NSAID medication. It would e.g. be worth investigating how many of these deaths could have been prevented by the GastroPanel screening, which reveals the risk of peptic ulcer disease.

On the basis of the Finnish SETTI study, it was estimated that 250 to 300 gastric cancer deaths among persons of age over 50 could be prevented in Finland each year. This could be achieved by screening of all elderly people and especially all suspected *H. pylori* positive patients for atrophic gastritis with GastroPanel. In risk patients, early gastric cancers and precancerous lesions can be found with gastroscopy in an asymptomatic and curable stage. In addition to the risk assessment

of gastric cancer, the GastroPanel / GastroView screening produce considerable additional valuable information (Table, page 10).

Professor Pasechnikov et al. have written (Pasechnikov VD, Chukov SZ, Kotelevets SM, et al. Invasive and non-invasive diagnosis of *Helicobacter pylori*-associated atrophic gastritis: A comparative study, Scand J Gastroenterol 2005; 40: 297-301): “The analysis of the literature data and results of our own research allow us to conclude that the serious medical and ethical problems of the “test and treat” strategy can be corrected simply and economically by replacing its ¹³C- urea breath or stool antigen test by the GastroPanel examination. Talley et al. (2004) indicate that in many countries, such as Sweden and the US, the “test and treat” strategy alone is not considered sufficient. The *H. pylori* tests of the “test and treat” strategy does not find atrophic gastritis and related risks, such as gastric cancer and precancerous lesions, which should be confirmed by gastroscopy and biopsy specimen examination and would be successfully treated. Consequently, GastroPanel, gastroscopy and biopsy specimen examinations reveal patient with precancerous lesions and early stage gastric cancers, and, therefore, save people from unnecessary deaths because of gastric cancer.” (16, Table, page 10).

The background of the GastroPanel innovation

The Australian doctors Barry J. Marshall and J. Robin Warren received the Nobel Prize for the discovery of *Helicobacter pylori*, and for elucidation of the role of this bacterium in gastritis and peptic ulcer diseases (1,2). The GastroPanel innovation of the Finnish company Biohit and its scientific collaborators allows the physicians to benefit from these significant findings better than before (3-5). Together these two discoveries promote the development of safe, ethical and cost effective evidence-based preventive medicine.

With *H. pylori* discovered as a cause of gastritis, publications of the Finnish Gastritis Research Group, Professors Max Siurala and Pentti Sipponen, and co-workers, on chronic gastritis and atrophic gastritis from the 1970's and 80's helped Professors Marshall and Warren to realize that the infection and gastritis are connected to the development of ulcer diseases and stomach cancer. This pioneering research of the Finnish physicians has links to understanding of the injurious effect of *H. pylori* on the gastric mucosa, forming the backbone of the GastroPanel examination (6-10).

Consequently, the GastroPanel examination is based on the long Finnish research tradition into chronic gastritis and associated gastric diseases on co-work with Professor Michael Samloff (11) and on Professor Osmo Suovaniemi's innovations, which have revolutionized microplate analyses worldwide and have been utilized so extensively and successfully since the 70's, that they can justifiably be called global laboratory and industrial

standards. Suovaniemi's innovations also resulted in rapid development of reliable non-radioactive microplate immunoassays, on which the GastroPanel biomarker tests are based (12).

Before the GastroPanel innovation, only invasive gastroscopy and biopsy specimen examination were available to identify a healthy stomach or atrophic gastritis, and related disease risks (Table, page 10). Consequently, the GastroPanel innovation (the latest patent, U.S. Patent No. 7,358,062, "Method for diagnosing atrophic gastritis") enables simple and non-invasive diagnosis for patients with dyspepsia, *H. pylori* infection and atrophic gastritis, including evaluating the risks of complications by gastroesophageal reflux disease (GERD) (19).



Biohit's scientific advisors, Professors Pentti Sipponen (left) and Matti Härkönen (right) with Nobel Prize winner Professor Barry Marshall.

GastroPanel biomarkers and GastroSoft

The biomarker tests of the GastroPanel innovation, pepsinogen I and II (PGI, PGII), gastrin-17 (G-17) and *H. pylori* antibodies, are validated to complement each other so as to form a diagnostic panel. The GastroSoft computer program is used for the interpretation of the GastroPanel results (Table, page 10). To obtain full benefit it is important to note that Biohit's biomarkers (PG I, PG II; G-17 and *H. pylori* antibodies) are assayed from the same blood (plasma) sample as a panel. The novel application GastroSoft aids interpretation of the results (3). The GastroPanel examination is intended for safe, ethical and cost-effective diagnosis and screening of dyspepsia, *H. pylori*

infection and atrophic gastritis and related risks (13-23), including gastric cancer and peptic ulcer disease as well as deficiency of vitamin B12, iron and calcium.

