

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

According to estimates presented by Dr. Anna-Liisa Karvonen, a Finnish specialist in gastroenterology, approximately 200 to 300 persons die in Finland each year as a result of bleeding from gastric and duodenal ulcers or the resulting consequences. 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 for *H. pylori* do not indicate, e.g., whether the patient has atrophic gastritis of the corpus and antrum of the stomach (see Table below). 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 (200 to 300 / a year in Finland), in connection with NSAID medication. It would be worth investigating, e.g., 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 a gastroscopy in asymptomatic and curable stage. In addition to the risk assessment of gastric cancer, the GastroPanel screening, diagnosing and check-ups produce a lot of additional, reliable and valuable information (see Table below).

By referring to own studies and scientific literature professor Pasechnikov et al conclude the following (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): *”Conclusion. 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.”* (see also Table below).

The Background of the GastroPanel Innovation

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 novel 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). These two discoveries together promote the development of safe, ethical and cost effective evidence-based and preventative 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

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- 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.

Table. Summary of the data provided by the GastroPanel examination and the ¹³C- urea breath test or stool antigen test of the “test and treat” strategy. The GastroSoft program supplies a patient report. The reports produced by GastroSoft are based on clinical studies comparing the results of GastroPanel examinations with 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 by the GastroPanel examination (www.biohit.com / Diagnostics).

GastroPanel	The GastroSoft report states:	¹³C - urea breath test or Stool antigen test report:
The diagnosis for		
Functional vs. organic dyspepsia. When GastroPanel indicates the gastric mucosa is healthy, 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 may give 40 – 50 % false negative results if the patient has a) atrophic gastritis and related risks, b) MALT lymphoma or c) bleeding peptic ulcer disease or d) if the patient is currently receiving antibiotics or PPIs (proton pump inhibitors). The GastroPanel *H. pylori* antibody test 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, a *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 I and 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 is 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.

GastroPanel examination - a gold standard in primary health care

GastroPanel examination is intended to determine *Helicobacter pylori* antibodies and the levels of pepsinogen I, pepsinogen II and gastrin-17 from a EDTA plasma sample.

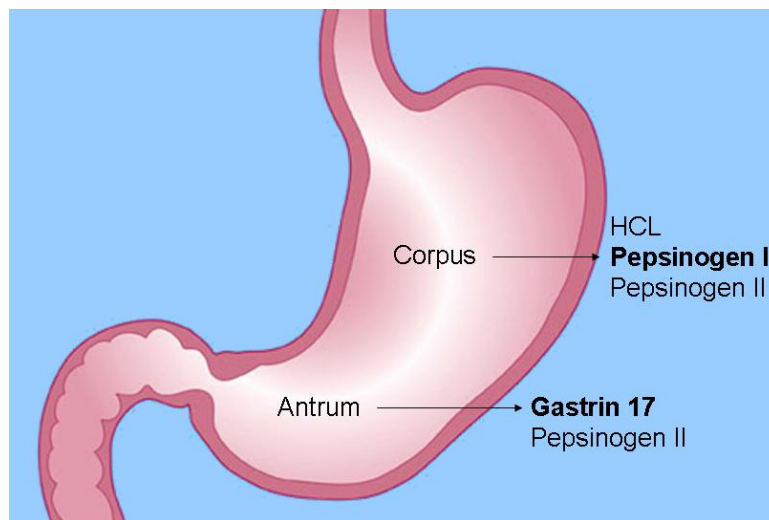


Figure. The levels of the GastroPanel-biomarkers, pepsinogen I and II, gastrin-17 and *H. pylori* antibodies measured from a plasma sample, diagnose atrophic gastritis of the entire mucosa of the stomach. *H. pylori* related gastritis usually starts in the antrum and expands proximally towards the corpus 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 is strongly dependent on the experience and competence of the gastroenterologist and pathologist. GastroPanel does not have such problems, irrespectively whoever does the GastroPanel blood tests. However, the diagnosis of atrophic gastritis obtained with GastroPanel is in good agreement with gastroscopy performed by skilful gastroenterologists and pathologists(4)

Since atrophic gastritis together with intestinal metaplasia is a multifocal process, it is difficult to accurately diagnose the extent of atrophic gastritis based on the 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 (5). Endoscopic biopsy histology is not a reliable gold standard (1). Whilst histological diagnosis is the current “gold standard” for comparison with biomarkers, it has limitations in diagnostic accuracy (2,3).

*When the GastroPanel biomarkers indicate the gastric mucosa is healthy (no *H. pylori* infection and / or no atrophic gastritis), the dyspepsia symptoms are often caused by functional dyspepsia or another disease not involving the gastric mucosa. GastroPanel can also be used to find the dyspepsia and gastroesophageal reflux patients who need gastroscopy as a further examination.*

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5. 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.