Undiagnosed atrophic gastritis may lead to vitamin B12 deficiency, which appears to affect up to 12% of the elderly population (18). Vitamin B12 deficiency is considered to be associated with development of dementia, depression and peripheral neuropathies. In all tissues and cells, vitamin B12 deficiency increases in the concentrations of homocysteine that is considered an independent risk factor for atherosclerosis, heart attacks and



strokes. The consequences of vitamin B12 deficiency are reversible if detected and treated early, but unfortunately, this is currently rarely the case. Vitamin B12 deficiency is becoming an increasing disease among the older population.

Calcium deficiency causes osteoporosis and increases the risk of broken bones (about 35,000–40,000 in Finland per year), which can be fatal in the elderly. In addition to the human tragedy caused by hip fractures (about 7,000 per year in Finland), they also give rise to a cautious annual estimate of over EUR 100 million in healthcare expenses.

The above-mentioned risks of various diseases in atrophic gastritis, as well as risks of failures in absorption of perorally administrated medicines, or increased risk of gastrointestinal and pulmonary infections related to hypochlorhydric stomach, concern the elderly population in particular but are also valid in younger age groups (29 - 36).

Due to atrophic gastritis with its related risks, it is recommendable that the GastroPanel examination be used as a routine screening examination for all patients over 45, and be included in the diagnostic practice of dyspepsia-like complaints

in patients of all ages (Figure, Table, page 10).

To ensure patient safety, the GastroPanel examination is also recommended prior to any proton pump inhibitor (PPI) therapy and *H. pylori* eradication therapy. These therapies do not cure precancerous lesions and early stage cancers because of atrophic gastritis, which GastroPanel reveals for further gastroscopy and biopsy specimen examinations and successful treatment at the early stage of cancer. GastroPanel is also able to assess the recovery of the loss of the function of gastric mucosa due to atrophic gastritis and the risk of GERD's complications after the treatment procedures (19).

Patients with autoimmune disease, such as autoimmune thyroiditis, diabetes, rheumatoid arthritis and SLE, may have autoimmune atrophic gastritis with related disease risks (e.g., gastric cancer), and, by contrast, patients with autoimmune atrophic gastritis may also have other autoimmune diseases. Therefore, it is recommendable that the clinicians will take this into consideration, especially now that GastroPanel and GastroView examinations are available for clinical practice as easy screening methods to reveal atrophic gastritis (37,38, Table, page 10).

Biomarker	Indications
Pepsinogen I	The lower the Pepsinogen I concentration, the more severe the corpus atrophy and related risks, such as gastric cancer and vitamin B12 deficiency
Pepsinogen II	High Pepsinogen II concentration may indicate non-atrophic gastritis derived from <i>H.pylori</i> infection
Pepsinogen I / Pepsinogen II	The lower the Pepsinogen I / Pepsinogen II ratio, the more severe the corpus atrophy and related risks, such as gastric cancer and vitamin B12 deficiency
Gastrin-17	The lower the Gastrin-17 concentration, the more severe the antrum atrophy and related risks, such as gastric cancer and peptic ulcer disease
<i>H.pylori</i> antibodies	<i>H.pylori</i> infection, which often leads to atrophic gastritis and related risks

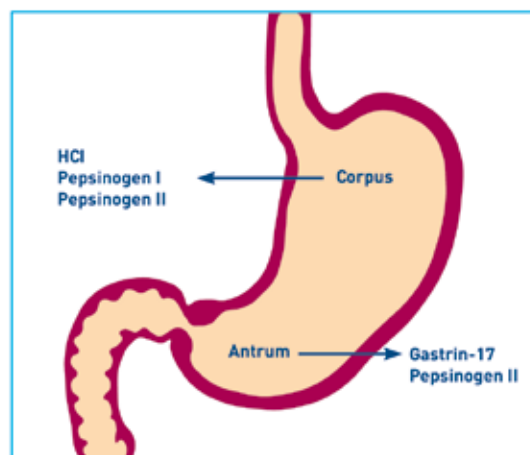


Figure. The levels of the GastroPanel-biomarkers, pepsinogen I and II, gastrin-17 and *H. pylori* antibodies measured from a plasma sample, diagnose atrophic gastritis of the entire mucosa of the stomach. *H. pylori* related gastritis usually starts in the antrum and expands proximally towards the corpus of the stomach. Stomach carcinogenesis is believed to begin with chronic active inflammation of the stomach mucosa, proceeding to extensive atrophy together with intestinal metaplasia, then to dysplasia, and finally to cancer. When comparing GastroPanel and gastroscopy, accurate diagnosis of atrophic gastritis cannot always be made from a few biopsy specimens covering an area of 15 - 20 square millimeters of the adult gastric mucosal surface area (about 80 000 square millimeters). In addition, the diagnoses of two pathologists may diverge. The quality of gastroscopy and biopsy specimen examinations are strongly dependent on the experience and competence of the gastroenterologist and pathologist. GastroPanel does not have such problems: just about anyone can perform the GastroPanel blood tests. However, the diagnosis of atrophic gastritis obtained with GastroPanel is in good agreement with gastroscopy and biopsy specimen examinations performed by skilful gastroenterologists and pathologists (24)

The use of GastroView and GastroPanel examinations

The GastroView examination (PGI, PGII and *H. pylori* antibodies) is recommended for health centres, emergency clinics, occupational health care and medical centres both in connection with health check-ups and for the diagnosis of dyspepsia, *H. pylori* infection and atrophic gastritis. The GastroView examination can be carried out at any time of the day, 24 hours a day. Fasting blood samples are not required, and the blood sample can be preserved even at room temperature.

However, the GastroPanel examination is always the examination of choice if a fasting blood sample can be obtained. This is because the GastroPanel examination determines both the GastroView tests and the level of gastrin-17 (G-17). Thus it provides more appropriate information also of structure and function of the antrum mucosa and of the risks of peptic ulcer disease and gastric cancer originating in the antrum. It also provides information on the risks associated with the complications of GERD. These include erosive oesophagitis and Barrett's oesophagus, both of which can progress into oesophageal cancer if left untreated. High levels of G-17 also help to confirm the presence of atrophic gastritis of the corpus when PGI levels and/or the ratio of PGI and PGII are low in plasma. Low levels of both PGI and G-17 indicate that the entire gastric mucosa (both antrum and corpus) is atrophied, which is the most severe and significant risk condition for gastric cancer.

Normal results in both GastroView and GastroPanel examinations mean, on the other hand, that

the entire stomach mucosa is intact and healthy (Figure and Table, page 10).

Since atrophic gastritis together with intestinal metaplasia is a multifocal process, it is difficult to accurately diagnose the extent of atrophic gastritis based on gastroscopy with a few biopsy samples. Furthermore, histological diagnosis of gastric atrophy depends on subjective judgment without a gold standard. Thus, there is a need for atrophic gastritis and its progression biomarkers, which are more convenient, free of discomfort or risk, economical and based on objective parameters (25). Endoscopic biopsy histology is not a reliable gold standard (26). Whilst histological diagnosis is the current "gold standard" for comparison with biomarkers, it has limitations in diagnostic accuracy (27,28).

When the GastroPanel biomarkers indicate a healthy gastric mucosa, the dyspepsia symptoms are often caused by functional dyspepsia or another disease not involving the gastric or esophageal mucosa (Table, page 10). GastroPanel can be used to find the dyspepsia and gastroesophageal reflux patients who need gastroscopy and biopsy specimen examinations to reveal possible precancerous lesions or early cancer to be successfully treated at the early stage.



Replacement of the ^{13}C urea breath test and the stool antigen test by GastroPanel may avoid malpractice

The claim, such as “First generation UBT: Easy to use and more reliable than serology tests” presumably aims to promote the sales of the ^{13}C urea breath test (UBT), and is misleading. The ^{13}C urea breath test and stool antigen test yield false negative results in the very cases where the correct diagnosis of an on-going *H.pylori* infection would be particularly important and even life saving (16), Table, page 10.

The ^{13}C urea breath test and the stool antigen test give false negatives in 40–50% of the cases if the patient has atrophic gastritis, MALT lymphoma or bleeding peptic ulcer disease, or if the patient is receiving antibiotics or PPI medication (39 - 45). The applicability of the ^{13}C urea breath test and the stool antigen test is only to detect whether the patient has *H. pylori* on the gastric mucosa – and nothing else – and only in patients without atrophic gastritis or other confounding factors (Table, page 10). Serology tests, such as GastroPanel’s *H. pylori* antibody test do not give false negative results, if the patient has atrophic gastritis, MALT lymphoma or bleeding peptic ulcer disease, nor if the patient is receiving antibiotics or PPI medication.

The ^{13}C urea breath test and the stool antigen test do not provide information on function of the gastric mucosa, and they cannot differentiate whether the stomach mucosa is intact or atrophic. If the patient has atrophic gastritis, it remains undiagnosed, as do the associated risks of gastric- and esophageal cancer, peptic ulcer disease, vitamin B12 deficiency and iron and calcium deficiency. In addition, if the ^{13}C urea breath test has not detected *H. pylori*, a 2-to-4-week PPI treatment trial commonly recommended may be unnecessary and could delay the diagnosis and treatment of more serious conditions. This may result in mal-

practice and even unnecessary deaths due to cancer if atrophic gastritis remains unnoticed and an early gastric cancer or precancerous gastric lesions remain untreated at early stages in which they still are curable. The human suffering and economic losses, as well as the knowledge of ignorance – even though the treatment praxis could easily have been amended to include all available examination methods, such as GastroPanel – may result in complaints and even litigations against the service providers and the medical profession.



Table. Summary of data provided by the GastroPanel examination and the ¹³C- urea breath test or stool antigen test of the “test and treat” strategy. The patient reports produced by GastroSoft are based on clinical studies comparing the results of GastroPanel examinations with the results from gastroscopy and biopsy specimen examinations. The serious medical and ethical problems of the “test and treat” strategy can be corrected simply and economically by replacing its ¹³C- urea breath test or stool antigen test with the GastroView round-the-clock examination (www.gastroview.com, www.gastroprofile.com) or with the GastroPanel examination (www.gastropanel.net, www.biohit.com/diagnostics -> Literature).

GastroPanel	The GastroSoft report states	¹³ C - urea breath test or Stool antigen test report:
The diagnosis for		
Functional vs. organic dyspepsia. When GastroPanel indicates healthy gastric mucosa, the dyspepsia complaints are often caused by functional dyspepsia or another disease not involving the gastric mucosa	YES	NO
H. pylori infection (gastritis)	YES	NOT RELIABLE ⁽¹⁾
Atrophic gastritis (damaged and severely dysfunctional gastric mucosa of the corpus or antrum or both)	YES	NO
The risks (due to atrophic gastritis) of		
Gastric cancer (in antrum and / or corpus)	YES ⁽²⁾	NO
Vitamin B12 deficiency (corpus)	YES	NO
Calcium, zinc and iron deficiency (corpus)	YES ⁽⁷⁾	NO
Peptic ulcer disease (antrum)	YES ⁽³⁾	NO
The risks of the complications of GERD		
Esophagitis and Barrett's esophagus	YES ⁽⁴⁾	NO
If necessary, a recommendation for		
Gastroscopy and biopsy examination	YES	NO
Treatment of <i>H. pylori</i> infection	YES ⁽⁸⁾	NOT RELIABLE ⁽¹⁾
Determination of vitamin B12 and homocysteine	YES	NO
Determination of calcium and iron	YES	NO
Follow-up examination to monitor		
the incidence of atrophic gastritis	YES ⁽⁵⁾	NO
the healing of the <i>H. pylori</i> infection	YES	NOT RELIABLE ⁽¹⁾
the healing of atrophic gastritis	YES	NO

⁽¹⁾The ¹³C- urea breath - and stool antigen tests give 40 – 50 % false negative results if the patient has a) atrophic gastritis, b) MALT lymphoma or c) bleeding peptic ulcer disease or d) if the patient is receiving antibiotics or PPIs (proton pump inhibitors). The GastroPanel *H. pylori* IgA/IgG antibody test combination does not have these types of false negative results.

⁽²⁾The risk of gastric cancer is very low without atrophic gastritis in corpus, antrum or both. But in some cases, an *H. pylori* infection without histologically observable atrophic gastritis may be associated with gastric cancer and peptic ulcer disease.

⁽³⁾No peptic ulcer disease with corpus atrophy (no acid, no ulcer). The risk of peptic ulcer disease is very low without antrum atrophy.

⁽⁴⁾Normal or high pepsinogen I and/or pepsinogen II ratio in association with low gastrin-17 (below 1.0 pmol/l) may indicate high acid (HCl) output and risks for the complications of gastroesophageal reflux disease (GERD).

⁽⁵⁾When the incidence of *H. pylori* -related atrophic gastritis is monitored, the patient can be offered targeted, safe treatment at the right time. The need for medication and the costs and adverse effects of medication can thus be reduced. If the patient has been diagnosed with peptic ulcer disease (gastric or duodenal ulcer), the *H. pylori* infection has to be treated (6). It should also be treated if the patient has atrophic gastritis. The patient and the doctor may also agree on eradication treatment for other reasons for example when the patient's close relatives have been diagnosed with gastric cancer.

⁽⁶⁾Press Release: The 2005 Nobel Prize in Physiology or Medicine, 3 October 2005 jointly to Barry Marshall and J. Robin Warren for their discovery of “the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease”: - “An indiscriminate use of antibiotics to eradicate *Helicobacter pylori* also from healthy carriers would lead to severe problems with bacterial resistance against these important drugs. Therefore, treatment against *Helicobacter pylori* should be used restrictively in patients without documented gastric or duodenal ulcer disease.” <http://nobelprize.org/medicine/laureates/2005/press.html>

⁽⁷⁾Adequate absorption of dietary calcium requires normal acid secretion that is impaired in atrophic gastritis and in long term PPI therapy. Subsequently, calcium is not absorbed normally in the gut, and the subjects are at risk for osteoporosis and hip fracture. Hypochlorhydric states such as atrophic gastritis and partial gastrectomy have long been known to cause iron deficiency anemia.

⁽⁸⁾Pepsinogen II level below 10 µg/l two months after the treatment indicates that the *H. pylori* eradication has succeeded. Increased level of pepsinogen II (over 10 µg/l) indicates active *H. pylori* gastritis or inflammation due to the use of non-steroidal anti-inflammatory drugs (e.g. aspirin) or strong alcohol. Dig. Liver Dis. 2005 Jul; 37(7):501-8. Epub 2005 Apr 18.



Point-of-Care tests

BHC also develops complimentary Point-of-Care (POC) tests. POC tests, an explosive growth area. With the need to test and treat with minimal delay, POC tests naturally complement laboratory screening of the population. BHC already markets the *H. pylori* Quick test, the Lactose intolerance Quick test and the Colon View Quick test for colorectal cancer screening and prevention. These products are already used routinely in several key market sectors, and are expected to become the tool of choice in the field of gastroenterology world-wide.

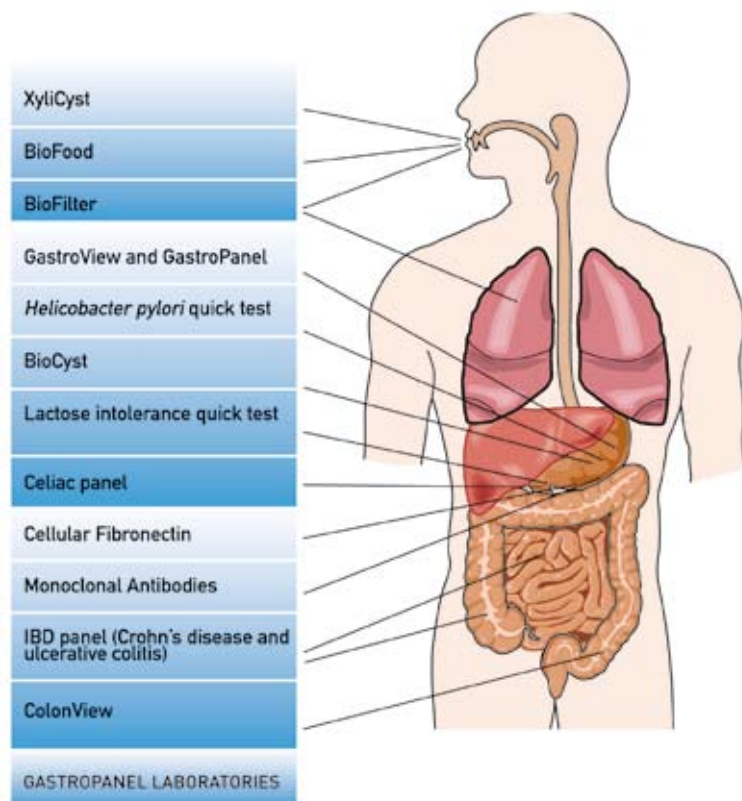
Cancer prevention

Acetaldehyde is a carcinogen found e.g. in tobacco smoke and in some dairy products, and which may be produced from sugar and alcohol by bacteria in the mouth and acid-free stomach. BHC has developed products that eliminate acetaldehyde from the saliva of smokers (XyliCyst tablets and chewing gum; ready for production, marketing, collaboration and licensing) and from tobacco smoke (BioFilter concept; ready for licensing) as well as from an acid-free stomach (BioCyst capsules; ready for production, marketing, collaboration and licensing), and from certain food products (BioFood method; ready for licensing).

The world-wide annual incidence of oral, pharyngeal, oesophageal, and gastric cancer is close to three million, the five-year survival rate being less than 5%. Therefore, it is essential to improve early detection of these diseases by accurate diagnostic methods (see above), and to minimize established risk factors such as acetaldehyde. The mentioned cancer prevention products are the result of intense basic research and clinical evaluations.

The market potential for BioCyst could be substantial, even billions of euros, because of the high number (approximately 500 million) of people having an acid-free stomach due to atrophic gastritis, which can be screened by GastroView and confirmed by GastroPanel and gastroscopy, and because of the increasing awareness of the carcinogenic and even addictive acetaldehyde. In addition, BioCyst capsules may protect also the patients who are treated by proton pump inhibitor (PPI) drugs, which cause an acid-free, acetaldehyde producing stomach against acetaldehyde.

For example, in Finland with the population of 5.3 million, there are approximately 450,000 patients who use PPI drugs. Consequently, if 50,000 patients with atrophic gastritis and 450,000 PPI-users protect themselves against carcinogenic acetalde-



hyde by taking BioCyst during each four meals a day, the market potential of BioCyst could exceed EUR 350 million in Finland (four BioCyst capsules/ one day EUR 2.0 x 365 days / one year x 500,000). BioCyst may prevent gastric and esophageal cancers. In addition to cancer prevention, XyliCyst may even help to stop smoking. XyliCyst and BioCyst have been classified as medical devices by the authorities, which will help their world-wide marketing considerably.

Analyzing Systems and GastroPanel laboratories

BHC's diagnostic products are components for BHC's analyzing systems, and more generally for microplate analyzers and analyzing systems world-wide (hundreds of thousands on the market place). In addition, BHC offers four different sized and priced comprehensive GastroPanel Laboratories for microplate immunoassays, such as GastroPanel, to health care authorities, hospitals, the private sector, well being centres etc. The laboratories serve the currently unmet medical, ethical and economic needs (e.g., to avoid unnecessary deaths due to gastric cancer, bleeding of peptic ulcer diseases etc.) and improve the laboratory praxis (to utilize the evidence based medicine) and save health care costs.



Contact details

BIOHIT OYJ

Laippatie 1
00880 Helsinki, Finland
Tel: +358-9-773 861
Fax: +358-9-773 86 200
E-mail: info@biohit.com
www.biohit.com

GERMANY

Biohit Deutschland GmbH
Raiffeisenstrasse 1
61191 Rosbach, Germany
Tel: +49-6003-82 820
Fax: +49-6003-828 222
info@biohit.de

JAPAN

Biohit Japan Co., Ltd.
NB Building 6F
2-15-10 Iwamoto-cho, Chiyoda-ku
Tokyo, 101-0032 Japan
Tel: +81-3-5822 0021
Fax: +81-3-5822 0022
sales@biohit.co.jp

U.K.

Biohit Ltd.
Unit 1, Barton Hill Way
Torquay, Devon TQ2 8JG,
United Kingdom
Tel: +44-1803-315 900
Fax: +44-1803-315 530
sales@biohit.demon.co.uk

FRANCE

Biohit SAS
2 Rue du Grand Chene
78830 Bonnelles, France
Tel: +33-1-3088 4130
Fax: +33-1-3088 4102
commercial.france@biohit.com

USA

Biohit Inc.
3535 Route 66, Bldg. 4
P.O. Box 308, Neptune,
N.J. 07754-0308, U.S.A.
Tel: +1-732-922 4900
Fax: +1-732-922 0557
pipet@biohit.com

RUSSIA

Biohit OOO, Saint-Petersburg
Biohit OOO
Vasilievskii Ostrov, line 5 - 68, building 4, letter D
199178, St. Petersburg
RUSSIA
Tel: +7-812-327 5327
Fax: +7-812-327 5323
main@biohit.ru

Biohit OOO, Moscow
Petrovsko-Razumovsky av. 29, building 2
103287 Moscow, Russia
Tel: +7-495-614 9550
Fax +7-495-613 5577
taras.pravdoljubenko@biohit.ru

CHINA

Biohit Biotech (Suzhou) Co Ltd.
Room 501, Office Block
Hotel Equatorial
65 Yan An Xi Lu
Shanghai, 200040
P. R. China
Tel: +86-21-6248 5589
Fax: +86-21-6248 7786
info.china@biohit.com

www.biohit.com/Diagnostics/Distributors

References

1. <http://nobelprize.org/medicine/laureates/2005/press.html>
2. http://www.yourhealthbase.com/database/rulcer_drugs.htm
3. <http://www.gastropanel.net>
4. <http://www.gastroview.com>
5. <http://www.gastroprofile.com>
6. Borch K, Axelsson K, Halgreen H, Damkjaer Nielsen M, Ledin T, Szesci PB. The ratio of Pepsinogen A to Pepsinogen C: A sensitive Test for Atrophic Gastritis. *Scan J Gastroenterol* 1989; 24: 870-876.
7. Dinis-Ribeiro M, da Costa-Pereira A, Lopes C, Barbosa J, Guilherme M, Moreira-Dias L, Lomba-Viana H, Silva R, Abreu N, Lomba-Viana R. Validity of Serum Pepsinogen I/II Ratio for the Diagnosis of Gastric Epithelial Dysplasia and Intestinal Metaplasia during the Follow-Up of Patients at Risk for Intestinal-Type Gastric Adenocarcinoma. *Neoplasia* 2004; 6(5):449-456.
8. Germana B, Di Mario F, Cavallaro LG, Moussa AM, Lecis P, Liatoupoulou S, Comparato G, Carloni C, Bertiato G, Battistel M, Papa N, Aragona G, Cavestro GM, Iori V, Merli R, Bertolini S, Caruana P, Franze A. Clinical usefulness of serum pepsinogens I and II, gastrin-17 and anti-*Helicobacter pylori* antibodies in the management of dyspeptic patients in primary care. *Digestive and Liver Disease* 2005;3:501-8.
9. Karnes WE, Samloff IM, Siurala M, Kekki M, Sipponen P, Kim SWR, Walsh JH. Positive Serum Antibody and Negative Tissue Staining for *Helicobacter pylori* in Subjects with Atrophic Body Gastritis. *Gastroenterology* 1992;101:167-174.
10. Sipponen P, Graham DY. Importance of atrophic gastritis in diagnostics and prevention of gastric cancer: application of plasma biomarkers. *Scand. J. Gastroenterol.* 2007;42 (1);2-10.
11. Varis K, Sipponen P, Laxén F, Samloff M, Huttunen JK, Taylor PR, Heinonen OP, Albanes D, Sande N, Virtamo J, Härkönen M & the Helsinki Gastritis Study Group. Implications of Serum Pepsinogen I in Early Endoscopic Diagnosis of Gastric Cancer and Dysplasia. *Scan J Gastroenterol* 2000; 35:950-956.
12. [http://www.google.com / search: "Osmo Suovaniemi vertical measurement principle" and "the King of Patents Osmo Suovaniemi in Finland 2002"](http://www.google.com/search?q=Osmo+Suovaniemi+vertical+measurement+principle+and+the+King+of+Patents+Osmo+Suovaniemi+in+Finland+2002)
13. Di Mario F, Franze A, Cavallaro LG. Non-Invasive Diagnosis for Gastric Diseases. *One Global Medicine s.r.l* 2004; 1-48, [www.biohit.com / Literature / Dignostics; 2004 Books](http://www.biohit.com/Literature/Diagnostics/2004Books)
14. DiMario F, Cavallaro LG, Liatopoulou A, et al. Accuracy of "serological gastric biopsy" in a cohort dyspeptic patients, Poster presentation at the DDW 2005, May 15-18, in Chigago, IL, USA
15. Nurgalieva Z, El-Zimaity H, Graham D, et al. Gastric atrophy in North America: Histology vs. Non-invasive testing, Poster presentation at the DDW 2005, May 15-18, in Chigago, IL, USA
16. Pasechnikov VD, Chukov SZ, Kotelevets SM, et al. Invasive and non-invasive diagnosis of *Helicobacter pylori*-associated atrophic gastritis: A comparative study, *Scand J Gastroenterol* 2005; 40:297-301
17. Sipponen P, Ranta P, Helske T, et al. Serum Levels of Amidated Gastrin-17 and Pepsinogen I in Atrophic Gastritis: An Observation Case-Control Study, *Scand J Gastroenterol* 2002 (7);785 –
18. Sipponen P, Laxen F, Huotari K, et al. Prevalence of Low Vitamin B12 and High Homocysteine in Serum in an Elderly Male Population: Association with Atrophic Gastritis and *Helicobacter pylori* infection, *Scand J Gastroenterol* 2003; 12:1209 – 14
19. Sipponen P, Vauhkonen M, Helske T, et al. Patients with Barrett's esophagus show low circulating levels of gastrin-17, *World J Gastroenterol* 2005;11(38):5988-5992
20. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer, *N Eng J Med* 2001; 345:784-789
21. Varis K, Sipponen P, Laxen F et al. the Helsinki Gastritis Study Group, Implications of serum pepsinogen I in early endoscopic diagnosis of gastric cancer and dysplasia, *Scand J Gastroenterol* 2000; 9; 950-956
22. Väänänen H, Vauhkonen M, Helske T, et al Non-Endoscopic Diagnosis of Atrophic Gastritis with a Blood Test. Correlation between Gastric Histology and Serum Levels of Gastrin-17 and Pepsinogen I. A Multicenter Study. *Eur J Gastroenterol Hepatol* 2003; 15; 885-891
23. Zagari RM, Nicolini G, Casanova S, et al Diagnosis of atrophic gastritis in the general population based upon a combination of three non invasive tests, *Gut* 2002; 51 (suppl 11);A39.
24. Väänänen H, Vauhkonen M, Helske T, et al Non-Endoscopic Diagnosis of Atrophic Gastritis with a Blood Test. Correlation between Gastric Histology and Serum Levels of Gastrin-17 and Pepsinogen I. A Multicenter Study. *Eur J Gastroenterol Hepatol* 2003; 15: 885-891.
25. Yanaoka, K et al, Risk of gastric cancer in asymptomatic, middle-aged Japanese subjects based on serum pepsinogen and *Helicobacter pylori* levels, *Int. J. Cancer* 2008; 123: 917 – 926.
26. Iijima K, Abe Y, Kikuchi R, Koike T, Ohara S, Sipponen P, Shimosegawa T. Serum biomarker tests are useful in delineating between patients with gastric atrophy and normal, healthy stomach. *World J Gastroenterol* 2009;15 (7):853-859.



27. Storskrubb T, Aro P, Ronkainen J, Sipponen P, Nyhlin H, Talley NJ, Engstrand L, Stolte M, Vieth M, Walker M and Agréus L. Serum biomarkers provide an accurate method for diagnosis of atrophic gastritis in a general population: The Kalixanda study. *Scand J Gastroenterol*, 2008; 43:1448-1455.
28. Ren JS, Kamangar F, Qiao YL, Taylor P, Liang H, Dawsey S, Liu B, Fan JH, Abnet C. Serum pepsinogens and risk of gastric and esophageal cancers in the General Population Nutrition Intervention Trial cohort. *Gut*, 2009; 58(5): 636-42.
29. Derendorf H, VanderMaelen CP, Bricki RS, MacGregor TR, Eisert W. Dipyridamole bioavailability in subjects with reduced gastric acidity. *J Clin Pharmacol* 2005;45:845-50
30. Lim SG, Sawyerr AM, Hudson M, Sercombe J, Pounder RE. Short report: the absorption of fluconazoli and itraconazoli under conditions of low intragastric acidity. *Aliment Pharmacol Ther* 1993;7:317-21
31. Centanni M, Gargano L, Canettieri G, Viceconti N, Franchi A, Delle Fave G, Annibale B. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. *N Engl J Med* 2006;354:1787-95
32. Tomilo DL, Smith PF, Ogundale AB, DiFrancesco R, Berenson CS, Eberhardt E, Bednarczyk E, Morse GD. Inhibition of atazanavir oral absorption by lansoprazole gastric acid suppression in healthy volunteers. *Pharmacotherapy* 2006;26:341-6
33. Martinsen TC, Bergh K, Waldum HL. Gastric juice: a barrier against infectious diseases. *Basic Clin Pharmacol Toxicol* 2005;96:94-102
34. Duchini A, Rogers VD. Diarrhea in the international Traveler. *Curr Treat Options Gastroenterol* 1999;2:251-7
35. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. *J Hosp Infect* 2003;54:243-5
36. Tryba M. The gastropulmonary route of infection – fact or fiction. *Am J Med* 1991;91:135S-146S
37. DiMario F and Malfertheiner P. Personal communication
38. Iori A, Cavallaro LG, Minelli R, Merli R, Novenne A, Maini A et al. Usefulness of GastroPanel for screening of atrophic gastritis patients with autoimmune thyroid diseases. *Digest Liv Dis* 2008;40:S28.
39. Gatta L, Perna F, Ricci C, et al. Effect of proton pump inhibitors and antacid therapy on ¹³C urea breath test and stool test for *Helicobacter pylori* infection. *Am J Gastroenterol* 2004;99:823-829
40. Graham KS, Graham DY. *Contemporary Diagnosis and Management of H. pylori – Associated Gastrointestinal Diseases*, Published by Handbooks in Health Care Co, Newtown, Pennsylvania, USA, 2002
41. Graham DY, Opekun AR, Hammoud F, Yamaoka Y, Reddy R, Osato MS, El-Zimaity HM. Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors. *Am J Gastroenterol*. 2003;98;1005-9.
42. Kokkola A, Rautelin H, Puolakkainen P, et al. Positive result in serology indicates active *Helicobacter pylori* infection in patients with atrophic gastritis. *J Clin Microbiol* 1998; 36 (6);1808-10.
43. Kokkola A, Rautelin H, Puolakkainen P et al. Diagnosis of *Helicobacter pylori*-infection in Patients with Atrophic Gastritis: Comparison of Histology, ¹³C Urea Breath Test, and serology. *Scand J Gastroenterol* 2000; 25;138-141
44. Kokkola A., Rautelin H, Puolakkainen P, Sipponen P, Färkkilä M, Kosunen TU. Diagnosis of *Helicobacter pylori* infection in Patients with Atrophic Gastritis: Comparison of Histology, ¹³C Urea Breath Test, and serology. *Scand J Gastroenterol* 2000;25;138-141.
45. Kokkola A, Rautelin H, Puolakkainen P, Sipponen P, Färkkilä M, Haapiainen R, Kosunen TU. Positive result in serology indicates active *Helicobacter pylori* infection in patients with atrophic gastritis. *J Clin Microbiol*. 1998; 36 (6) 1808 -10

More articles at www.biohit.com/Diagnostics



Innovating for Health